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

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

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Abstract

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

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Objectives: To estimate the effectiveness and cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial or single-chamber ventricular pacemakers in the treatment of bradycardia due to sick sinus syndrome (SSS) or atrioventricular block (AVB).
Data sources: Electronic databases and relevant Internet sites. Contact with device manufacturers and experts in the field.
Review methods: A systematic review was carried out of randomised controlled trials (RCTs). The quality of selected studies was appraised using standard frameworks. Meta-analyses, using random effects models, were carried out where appropriate. Limited exploration of heterogeneity was possible. Critical appraisal of economic evaluations was carried out using two frameworks. A decision-analytic model was developed using a Markov approach, to estimate the cost-effectiveness of dual-chamber versus ventricular or atrial pacing over 5 and 10 years as cost per quality-adjusted life-year (QALY). Uncertainty was explored using one-way and probabilistic sensitivity analyses.
Results: The searches retrieved a systematic review of effectiveness and cost-effectiveness published in 2002, four parallel group RCTs and 28 cross-over trials. Dual-chamber pacing was associated with lower rates of atrial fibrillation, particularly in SSS, than ventricular pacing, and prevents pacemaker syndrome. Higher rates of atrial fibrillation were seen with dual-chamber pacing than with atrial pacing. Complications occurred more frequently in dual-chamber pacemaker insertion. The cost of a dual-chamber system, over 5 years, including cost of complications and subsequent clinical events in the population, was estimated to be around £7400. The overall cost difference between single and dual systems is not large over this period: around £700 more for dual-chamber devices. The cost-effectiveness of dual-chamber compared with ventricular pacing was estimated to be around £8500 per QALY in AVB and £9500 in SSS over 5 years, and around £5500 per QALY in both populations over 10 years. Under more conservative assumptions, the cost-effectiveness of dual-chamber pacing is around £30,000 per QALY. The probabilistic sensitivity analysis showed that, under the base-case assumptions, dual-chamber pacing is likely to be considered cost-effective at levels of willingness to pay that are generally considered acceptable by policy makers. In contrast, atrial pacing may be cost-effective compared with dual-chamber pacing.
Conclusions: Dual-chamber pacing results in small but potentially important benefits in populations with SSS and/or AVB compared with ventricular pacemakers. Pacemaker syndrome is a crucial factor in determining cost-effectiveness; however, difficulties in standardising diagnosis and measurement of severity make it difficult to quantify. Dual-chamber pacing is in common usage in the UK. Recipients are more likely to be younger. Insufficient evidence is currently available to inform policy on specific groups who may benefit most from pacing with dual-chamber devices. Further important research is underway. Outstanding research priorities include the economic evaluation of UKPACE studies of the classification, diagnosis and utility associated with pacemaker syndrome and evidence on the effectiveness of pacemakers in children.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Atrial fibrillation/flutter 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 disorganised and abnormal manner.

Atrioventricular block Defective conduction at the atrioventricular node.

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

Bundle of His A bundle of modified heart muscle that transmits the cardiac impulse from the atrioventricular node to the ventricles, causing them to contract.

Chronotropic incompetence The inability of the heart to increase its rate appropriately in response to increased activity or metabolic need (e.g. exercise).

Escape rhythm Rhythm of at least three ectopic complexes (escape beats). The rate varies with the origin: SA-node 50–60 bpm; atria and atrioventricular-junction 40–60 bpm; ventricles 30–40 bpm.

Holter monitoring A device that records heart rate and rhythm over a 24-hour period.

Incremental cost effectiveness ratio The main output of economic analysis. The ratio of differences in costs to differences in outcome (measured as quality-adjusted life-years in this report) between two options, that is, the extra cost involved in realising an additional unit of outcome.

International normalised ratio A measure of the degree of anticoagulation achieved using warfarin (INR=1.0 is equivalent to no anticoagulation).

Mobitz type I block Also called Wenckebach block. Electrocardiographic pattern of second degree atrioventricular block, with a stable interval between atrial contractions and a progressive increase in the PR interval until a P wave fails to conduct.

Mobitz type II block A conduction failure that occurs at time intervals with a stable interval between atrial contractions.

Physiological pacing Pacing mode that reproduces the natural sequence of atrioventricular contractions. This is achieved with the preservation of atrioventricular synchrony and rate response. This is a generic term for pacing that includes both dual-chamber and atrial, single-chamber pacemakers.

Rate hysteresis A programmable feature in some pacemakers which, should the intrinsic rate fall below the hysteresis escape rate, there is one cycle of pacing at the escape rate followed by pacing at the programmed base rate until the pacemaker is again inhibited by a sensed event.

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/sinus node dysfunction Progressive fibrotic degeneration of the sinus node causing delays in or failure of conduction. These clinical manifestations are characterised by symptoms of sinus bradycardia or arrest, sinoatrial block or alternation of bradyarrhythmia with tachyarrhythmia.

continued

Glossary *continued*

Sinus node Collection of cells located on the right atrium at the base of the vena cava. The sinus spontaneously depolarises, triggering rhythmic heart contraction.

Tachyarrhythmia Abnormally fast heart rhythm.

Tachycardia Increased heart rate.

Thromboembolism A blood clot that forms within a blood vessel (thrombus) and travels through the bloodstream to another part of the body.

Wenckebach block Synonym of Mobitz type I block.

List of abbreviations

ABHI	Association of British Healthcare Industries
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
Adj HR	adjusted hazard ratio
AF	atrial fibrillation
AHA	American Heart Association
AHRE	atrial high-rate episode
AV	atrioventricular
AVB	atrioventricular block
BPEG	British Pacing and Electrophysiology Group
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCAD	Central Cardiac Audit Database
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CiC	commercial in confidence
COPD	chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CTOPP	Canadian Trial of Physiological Pacing
CVD	cardiovascular disease
DARE	Database of Abstracts of Reviews of Effectiveness
DCP	dual-chamber pacing
DES	discrete event simulation
DRG	Diagnostic Resource Group
EF	ejection fraction
EQ-5D	EuroQol 5 Dimensions
FDA	Food and Drug Administration
HF	heart failure
HR	hazard ratio
HRG	Health Resource Group
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
INR	international normalised ratio
IQR	interquartile range
ITT	intention-to-treat
KM	Kaplan–Mayer
LOCF	last observation carried forward
MI	myocardial infarction
MOST	Mode Selection Trial in Sinus Node Dysfunction

continued

List of abbreviations *continued*

MRC	Medical Research Council
MRI	magnetic resonance imaging
NA	not applicable
NASPE	North American Society of Pacing and Electrophysiology
NHP	Nottingham Health Profile
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NNT	number needed to treat
NRR	National Research Register
ns	not significant
NYHA	New York Heart Association
OR	odds ratio
PASE	Pacemaker Selection in the Elderly
PCI	percutaneous coronary intervention
PCT	primary care trust
PM	pacemaker
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QLAP	Quality of Life Assessment Package
QoL	quality of life
RCI	Research Cost Initiative
RCT	randomised controlled trial
RR	relative risk
SA	sinoatrial
SAN	sinoatrial node
SAS	Specific Activity Scale
SCP	single-chamber pacing
SD	standard deviation
SE	standard error
SF-36	Short Form 36
SIP	Sickness Impact Profile
SMD	standardised mean difference
SND	sinus node disease
SSS	sick sinus syndrome
TIA	transient ischaemic attack
TTO	time trade-off
Tx	treatment
UHR	unpaced heart rate
VAS	visual analogue scale
YHEC	York Health Economics Consortium

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Note

Confidential information was removed from this version of the report but was considered by the appraisal committee of the National Institute for Health and Clinical Excellence

In the discussion of pooled results from three published studies and one unpublished trial, the results for the three individual published trials are reported, but the subsequent meta-analysis consists of the pooled results from all four trials. This preserves the confidentiality of the unpublished trial while aiming for as much transparency as possible on the overall effectiveness of the technology.

Executive summary

Objective

The objective of the assessment was to estimate the effectiveness and cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial or single-chamber ventricular pacemakers in the treatment of bradycardia due to sick sinus syndrome (SSS) or atrioventricular block (AVB).

Description

A pacemaker consists of a small, battery-powered generator and one or more leads. In a single-chamber system, one lead is used, most commonly pacing the right ventricle. Dual-chamber pacemakers have two leads, placed in the right atrium and right ventricle. They act synchronously when a slow natural heart rate is detected to mimic the sequential physiological contraction of the atria and ventricles.

Single-chamber pacemakers may be atrial or ventricular. Atrial pacemakers are used where slow heart rate is due only to sinoatrial disease, i.e. where conduction between the atria and ventricles is intact. Single-chamber ventricular pacemakers, which are much more commonly used in practice, are appropriate where conduction between the atria and ventricles is impaired.

Epidemiology and background

Bradycardia is abnormally slow heart rate. SSS is present when the heart's natural pacemaker, the sinoatrial node, fails to initiate cardiac contraction. It is mainly the result of chronic fibrodegenerative processes or local calcification in the atrial wall. Prevalence is around 0.03% and rises with age. AVB denotes defective conduction of the atrioventricular conduction system. It may be progressive, with higher grades carrying worse prognosis. Prevalence is around 0.04% and is higher in the elderly and in men.

Methods

A systematic review was carried out of randomised controlled trials (RCTs) of the effectiveness of dual-chamber pacemakers in the relevant populations compared with either ventricular or atrial devices. Studies were identified by searching electronic databases and relevant Internet sites, contact with device manufacturers and experts in the field, and searching bibliographies of studies retrieved. Inclusion criteria were applied by two researchers and related to the populations of interest, study types (systematic reviews or RCTs), language (English only), interventions (minimum 48 hours) and outcomes (restricted to patient-based measures). Data were extracted by one researcher and checked by another. Tabulation and narrative synthesis were carried out. Quality was appraised using standard frameworks, but not summary scores. Meta-analyses, using random effects models, were carried out where appropriate. Limited exploration of heterogeneity through stratification was possible.

A literature search was carried out for published economic evaluations or systematic reviews of such studies. Economic evaluations submitted to the NHS National Institute for Health and Clinical Excellence were obtained. Critical appraisal was carried out using two frameworks, for generic and decision-analytic economic evaluations.

A decision-analytic model was developed in a spreadsheet program, using a Markov approach, to estimate the cost-effectiveness of dual-chamber versus ventricular or atrial pacing over 5 and 10 years from the perspective of the UK NHS as cost per quality-adjusted life-year (QALY). Uncertainty was explored using one-way and probabilistic sensitivity analyses.

Results

Number and quality of studies, and direction of evidence

The searches retrieved a systematic review of effectiveness and cost-effectiveness published in 2002, four parallel group RCTs and 28 cross-over trials.

The quality of the systematic review was good. It was used as the basis for reporting the existing published economic literature as no additional published studies of this type were identified.

The quality of the parallel group studies was reasonable. They included over 7000 participants and ran over 3–5 years, measuring clinically relevant outcomes [e.g. death, pacemaker syndrome, atrial fibrillation (AF), stroke, functional capacity and heart failure]. Two were trials of mode (in which a dual-chamber pacemaker is inserted and randomised to act in dual- or single-chamber mode) and two were trials of device, in which patients were randomised before implantation. One was in people with SSS only (MOST), two were in mixed populations (PASE and CTOPP) and one was in people with AVB only (UKPACE).

There was no significant effect on mortality in single trials or meta-analysis. Dual-chamber pacing had a favourable and statistically significant effect on AF (pooled odds ratio = 0.76), but not on stroke or heart failure, although non-significant trends in favour of dual-chamber pacing were shown in some trials. The effect on AF was time dependent and more marked in trials including people with SSS. Functional capacity was not significantly improved. Effects on quality of life varied according to measurement method, were not large, may be subject to bias in one trial (MOST) and were likely to reflect differences in the incidence of pacemaker syndrome.

Pacemaker syndrome was reported only in trials of mode and occurred in more than a quarter of participants on ventricular pacing. It was associated with reduction in quality of life. In trials of mode, reprogramming to dual-chamber pacing was straightforward and achieved in most cases with improvement of symptoms. In trials of device, upgrading required an invasive procedure and this was carried out in less than 5% of cases.

The cross-over trials were much smaller and of shorter duration, with less complete reporting of methods and a wider range of outcomes studied. The shorter duration precluded the measurement of outcomes such as mortality, although positive effects were shown for some individual symptoms and exercise capacity (although this outcome is confounded by the use of rate-responsive pacemakers). The cross-over trials were carried out, in general, earlier than the larger parallel studies.

Summary of benefits

Dual-chamber pacing was associated with lower rates of atrial fibrillation, particularly in SSS, than ventricular pacing, and prevents pacemaker syndrome. Higher rates of atrial fibrillation were seen with dual-chamber pacing than with atrial pacing. Complications occurred more frequently in dual-chamber pacemaker insertion.

Costs

The cost of pacemaker systems was highly variable. Dual-chamber devices are more expensive owing to the additional lead, more time involved in implantation and higher risk of complications. The need to upgrade single-chamber to dual-chamber devices offsets the additional acquisition costs over time. The cost of a dual-chamber system, over 5 years, including cost of complications and subsequent clinical events in the population, was estimated to be around £7400. Because of the additional clinical consequences of pacemaker syndrome and atrial fibrillation (and its sequelae) the overall cost difference between single and dual systems was not large over this period: around £700 more for dual-chamber devices.

Cost-effectiveness

Published economic analyses were not informative. Sponsor evaluations were of variable quality and suggested that dual-chamber pacing was likely to yield benefits at low cost (or with savings to the NHS).

In the PenTAG model, the cost-effectiveness of dual-chamber compared with ventricular pacing was estimated to be around £8500 per QALY in AVB and £9500 in SSS over 5 years, and around £5500 per QALY in both populations over 10 years.

Atrial pacing dominated dual-chamber pacing at 5 and 10 years (i.e. was more effective at lower cost).

Sensitivity analyses

There was considerable uncertainty in the models of cost-effectiveness, much arising because the differences in costs and benefits are small and so the incremental cost-effectiveness ratio is potentially subject to large variation.

In the comparison of dual and ventricular pacing, the differential cost of devices is clearly important. The incidence, duration and severity of pacemaker syndrome was a critical determinant of cost-effectiveness. Under more conservative assumptions regarding the persistence of mild pacemaker syndrome, the cost-effectiveness of dual-chamber pacing was around £30,000 per QALY. AF rates were a further source of uncertainty, in terms of overall relative risk and the relationship between risk and time.

The probabilistic sensitivity analysis showed that, under the base-case assumptions, dual-chamber

pacing was likely to be considered cost-effective at levels of willingness to pay that are generally considered acceptable by policy makers.

Atrial pacing dominated dual-chamber pacing under all assumptions.

Limitations of the calculations (assumptions made)

There were significant uncertainties and limitations in the underlying data. Pacemaker syndrome is the subject of clinical debate and its impact on quality of life is not clear. The utility values used in the model were inferred rather than measured directly in people with pacemaker syndrome.

The data underlying the analysis of dual versus atrial pacing were limited, being derived from a single small trial.

Other important issues regarding implications

Over 70% of the eligible population currently receive dual-chamber pacemakers, although overall UK pacing rates are lower than in the rest of Europe.

Around 10% of candidates for pacing are likely to have atrial fibrillation at the time of implant, and so a theoretical maximum for diffusion of dual-chamber pacing is around 90% of the eligible population.

Conclusions

Dual-chamber pacing results in small but potentially important benefits in populations with SSS and/or AVB compared with ventricular pacemakers. There is no evidence of superiority in terms of mortality in the medium term (up to 5 years), which increases the importance of intermediate outcomes such as AF and of impacts on quality of life through, for example, pacemaker syndrome.

As well as the potential avoidance of a small number of important cardiovascular disease consequences, pacemaker syndrome is a crucial factor in determining cost-effectiveness. However, difficulties in standardising diagnosis and measurement of severity make it difficult to quantify precisely its impact.

At 5 years, dual-chamber pacing in SSS and AVB is likely to yield additional QALYs at a cost of less than £10,000, although there is some uncertainty around this estimate, particularly with regard to pacemaker syndrome. More conservative assumptions suggest that the cost-effectiveness ratio may be around £30,000 per QALY.

The evidence base comparing dual-chamber with single atrial pacing is much smaller and less robust. A single, small, parallel pilot RCT is available and informs the cost-effectiveness analysis. This suggests that atrial pacing is likely to be cost-effective compared with dual-chamber pacing.

Dual-chamber pacing is in common usage in the UK. Recipients are more likely to be younger. Insufficient evidence is currently available to inform policy on specific groups who may benefit most from pacing with dual-chamber devices, although overall the assessment is that the technology is likely to yield benefits at a level that is generally considered acceptable value for money compared with ventricular devices.

Need for further research

The following areas are recommended for further research.

- An individual patient data meta-analysis of existing trials is required and underway.
- Further trials of dual versus atrial pacing are required and one is underway (DANPACE).
- Publication of the economic evaluation of UKPACE and reporting of utility by health state is needed urgently.
- Further research into the classification, diagnosis and utility associated with pacemaker syndrome is needed.
- There is currently no evidence for the effectiveness of pacemakers in children.

Chapter 1

Aim of the assessment

The aim of this health technology assessment is to estimate the effectiveness and cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial or single chamber ventricular pacemakers in the treatment of bradycardia due to sick sinus syndrome (SSS) or atrioventricular block (AVB).

Chapter 2
Background

Atrioventricular block and sick sinus syndrome

Definitions

Pathological bradycardia is a heart arrhythmia characterised by an abnormally slow rate [below 60 beats per minute (bpm) during the day and 50 bpm at night]. Bradycardia may be caused by a range of conditions affecting the heart's conduction system.[1]

SSS is an irreversible dysfunction of the sinus node, a small area situated in the right atrial wall composed of cells that depolarise spontaneously and act as the heart's natural pacemaker. SSS includes a spectrum of arrhythmias with diverse underlying mechanisms such as sinus bradycardia, sinus arrest, sinoatrial (SA) block, SSS and the bradycardia–tachycardia syndrome.

A failure in sinus activity may result in sinus pause or sinus arrest, i.e. failure of the atria to start a timely contraction. Sinus exit block occurs when depolarisation waves fail to travel across atrial tissues.

There are several degrees of progressive SA disease.[2] Bland asymptomatic prolongation of sinoatrial conduction is called first degree SA block. The failure of periodic sinus node impulses characterises second-degree SA block. A progressive and increasing prolongation of sinoatrial conduction time, associated with an occasional failure of conduction, is termed sinoatrial Wenckebach periodicity. Advanced second degree sinoatrial block occurs when an occasional interruption occurs without alteration of the periodicity of rhythm.

Slow sinus rhythm can allow atrial ectopic beats to occur, which in turn may trigger tachyarrhythmias, typically atrial fibrillation (AF).[2] This may result in alternating fast and slow rhythms: bradycardia–tachycardia syndrome.[1–3]

AVB means defective conduction at the atrioventricular (AV) node. This is a discrete connection between the right atrium and the ventricles, which captures depolarisation waves from the atrial walls and conducts them through the ventricles via the intraventricular (or His–Purkinje) conduction system. This is a branching structure, comprising the bundle of His and the right and left bundle branches. The left bundle branch is further divided into the anterior and posterior fascicles.

AVB can progress from first degree, a benign form characterised by atrial contraction followed by a minimal conduction delay to the ventricles, to partial (second degree) or complete (third degree) AVB. Second degree block occurs when conduction to the ventricle is progressively delayed until an occasional failure of conduction occurs (Mobitz I or Wenckebach block) or when conduction fails at occasional intervals without progressive prolongation of the conduction time (Mobitz II). Advanced second degree block occurs when conduction fails at fixed regular intervals (2:1, 3:1, or more rarely 4:1 or 5:1).

A block in AV conduction may occur at the bundle of His. The complete block of the right or left bundle branches produces late activation of the corresponding ventricle. Complete failure of conduction (third degree, or complete heart block) only occurs if all three fascicles become involved. In these circumstances, the atrial rate is generally greater and independent of ventricular rate.

Aetiology

Diseases of the conduction system have diverse intrinsic or extrinsic aetiology.[4]

SSS is mainly the result of chronic fibrotic degenerative processes or calcification of the sinus node and/or the surrounding atrial tissues. These processes become more common with increasing age and may occur over years. Commonly coexisting anatomical findings in SSS are coronary arteriosclerosis, with associated ischaemic heart disease (IHD)[5] or calcification of the aorta.

Since the AV node and intraventricular conducting structure are within the cardiac septum, they may be affected by myocardial ischaemia or infarction.[1] AVB may also be associated with chronic degenerative fibrosis, coronary arteriosclerosis and cardiomyopathy, or other cardiovascular disease (CVD) such as aortic stenosis, hypertension or

pulmonary embolism. Congenital heart block may occur in isolation or in association with other structural heart disease such as transposition of the great vessels, atrial and ventricular septal defects, Fallot's tetralogy and pulmonary stenosis. Infectious diseases, such as diphtheria, rheumatic fever, bacterial endocarditis and viral myocarditis, may cause SSS and heart block.[4] Sarcoidosis is believed to be a largely undiagnosed cause of AVB.

Pharmaceutical agents (e.g. digoxin, digitalis, verapamil or β-blockers) may cause bradycardia and impair AV conduction.

Prevalence of AVB and SSS

Information on the community prevalence of AVB and SSS is sparse and difficult to interpret as studies have been carried out in different populations and at different times, and use varying case definitions. The prevalence of SSS is believed to be around 0.03%.[6]

Using four large epidemiological studies carried out in Belgium, De Bacquer and colleagues[7] estimated the community prevalence of any degree of AVB as 0.1% in women and 0.2% in men. Prevalence was not as strongly age dependent for AVB as for other ECG abnormalities (e.g. left ventricular hypertrophy or T-wave changes), being 0.1% in most age groups above 25 years. Prevalence increased in men above the age of 65 years.

The Reykjavik study,[8] a prospective cohort of individuals born in the first three decades of the twentieth century and followed up from 1967 to 1991, reported a prevalence of third degree (complete) AVB of 0.04%.

Other sources have provided lower estimates, 0.015–0.02% for the UK and the USA, although these data are now over 30 years old.[9,10]

Symptoms

Symptoms of bradycardia may be intermittent or non-specific, particularly in the elderly. These may include fatigue on exertion, dyspnoea and chest pain or symptomatic hypotension. Established chronic bradycardia may impair cardiac output, resulting in variable symptoms of mild heart failure. Patients may experience palpitations. Bradycardia may cause symptoms of cerebral ischaemia, with dizziness, light-headedness, confusion or blackouts and falls.

First degree AVB is asymptomatic and benign in most cases. However, it may become symptomatic in the elderly with symptoms associated with haemodynamic changes, particularly during exercise. Second and third degree block are more likely to become symptomatic.

Diagnosis

The diagnosis of SSS or AVB rests on the correlation of symptoms with electrocardiographic findings. These may involve a range of mostly non-invasive tests, such as resting ECG, ambulatory ECG or Holter monitoring aiming to confirm the association of symptoms and evidence of dysfunctional conduction. A standardised or widely accepted test protocol is not available.

AV conduction may be assessed by ECG or Holter monitoring. Adequate nodal conduction, tested in individuals with SSS only, is defined as presence of 1:1 conduction at rates of 140 bpm.[11] Conversely, the appearance of Wenckebach block at rates lower than 140 bpm is considered a sign of incipient AVB. Inadequate AV conduction may become evident during exercise testing for other IHD.

Non-invasive techniques may sometimes involve autonomic system stimulation.[2] These include the Valsalva manoeuvre, carotid sinus massage and the tilt test. Such tests are conducted mainly to exclude other underlying causes of bradycardia (e.g. carotid sinus syndrome).

Prognosis

The prognosis of SSS is variable, difficult to predict,[2,12] and related to the presence and severity of associated hypertension or coronary heart disease (CHD).[5,13] The position is similar for AVB, where underlying abnormalities are more important in determining prognosis than heart block itself.

It is not clear whether bradycardia is an independent risk factor for cardiovascular mortality, although falls as a result of dizziness or fainting carry a significant risk of morbidity and mortality in the elderly population. However, bradycardia in association with haemodynamic changes may affect prognosis.[14] For example, in elderly patients with decreased ventricular function, bradycardia may lead to congestive heart failure. The interaction between AF and bradycardia may be particularly important in the development of heart failure owing to the loss of the atrial contribution to diastolic ventricular filling with consequent reduction in cardiac output. Hypertension may also play an important part in the development of heart failure in association with bradycardia.

TABLE 1 *Specific Activity Scale*

SAS class	Description
I	The patient can perform to completion any activity requiring ≥ 7 metabolic equivalents
II	The patient can perform to completion any activity requiring ≥ 5 metabolic equivalents but cannot or does not perform to completion activities requiring ≥ 7 metabolic equivalents
III	The patient can perform to completion any activity requiring ≥ 2 metabolic equivalents but cannot or does not perform to completion activities requiring ≥ 5 metabolic equivalents
IV	The patient cannot or does not perform to completion any activity requiring ≥ 2 metabolic equivalents

Impact: disability and quality of life

The American Heart Association (AHA)/New York Heart Association (NYHA) scale is used extensively to describe functional limitation in a wide range of cardiac conditions.[15] Patients are classified into four groups:

- Class I: patients have cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
- Class II: patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
- Class III: patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
- Class IV: patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Specific Activity Scale (SAS) (*Table 1*) has been used in clinical trials of pacemakers, although it has not been validated in this population.[18] The SAS is based on the metabolic load (metabolic equivalent) associated with the most strenuous activity performed by the patient, determined with a questionnaire based on performance in activities of daily living.

Quality of life is clearly reduced in conditions that benefit from cardiac pacing. Woodend and colleagues[16] investigated patients' and their families' ratings of the most important elements contributing to well-being after a pacemaker intervention. These were compared with the views of clinical staff. Among the physical aspects of quality of life, general health and mobility were cited as priorities for patients and their families. While clinical staff of cardiology services rated exercise tolerance as important, patients' priorities were focused on symptom relief, diet and time spent in hospital. Among psychological aspects of quality of life, patients identified the importance of self-esteem, satisfaction with life and confidence. Clinical staff felt that depression and anxiety or fear of recurrence or death were most important.

Clinicians and patients emphasised the importance of control over social and family life, interpersonal relationships and changes in marriage and family as aspects of quality of life that were affected by their condition and improved by cardiac pacing.

Stofmeel and colleagues carried out a systematic review of quality of life measures used in studies of the impact of pacemakers published up to 1998.[17] Studies included were predominantly observational and a much wider range of measures was identified than has been used in the trials of dual- and single-chamber pacemakers reported later in this assessment. Disease-specific and generic measures have been used to measure quality of life in this population as well as new measures constructed from pre-existing scales for the specific purpose of measuring the impact of cardiac pacing on quality of life.

Generic measures used include the Short Form 36 (SF-36), Sickness Impact Profile (SIP) and Nottingham Health Profile (NHP). These include domains of physical capacity, emotional and cognitive functioning, social life, self-perceived health and pain. Reliability and validity have been widely studied and are considered acceptable.

Disease-specific measures may be more sensitive than generic measures to particular aspects of quality of life. Stofmeel and colleagues identified several cardiac disease-specific quality of life

TABLE 2 *Definition of generic anti-bradycardia pacing codes (NASPE/BPEG)*

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

Adapted from Bernstein and colleagues.[21]

measures used in pacing studies.[17] They note that none of the measures had been validated in this population.

The Karolinska questionnaire is a composite measure including generic domains (physical, emotional, cognitive, social, self-perceived health and life events) in addition to specific cardiovascular questions (e.g. chest pain).

The Hacettepe questionnaire was also derived from pre-existing questionnaires and adapted for use in people with pacemakers. It includes eight dimensions: general well-being, physical symptoms, activity, sleep, appetite, sexual dysfunction, cognitive function, social participation and work performance. However, it includes no questions specifically related to arrhythmias and has not been validated in people with pacemakers.

A more recent disease-specific health measure is the Quality of Life Assessment Package (QLAP).[16] The QLAP has been partially validated in people with pacemakers and includes four domains: physical, psychological, activity and social.

Current service provision and description of new intervention

Pacemakers reduce morbidity and improve quality of life.[19]

Drug therapy (atropine, β-adrenergic drugs and theophylline) are less effective than pacing in people with pathological irreversible bradycardia[2,19,20] and are not generally used in clinical management. Drug therapy is therefore not considered further in this assessment.

The remainder of this section describes different types of pacemaker and current guidelines for their use.

Classification of pacemakers

Pacemakers consist of a small, battery-powered electrical generator and one or more electrodes (leads). In single-chamber pacemakers, the lead is positioned on the right ventricle or right atrium. The lead senses whether intrinsic depolarisation has taken place within the heart. When this does not occur, an electrical impulse is sent from the generator to paced chamber via the lead and contraction is initiated.

Dual-chamber pacemakers have two leads, one positioned on the right ventricle and one on the right atrium.

A range of features is available in dual- and single-chamber pacemakers. These pacing parameters describe the characteristics and functions of different types of device. Where the functions of a pacemaker permit, reprogramming can be carried out non-invasively.

The North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) jointly revised pacemaker nomenclature in 2002.[21] This established the Generic Code for Anti-bradycardia Pacing. The Generic Code is composed of elements ('positions') describing: the chamber paced (position I), chamber sensed (position II), response to sensing (position III) and rate modulation (position IV) (*Table 2*).

Position II indicates the chamber where spontaneous depolarisation is detected if it occurs outside the pulse generator's preset refractory periods. The action of the pacemaker in response to spontaneous cardiac depolarisation is described by position III. The pacemaker's pulse may be inhibited (the escape interval is reset without pacing if a spontaneous beat is sensed) or triggered (with the emission of a pulse when it is sensed that no spontaneous beats have occurred).

Position IV describes the incorporation of an extrinsic sensor to provide 'rate modulation' or 'rate responsiveness'. Position V has been omitted since it is not covered in this report.

Rate modulation allows the pacemaker rate to be increased in response to physiological demands (e.g. during exercise). Sensors detect parameters such as respiratory rate, minute ventilation, right ventricular pressure, central venous temperature, evoked QT interval and oxygen saturation, and pacing rate is increased accordingly.[11]

Rate hysteresis is a feature of multiprogrammable pacemakers in which the device triggers at a sensed heart rate that is lower than the pacemaker rate (e.g. the pacemaker may be triggered when the heart rate falls to 60 bpm but operates at a rate of 72 bpm). In most cases the pacemaker will continue to stimulate heart activity unless intrinsic activity exceeds the operating rate, although some devices periodically check the underlying rhythm (search hysteresis). Rate hysteresis ensures that the pacemaker works only when necessary. Newer dual-chamber pacemakers may also include mode-switching algorithms that track AF or other tachyarrhythmias and, when these occur, trigger ventricular pacing to avoid tachycardia.[11]

Physiological pacing is a general attribute for any type of pacing that has the capacity of preserving the physiological AV synchrony. This is achieved by replicating as closely as possible the sequence of contraction started in the atrium and transmitted to the ventricle with appropriately calibrated timing. Dual-chamber and single atrial chamber pacing with rate-responsiveness are physiological pacing modes.

Synchronous single-chamber pacemakers are a type of single-chamber pacemaker that achieve AV synchrony. The NASPE/BPEG code is VDD. The device can only pace the ventricles, but senses electrical activity in both the atrium and ventricle. It may be considered in people with intact sinus node and without atrial hypertrophy. The lead contains an electrode that senses and paces the ventricle, but also additional electrodes that sit within the atrium. These sense atrial activity but cannot pace the atrium. Where atrial activity is sensed, the ventricular lead is inhibited to allow AV conduction. If no ventricular activity is sensed, the ventricular lead is used to pace the ventricle. In this way, the ventricular rate is made dependent on the atrial rate (i.e. physiological pacing) and superimposition of atrial and ventricular contractions is avoided. Opinion varies regarding the value of VDD pacemakers, in which atrial sensing may be difficult to achieve, and they are not extensively used.

Guidelines on indications for pacemaker implantation and programming

The American College of Cardiology (ACC), the AHA and NASPE have produced guidelines on pacemaker type and programming in relationship to underlying disease.[22] The ACC/AHA/NASPE guidelines are based on classes of evidence. Class I means conditions for which there is evidence or consensus around the benefit of pacing. Class II refers to conditions where conflicting evidence or opinion exists, and is further subdivided into class IIa, where the weight of evidence/opinion is in favour of usefulness/efficacy, and class IIb, in which usefulness/efficacy is less well established by evidence/opinion. Class III includes conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. The AHA/NASPE guidelines were updated in 2002.

The AHA guidelines on pacing in sinus node disease and AVB are shown in *Table 3*. Pacing is recommended in all individuals with permanent AVB, since this is often associated with underlying CVD and a poor prognosis regardless of the presence and intensity of symptoms. The prognosis in transient AVB is more favourable, although this may only be in the short term, since progression towards permanent block is common.

In 1991, BPEG established guidelines for pacemaker selection according to type, programming and recommending pacemaker modes based on underlying indications.[11,19]

- The modes identified are summarised in *Table 4*. The ventricle should be paced if AVB is manifest or possible.
- The atrium should be sensed/paced if atrial activity is present or unless contraindicated. This may occur in the presence of atrial fibrillation, since atrial sensing may potentially induce inappropriate tracking of atrial tachyarrhythmias and trigger ventricular tachycardia.
- Rate response is necessary if the patient is active or lacks chronotropic response.
- Rate hysteresis may be valuable if bradycardia is intermittent.

Current pacemaker usage

Data in this section are taken from the UK Pacemaker Database, supplied by Dr David

TABLE 3 *AHA guidelines on indications for pacing*

Class I	Class II	Class III
1. Any second degree heart block with symptomatic bradycardia 2. Any third degree heart block with the exception of transient forms (i.e. due to drug toxicity or infectious disease) and class II, point 3 3. Chronic bifascicular or trifascicular heart block with intermittent heart block or with type II second degree heart block 4. AV block after MI 5. Sinus node dysfunction	1. First degree AVB with symptoms suggestive of pacemaker syndrome 2. Asymptomatic type I and II second degree heart block 3. Asymptomatic complete heart block with average ventricular rates ≥ 40 bpm 4. Syncope not proven due to AVB and when other causes have been excluded 5. Sinus node dysfunction in the absence of documented presence of bradycardia	1. Any asymptomatic first degree and type I supra-Hisian second degree AVB 2. AVB expected to resolve (i.e. drug toxicity) 3. Fascicular block with first degree or no AVB 4. Transient AVB (MI) without conduction defects 5. First degree AVB with old bundle branch block 6. Asymptomatic sinus node dysfunction due to long-term drug treatment and clearly associated with non-essential drug therapy

MI, myocardial infarction.

TABLE 4 *BPEG guidelines on pacing modes*

Indication for pacing		Type of pacemaker recommended
SSS	Without heart block	Atrial, inhibited, with rate response, AAI, AAIR
	With heart block	Dual chamber, DDDR, DDIR, DDD, DDI
AVB	Without chronic AF	Dual chamber, DDD or VDD
	With chronic AF	Ventricular, VVIR or VVI

Cunningham. Data on overall implant rates for the UK were taken from the Pacemaker Database Report, 2002.[23] In addition, more detailed information was obtained for the purposes of this assessment on England and Wales only, including registrations for 2003.

The Pacemaker Database is part of the Central Cardiac Audit Database (CCAD). Information on the coverage and completeness of the Database is available from the Directory of Clinical Databases.[24] According to this source, the Pacemaker Database covers all of the UK population, with at least 97% of the eligible pacemaker population, with completeness of data of at least 95%.

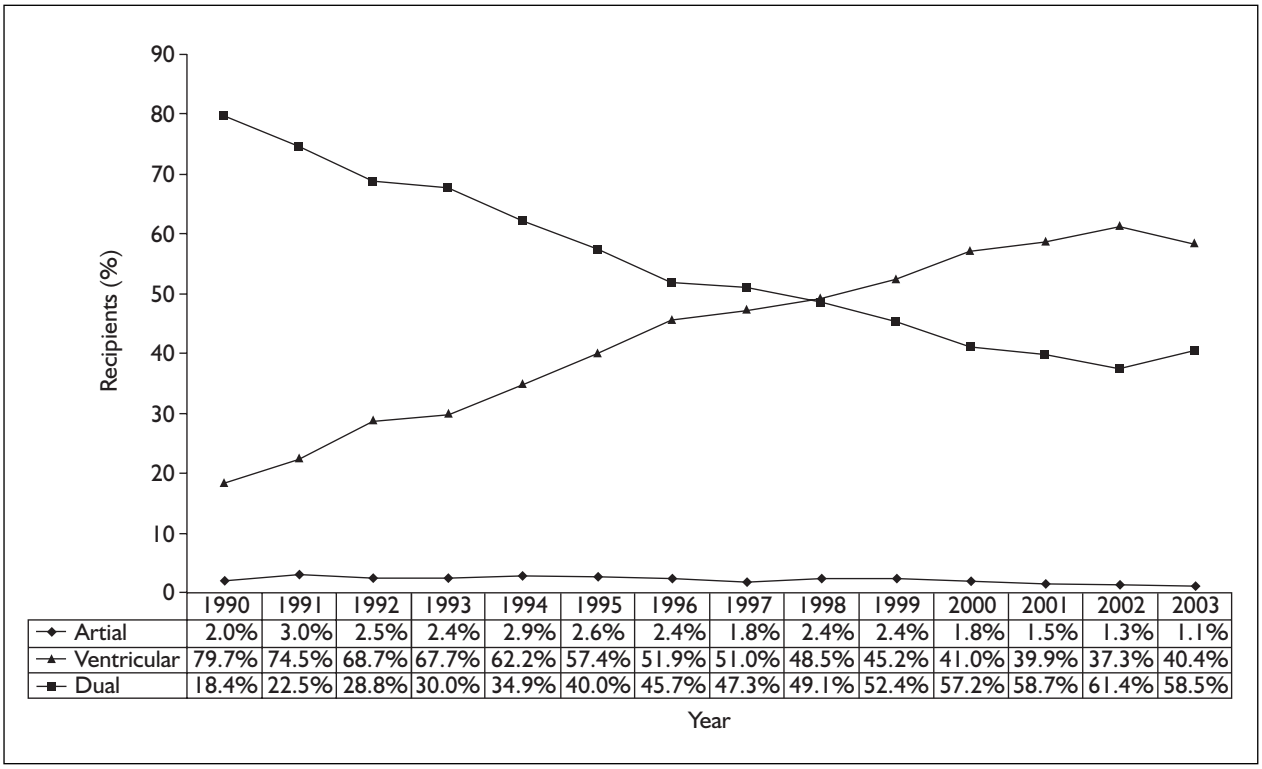
There were 25,397 pacemaker implants in 2002 in the UK,[23] of which three-quarters were new implants and one-quarter replacements. The corresponding rates of new implants were 305.3 per million in England and 323.5 per million in Wales. The Database Report[23] estimates that 1340 registrations for the year 2002 were missing at the time of print, bringing the total estimated number of pacemakers implanted to 27,737 for that year.

Implants were carried out in 164 centres in the UK, of which 131 were in England and six in Wales.

Dual-chamber pacing has steadily increased as a proportion of all pacemaker insertions in the past 10 years[23] (*Figure 1*) and accounted for 58.5% of the total in 2003. Use of dual-chamber devices has exceeded single chamber since 1995/96. Of dual-chamber devices inserted in 2003, about half were rate responsive (DDDR) and half not (DDD). About 40% of implants were ventricular: 16.4% of the total were VVI and 24% VVIR. The use of atrial pacemakers was considerably less, only 1.1% of the total, and has fallen by about half in the past 10 years.[23]

The majority of pacemakers were inserted for heart block or SSS (77%).[23]

In patients with SSS, two-thirds were attributed to conduction tissue fibrosis.[23] Other conditions associated with pacing in people with SSS were congenital heart defects (0.9%) and myocardial ischaemia or infarction. Tissue fibrosis was also the most common underlying cause recorded on the



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Artial	2.0%	3.0%	2.5%	2.4%	2.9%	2.6%	2.4%	1.8%	2.4%	2.4%	1.8%	1.5%	1.3%	1.1%
Ventricular	79.7%	74.5%	68.7%	67.7%	62.2%	57.4%	51.9%	51.0%	48.5%	45.2%	41.0%	39.9%	37.3%	40.4%
Dual	18.4%	22.5%	28.8%	30.0%	34.9%	40.0%	45.7%	47.3%	49.1%	52.4%	57.2%	58.7%	61.4%	58.5%

FIGURE 1 *Pacing mode at first implant, 1990–2003, England and Wales. Data source: reproduced by kind permission of the UK National Pacemaker Database © 2004. Totals are less than 100% owing to registration errors.*

pacing database for complete heart block (59%). Twenty per cent of implants were due to AV node ablation, 11% for myocardial ischaemia or infarction and 4% for congenital heart block.

In complete heart block (*Figure 2*), dual-chamber pacemakers were inserted in nearly 69%, of which one-third were rate responsive.[23] Single-chamber ventricular pacing accounted for 31% of total implants for this indication, with 59% rate responsive.

In SSS (*Figure 3*), 73.8% of pacemakers inserted were dual chamber.[23] Of these, 38% were rate responsive and 62% not. Twenty-three per cent of implants for SSS were single-chamber ventricular pacemakers (of which half were rate responsive). Atrial pacemakers made up a small minority of implants, being 3.5% of the total for this indication.

Dual-chamber pacemakers are not used in people with AF, which may be found in around 10% of cases. Maximal use of dual-chamber pacemakers is unlikely, therefore, to exceed around 90% of cases of bradycardia due to SSS and/or AVB.

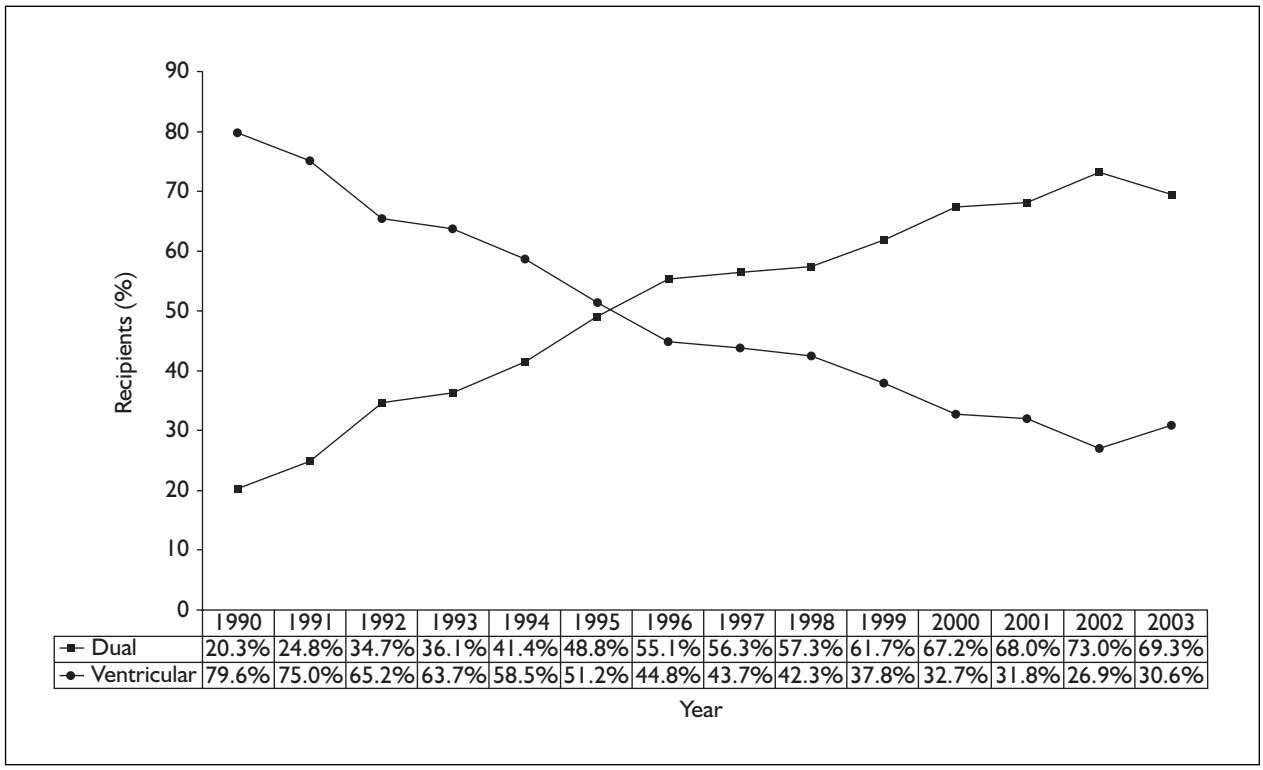
In 2003, the mean age of people at implant was 75.6 years. *Figure 4* shows that single-chamber ventricular pacemakers are more likely to be inserted in people older than 75 years.

Generator life expectancy

A pacemaker generator has an expected life of 5–12 years. *Figure 5* shows generator survival for different types of pacemaker in England and Wales since 1990.

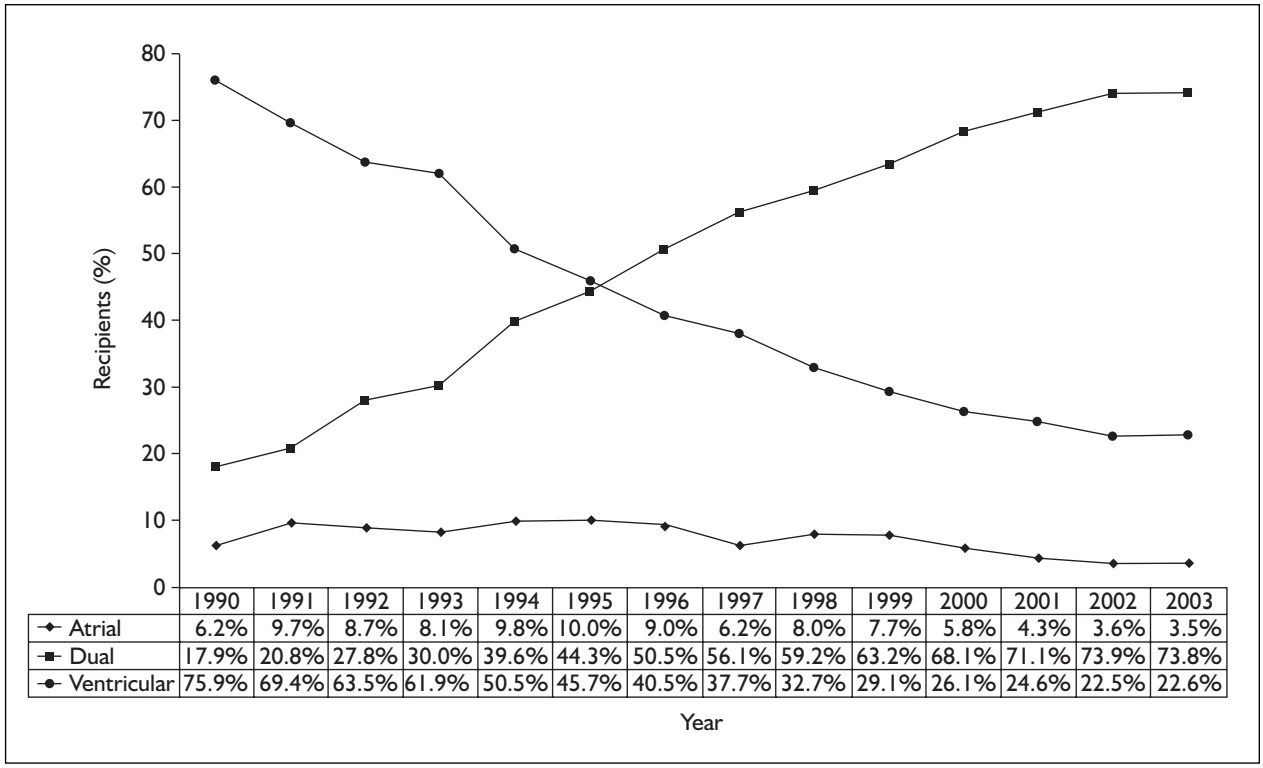
Implantation procedure

Implantation is usually carried out in a cardiac catheterisation laboratory by a cardiologist and support staff (a nurse and a radiographer). The insertion is usually carried out under local anaesthesia.[25,26] Leads are inserted into the subclavian or cephalic vein, advanced onto the right atrial appendage and/or ventricular apex using fluoroscopy, and finally secured. During implantation of the leads, electrophysiology tests are carried out to assess threshold (i.e. the lowest current that achieves stable capture of the myocardium), electrogram sensing (to assess the electrical amplitude of spontaneous depolarisation) and mechanical stability, and to exclude the presence of diaphragmatic pacing.[19] The pulse generator is then secured to the lead and implanted into a subcutaneous pocket. Recipients are given perioperative antibiotic



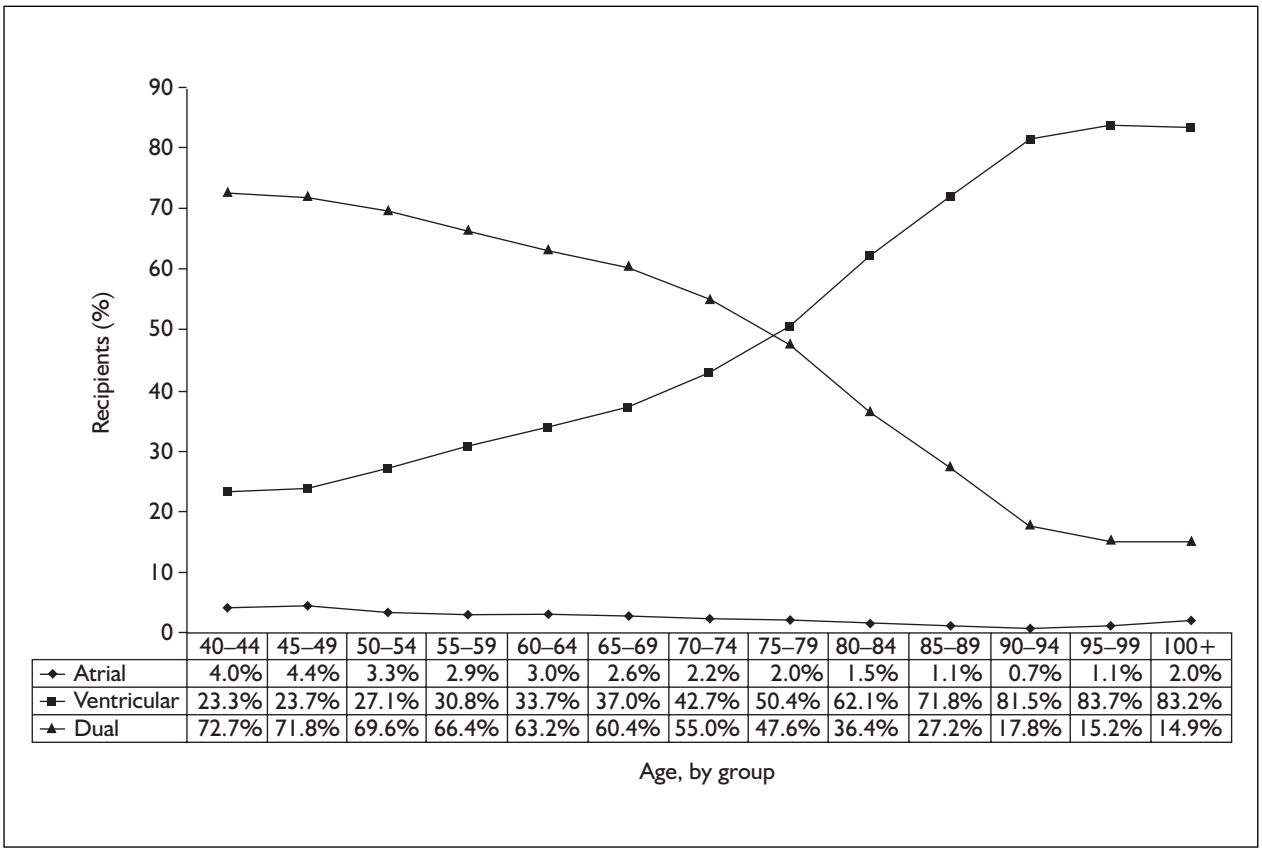
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Dual	20.3%	24.8%	34.7%	36.1%	41.4%	48.8%	55.1%	56.3%	57.3%	61.7%	67.2%	68.0%	73.0%	69.3%
Ventricular	79.6%	75.0%	65.2%	63.7%	58.5%	51.2%	44.8%	43.7%	42.3%	37.8%	32.7%	31.8%	26.9%	30.6%

FIGURE 2 *Pacing modes in people with complete AVB, 1990–2003, England and Wales. Data source: reproduced by kind permission of the UK National Pacemaker Database © 2004. Totals are less than 100% owing to registration errors.*



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Atrial	6.2%	9.7%	8.7%	8.1%	9.8%	10.0%	9.0%	6.2%	8.0%	7.7%	5.8%	4.3%	3.6%	3.5%
Dual	17.9%	20.8%	27.8%	30.0%	39.6%	44.3%	50.5%	56.1%	59.2%	63.2%	68.1%	71.1%	73.9%	73.8%
Ventricular	75.9%	69.4%	63.5%	61.9%	50.5%	45.7%	40.5%	37.7%	32.7%	29.1%	26.1%	24.6%	22.5%	22.6%

FIGURE 3 *Pacing modes in people with SSS, England and Wales, 1990–2003. Data source: reproduced by kind permission of the UK National Pacemaker Database © 2004.*



	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90–94	95–99	100+
Atrial	4.0%	4.4%	3.3%	2.9%	3.0%	2.6%	2.2%	2.0%	1.5%	1.1%	0.7%	1.1%	2.0%
Ventricular	23.3%	23.7%	27.1%	30.8%	33.7%	37.0%	42.7%	50.4%	62.1%	71.8%	81.5%	83.7%	83.2%
Dual	72.7%	71.8%	69.6%	66.4%	63.2%	60.4%	55.0%	47.6%	36.4%	27.2%	17.8%	15.2%	14.9%

FIGURE 4 *Pacing modes at first implant, by age of recipient, 1990–2003, England and Wales. Data source: 180,000 new implants. Reproduced by kind permission of the UK National Pacemaker Database © 2004.*

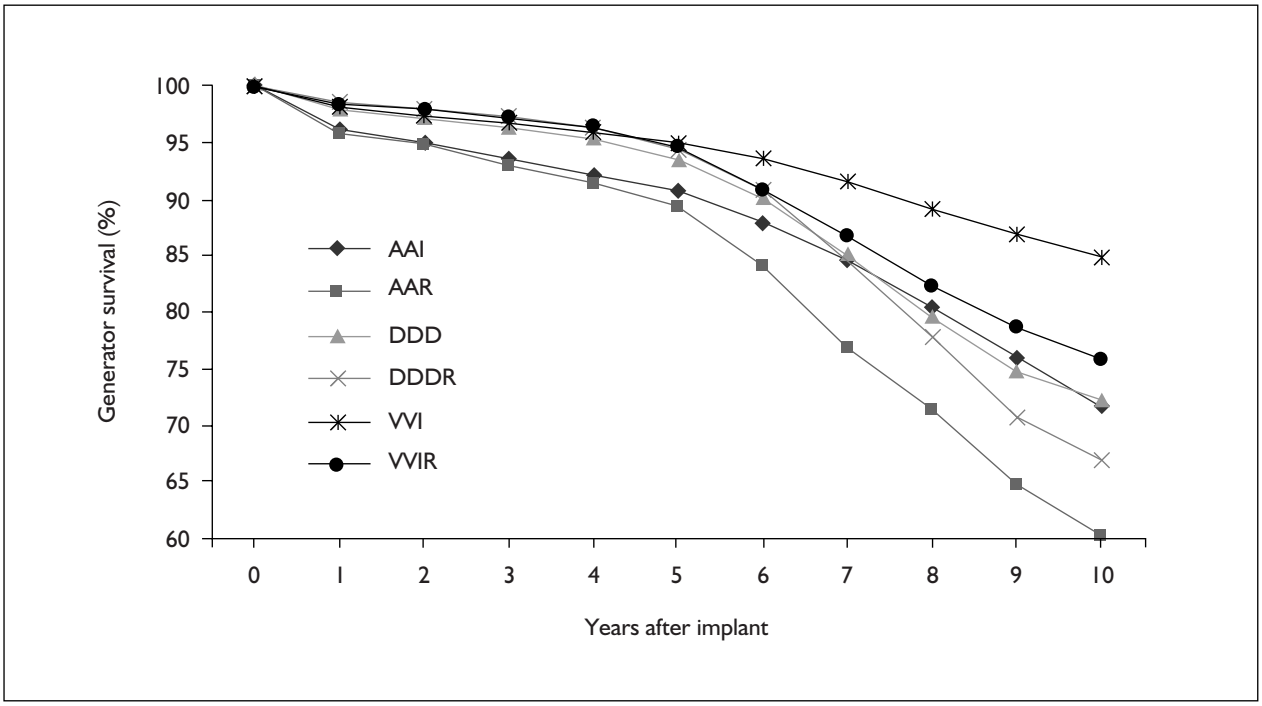


FIGURE 5 *Generator survival (all causes)*

prophylaxis. The implant usually entails one overnight stay in hospital.

Dual-chamber pacemaker insertion is more time consuming than single-chamber ventricular pacemaker insertion, because of the insertion of an additional lead. Atrial leads may be more difficult to implant since AF may occur during implantation, prolonging the duration and therefore the cost of implantation.

Adverse events

Perioperative complications

Perioperative complications relate to venous access and lead displacement, and include pneumothorax, haemothorax, haematoma and infections.[27]

The incidence of complications is small but not negligible. Tobin and colleagues[27] estimated a total incidence of 4.2% in a large series of patients in the USA. Half of these events were lead displacement (2.4%), both atrial and ventricular. Pneumothorax occurred in 1.5% of cases. More recent studies of complications are included in the results section of this review (see section 'Adverse effects of implantation', p. 61) and include lead displacement, pneumothorax, cardiac perforation and tamponade, with haemothorax rarely reported (0.1%[27] to 0.4%[28]). Lead and pacemaker pocket infections are uncommon, ranging from 0.25%[29] to 0.58%[28] of cases.

Complications may result in considerable increases in costs. Ferguson and colleagues[28] studied the cost of complications in one US hospital and found that systemic infections arising from the generator pocket were the most resource-intensive adverse events, leading to an additional 2-week hospital stay. In the same study, haematoma drainage and lead displacement led to 5.5 and 2.5 additional hospital days, respectively.

Later complications

In the medium term, the generator may develop an intrinsic malfunction or may be affected by an extrinsic source of electromagnetic radiation, such as magnetic resonance imaging (MRI) scanning. In these instances replacement of the generator may become necessary. Lead fracture or insulation breakdown can occur. Lead displacement and cardiac perforation may occur after some delay.

The PASE study estimated that approximately one-quarter of complications were reported after discharge from hospital.[29] Late-onset infection may also occur and can be local, for example due to mechanical erosion of the pocket, or systemic, including endocarditis or septicaemia. Subclavian venous thrombosis, which is rarely symptomatic, was reported in 0.5% of recipients in the PASE study. It is believed that the incidence of this complication may be higher than generally suspected, but it seldom causes adverse events.

Pacemaker syndrome

Pacemaker syndrome is a symptom complex related to the presence of a ventricular pacemaker. It has been attributed to the superimposition of atrial and ventricular contractions.[30] Pacemaker syndrome is predominantly associated with single-chamber ventricular pacing. However, it has been reported in dual-chamber pacing, despite the potential to programme AV delay in dual-chamber devices.[31] Symptoms of pacemaker broadly suggest low cardiac output and may resemble congestive heart failure, such as dizziness, weakness and fatigue, shortness of breath on exertion or when lying flat, and ankle swelling.

Ausubel and Furman[30] reviewed the possible causes of pacemaker syndrome and report a wide range of associated symptoms (*Table 5*). As discussed later in this assessment, the definitions of pacemaker syndrome used in trials of pacing modes varied.

The underlying mechanisms contributing to pacemaker syndrome have been widely studied but remain incompletely understood. However, at least two specific mechanisms appear to be important. First, loss of the contribution to ventricular filling from synchronous atrial contraction may lead to reduced cardiac output. During ventricular pacing, cardiac output may be reduced by 10–35%. In some cases output may be reduced to levels below those found during unpaced bradycardia.[32]

Second, retrograde conduction from the ventricle to the atrium may lead to asynchronous atrial contraction against a closed atrioventricular valve, increasing pressure on the venous system in both sides of the circulation, and producing signs and symptoms of cardiac failure.[19] Retrograde conduction is present in up to 60% of people with pacemakers, particularly where SSS was the indication for pacing and AV node function is retained.[30] Retrograde conduction is difficult to observe without intracardiac electrography.

Valvular disorders (e.g. aortic stenosis and mitral or bicuspid incompetence) and other forms of progressive cardiac disease (e.g. left ventricular hypertrophy) may increase the severity of pacemaker syndrome.[33]

TABLE 5 *Symptoms and signs of pacemaker syndrome*

Hypotension	Apprehension	Tachypnoea
	Diaphoresis	Fluctuating blood and pulse pressure
	Shock	Irregular peripheral pulse
	Orthostatic changes	Cannon waves in the neck veins
		Distension of neck veins
Low cardiac output	Lethargy	Pulsatile liver
	Early fatigability	Pulmonary rales
	Light-headedness	Regurgitant murmurs with pacing
		Variability of heart sounds or murmurs
Congestive heart failure	Dyspnoea	Tachycardia
	Orthopnoea	
	Oedema	
Neurological symptoms	Near-fainting	
	Dizziness	
	Confusion	
Haemodynamic symptoms	Right upper quadrant pain	
	Pulsations in neck or abdomen	
	Cough	
	Chest colds	
Arrhythmia	Palpitations	

From Ausubel and Furman (1985).[30]

The incidence of pacemaker syndrome is difficult to establish and reports vary. A widely quoted figure is up to 7%,[34] although much higher rates are reported in some clinical trials of pacing modes. Although pacemaker syndrome commonly presents fairly soon after implantation, it is not uncommon for onset to be late.[35] This may be due to late development of retrograde conduction, or to the development or progression of pathology unrelated to the pacemaker. Accurate diagnosis of pacemaker syndrome is difficult and although a wide range of tests has been developed, none is widely used. Retrograde conduction is difficult to observe using conventional electrocardiography, although intra-atrial conduction may be assessed at the time of pacemaker insertion.

No reliable test has been reported to predict who will develop pacemaker syndrome.[30]

Pacemaker dependency

There are several degrees of need for pacing. Individuals may receive a pacemaker for transient episodes of bradyarrhythmias, with more or less long spells of adequate spontaneous heart rate. These individuals will not be pacemaker dependent and will be paced only during spells when spontaneous rate fails to reach the adequate threshold set by the pacemaker. Alternatively, the spontaneous heart rate may be slow for most of the time, with the pacemaker taking over for most of the time in individuals with this characteristic. These individuals are pacemaker dependent.

An alternative characterisation of pacemaker dependency involves the proportion of beats paced over the total number of beats, that is, an individual is pacemaker dependent when the majority of beats are triggered by the pacemaker.

Chronotropic incompetence

Chronotropic incompetence is the inability of the sinus node to react adequately to exercise or other metabolic stress with an increase in heart rate. However, methods for establishing chronotropic incompetence in clinical practice are not well established. Although the mechanisms underlying the development of the condition are not clear, it may have important prognostic and therapeutic implications (i.e. the use of rate-responsive pacemakers). The clinical importance of chronotropic incompetence in individual cases may not be apparent unless there is a response to the use of a rate-responsive device.[36]

Current service cost

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

- price of the generator and leads
- implantation procedure: setting and personnel
- personnel involved before and after implantation

- management of perioperative complications
- management of late complications
- replacement or upgrade at the end of the life of the pacemaker or in response to changing clinical need.

The price of generators differs by mode of pacing, with dual-chamber pacemakers being more expensive than single-chamber devices. In addition, costs are increased if the pacemaker is rate modulated or has additional features, such as atrial tracking algorithms (mode-switch) in dual-chamber pacemakers.

Lead prices are less variable than generator costs and are proportional to the number of leads implanted, that is, one for single chamber and two for dual chamber. Leads may be of several types including steroid eluting leads, bipolar or unipolar leads. Leads may include a device for adjusting adherence to the atrial wall (active or passive fixation screw-in leads).

Further details on the cost of pacemakers are given in Chapter 5 (section 'Hardware costs', p. 82).

Chapter 3

Methods for systematic literature review

This section describes the methods used in the systematic review component of the assessment, which synthesises all available and appropriate literature on the effectiveness and cost-effectiveness of dual-chamber pacing.

Research questions

- What is the effectiveness of dual-chamber pacemakers compared with single-chamber atrial and ventricular pacemakers in people with bradycardia due to SSS or AVB?
- What is the cost-effectiveness of dual-chamber pacemakers compared with single-chamber atrial and ventricular pacemakers in SSS or AVB?

Assessment team and expert advisory group

A team comprising Emanuela Castelnuovo, Dr Ken Stein, Ruth Garside, Dr Martin Pitt and Liz Payne carried out the assessment.

A clinical expert advisory group provided support to the assessment team throughout the development of the assessment and commented on drafts of this report. The Advisory Group included Dr John Dean, Dr Richard Charles, Dr Neil Sulke and Dr William Toff (see Appendix 1).

Search strategy

A range of electronic databases was searched for published studies of effectiveness and cost-effectiveness or cost–benefit of dual-chamber pacing, encompassing completed or ongoing research: MEDLINE, Cochrane Library [Central, Cochrane Database of Systematic Reviews (CDSR)], EMBASE, ISI–Web of Knowledge, Web of Science Proceedings, BIOSIS, Database of Abstracts of Reviews of Effectiveness (DARE), HTA and Biomed Central. In addition, the websites of the National Research Register (NRR), Current Controlled Trials and US Food and Drug Administration (FDA) were searched. The full search strategy is detailed in Appendix 2.

Bibliographies were searched for further relevant publications. Members of the Advisory Group were asked to identify additional published or unpublished studies. Submissions to the National Institute for Health and Clinical Excellence (NICE) by technology sponsors as part of the NICE appraisal process were checked for additional published and unpublished literature.

The specialised registry of the Cochrane Heart Group was searched by a member of that group.

Inclusion and exclusion criteria

Population

Adults and children recruited in secondary and tertiary care centres with a primary diagnosis of acquired symptomatic bradycardia, secondary to SSS, AVB, or chronic bifascicular block, and individuals with symptomatic bradycardia were included. People at any stage of disease progression were considered, subject to their eligibility for permanent pacing.

Exclusion criteria

Studies were excluded if they reported on the following populations:

- people with carotid sinus syndrome and malignant vasovagal syncope
- people with a primary diagnosis of congestive heart failure or cardiomyopathy
- people with a primary diagnosis of AF, or AF from other causes without concomitant SSS or AVB
- people with a primary diagnosis of isolated tachycardia or tachycardia from other causes without concomitant SSS or AVB.

Intervention

Studies of dual-chamber pacemakers compared with single-chamber pacemakers (ventricular, atrial or both, separately reported) for the treatment of symptomatic bradycardia in eligible population groups were included.

Exclusion criteria

Studies were excluded if reporting on the following pacing types:

- biventricular
- biatrial
- triple chamber
- any type of temporary or diagnostic pacing.

Studies on dual-chamber, therapeutic, permanent pacemakers with any of the above were excluded when results were not reported separately.

Outcomes

The following patient-based outcomes were included:

- mortality (all-cause and cardiovascular)
- stroke
- atrial fibrillation
- heart failure
- exercise capacity
- symptoms of breathlessness, fatigue, chest pain, dizziness, palpitations and sleep disturbance
- functional status
- quality of life
- adverse events of implantation (perioperative mortality and non-fatal complications)
- pacemaker syndrome.

Composite outcomes made up of the above were also included.

Type of studies

Systematic reviews or randomised, controlled parallel or cross-over trials were included in the assessment of effectiveness.

Exclusion criteria

The following studies were excluded:

- non-randomised studies of effectiveness, case series and case reports, *n* of 1 trials, case–control studies and cohort studies
- studies in which insufficient methodological details were reported to allow critical appraisal
- studies of less than 48 hours' duration
- studies on patients with clinical indications for pacing other than those considered in this TAR
- preclinical studies, models or electrophysiology experimentation on human or other biological material
- studies in animal models
- studies not published in English, and for which translation in English is not available.

In the review of cost-effectiveness studies, reviews of economic studies were included. Individual studies were considered only if they were full economic evaluations (i.e. those that considered costs and outcomes).

Identification

Studies identified from the literature search were independently assessed by two researchers for inclusion, with disagreement resolved by discussion. Full papers were retrieved and screened independently by two researchers (EC and RG) for inclusion, with disagreement resolved by discussion.

Data extraction strategy

A data extraction sheet was developed by one researcher (EC) and piloted on a small subsample of papers. Data were extracted by one researcher (EC) and checked by another (RG). Data were extracted retaining actual numbers where provided, or other summary measures as detailed in the published study.

Quality assessment strategy

Methodological quality of RCTs was assessed using the criteria reported in the Centre for Reviews and Dissemination (CRD) Report No. 4,[37] Appendix 2, detailed in *Table 6*. This framework addresses the potential for the following biases:

- selection bias, reflecting differences between characteristics of participants in each arm that may have an impact on treatment effect
- performance bias, reflecting differences in all other treatment received during the intervention that may modify differences in effect between intervention and comparison
- detection bias, with differences in classification and measurement of outcomes in relationship to knowledge of treatment provided or received
- attrition bias, reflecting differences in successfully maintaining the initial random compositions of the two arms.

The aim of the framework is to identify areas where limitations exist. In this respect, one item on the list, compliance, has not been considered, owing to the nature of pacing.

It is now recognised that studies may have been conducted with appropriate methods in spite of limited reporting.[38]

The checklist used is reported in *Table 6*, with indications on the criteria used to assess each of the items included.

TABLE 6 *Criteria for quality assessment of trials included in the review*

Item	Coding	Criteria for assessment
Randomisation sequence generation	Adequate Partial Inadequate Unknown	Adequate: random number table or computerised central allocation Partial: envelopes Inadequate: alternation, case record numbers, birth date
Concealment of allocation	Adequate Inadequate Unclear Unknown	Adequate: convincing evidence that allocation cannot be predicted Inadequate: evidence of possible knowledge of allocation Unclear: lack of sufficient/complete detail to draw conclusions on allocation
Similarity of groups at baseline	Reported Unknown	Reported: list of prognostic factors is available and complete
Eligibility criteria specified	Adequate Partial Inadequate Unknown	Adequate: list of criteria provided and applied Partial: this option was not considered
Blinding of assessors	Adequate Inadequate Unknown	Adequate: assessment must be independent, or unaware of assignment. For objectively measurable outcomes (e.g. deaths), blinding was rated 'adequate' regardless of assessors' blinding
Blinding of care provider	Adequate Partial Inadequate Unknown	Adequate: as above, with respect to methods for the delivery of care under evaluation and additional routine care (e.g. concomitant medication)
Co-intervention, equal at baseline	Adequate Partial Inadequate Unknown	Adequate: all relevant co-interventions have been included in baseline information
Co-intervention, equal during follow-up	Adequate Partial Inadequate Unknown	Adequate: changes in co-interventions that have a therapeutic effect on end-points of the study have been reported in full Partial: indications are provided on additional interventions delivered Inadequate: no qualifying statement is provided on the differential provision in the intervention and comparator arm
Participants blinded	Adequate Partial Inadequate Unknown	Adequate: as above, with respect to awareness of recipient. Side-effects have been considered a potential source of information on allocation the to recipient
Code break to participants	Reported Unknown	When reported, the potential for treatment effect to be a source of unblinding has been considered
Results for primary outcome measure	Adequate Partial Inadequate Unknown	Adequate: central estimate and precision (SD) Partial: central estimate without precision (SD) or suboptimal method for describing central estimate (e.g. median) Inadequate: evidence of use of measures that are not recommended. In the case of cross-over trials, the use of non-paired statistical tests was considered inadequate
ITT analysis	Adequate Inadequate	Adequate: including all randomised population. In the case of survival analysis, inclusion of missing cases and explanation for censoring methods. LOCF with explanations of the impact on estimates was considered adequate. For cross-over trials, inclusion of recipients who concluded both periods and explicit statement on methods for extrapolating missing values was considered adequate

continued

TABLE 6 *Criteria for quality assessment of trials included in the review (cont'd)*

Item	Coding	Criteria for assessment
		Inadequate: per-protocol analysis or evidence that losses to follow-up have been excluded. For survival analysis, inclusion of individuals who reached end-points only. For cross-over trials, exclusion of individuals who did not complete the two periods, or where the exclusion of individuals was not accounted for
Missing values	Adequate Partial Inadequate Unknown	Adequate: methods for extrapolation are explained
Loss to follow-up	Adequate Partial Inadequate Unknown	Adequate: provision of (a) numbers randomised, (b) numbers lost to follow-up
ITT, intention-to-treat; LOCF, last observation carried forward.		

The framework established by the Quality of Reporting of Meta-analyses (QUORUM) statement was used for the critical appraisal of systematic reviews.[39]

The quality of cost–effectiveness and cost–utility studies were assessed using the frameworks published by Sculpher and colleagues[40] and Drummond and Jefferson.[41]

Where subgroup analyses were reported, their methodological quality was considered using the following framework:

- sample size, with two possibilities: all participants were included in the subanalysis or some were excluded based on preselection criteria
- whether the analysis was preplanned
- whether the baseline equality of groups was maintained in the subgroup
- whether blinding was maintained
- whether the power calculation in the original trial included the subgroup analysis
- whether the subgroup was analysed on an ITT basis
- whether loss to follow-up was reported and how this compared to loss to follow-up in the main study.

Data synthesis

The results of individual trials were pooled using random effects meta-analysis, carried out in Review Manager Software version 4.2. The summary statistic was, by default, the odds ratio. A standard test for heterogeneity was carried out in each case and the proportion of variation due to heterogeneity as opposed to chance reported using the I^2 statistic.[42] Limited exploration of heterogeneity was carried out by stratification.

Chapter 4

Results of systematic review

Number of studies identified

In total, 2330 studies were identified by the literature search and considered for inclusion on the basis of information reported in abstracts or by obtaining and assessing full study reports. The contribution of each source is reported in Appendix 2. *Figure 6* shows a chart of inclusion and exclusion. The reasons for exclusion of studies are given in detail in Appendix 3.

In addition, one systematic review, originally published as part of a health technology assessment report by the University of Birmingham in 2002, included reviews of studies of clinical and cost-effectiveness.[43] Since the searches for the current assessment have been completed, the Birmingham review has been updated and published as a review in the Cochrane Library.[44] The discussion of the Birmingham review in this assessment refers to the 2002 publication.

Thirty-four individual clinical trials were found, 32 comparing the clinical effectiveness of dual-chamber pacing to ventricular pacing and three comparing dual-chamber to atrial pacing (one study carried out a comparison of dual-chamber pacing to both atrial and ventricular pacemakers).

The recently completed but unpublished UKPACE study was identified from contacts with researchers and was included in this review, but maintained as confidential at the request of the investigators.[45]

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

Two studies included in the Birmingham systematic review were not included in this review. These were a published study by Mattioli and colleagues[46] and a study by Wharton and colleagues[47] that was available only in abstract form and did not include sufficient details to permit assessment of methodological quality.

The study by Mattioli and colleagues[46] was excluded since it failed to provide sufficient details to assess methodological characteristics. Although individuals were randomly assigned to physiological or ventricular pacing, baseline characteristics were not reported by pacing mode. For this reason, methodological features could not be verified. In particular, selection bias could not be assessed.

In addition, the Mattioli trial included an unknown proportion of participants with a diagnosis of cardioinhibitory carotid syndrome that placed the study outside the protocol of this review.

Since the Mattioli trial was much smaller than the other parallel-design randomised controlled trials (RCTs), the impact of exclusion is likely to be small on the synthesis of research findings, since it brings little additional power to meta-analyses. It is also likely to increase heterogeneity in a pooled analysis, since it included a high proportion of VDD pacemakers in the physiological group.

The results of the review of economic evaluations are reported in Chapter 5.

Clinical effectiveness of dual-chamber versus single-chamber ventricular pacing

Systematic review

The systematic review published in 2002 as part of a health technology assessment carried out at the University of Birmingham by Dretzke and colleagues[43] included 30 randomised trials (four parallel group design and 26 cross-over) published up to 2001. The review compared single-chamber ventricular to dual-chamber pacemakers only. It is a good quality systematic review and is described in more detail in Appendix 8. The authors concluded that RCTs of dual-chamber pacing were of poor quality (Jadad scores on average 1/5), with cross-over trials being of slightly better quality (Jadad scores 2/5 or 4/5). At that time, the evidence in favour of dual-chamber pacing was judged 'borderline'. However, the authors concluded that there was a significant reduction in mortality, pacemaker symptoms and exercise capacity with dual-chamber pacing. They also concluded that "the clinical effectiveness findings support the current British Pacing and Electrophysiology Group guidelines[11] that

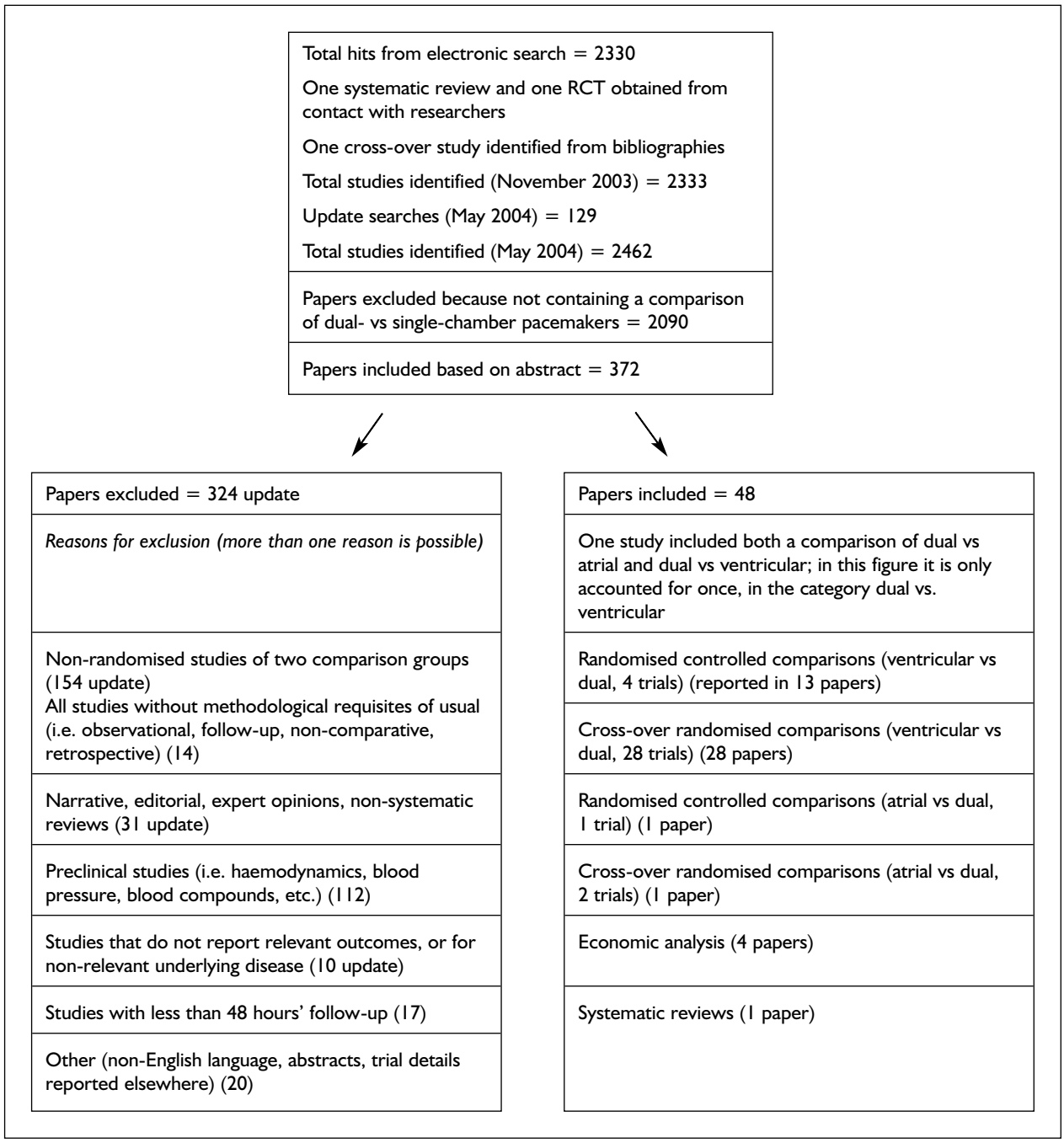


FIGURE 6 *Number and type of studies excluded, with reasons for specific exclusions*

recommend dual chamber (over single [ventricular] chamber) pacing for AV block".[43]

The results of Dretzke and colleagues[43] are not reported in the main body of this report in order to prevent repetition. Differences between the current HTA and the review by Dretzke and colleagues include the following:

- The present literature searches identified a large parallel trial (MOST[48]) and one cross-over trial[49] and reports of additional and relevant analyses of important, large RCTs (e.g. quality of life) published since completion of the previous review. One additional cross-over study was identified.[50] In addition, one large RCT conducted in the UK became available in an unpublished confidential form during the drafting of this review (UKPACE[45]).
- This HTA uses slightly different inclusion/exclusion criteria (e.g. the studies by Mattioli and colleagues[46] and Wharton and

colleagues,[47] discussed in the previous section were excluded).
- Some potentially important subgroup analyses were not considered in the Birmingham review (e.g. the role of pacemaker dependency).

However, the data extraction tables from Dretzke and colleagues were used for cross-over studies to increase the efficiency of this assessment, updating these with one study published since completion of the Birmingham review and one study that was omitted from the original review.[49;50] Critical appraisal of the cross-over studies was repeated.

In February 2004, after the searches that informed this HTA had been completed, an updated version of the Dretzke review was submitted for publication in the Cochrane Library.[44]

The following section discusses the characteristics and methodological quality of individual randomised trials. Parallel group and cross-over trials are considered separately. Three published (and one unpublished) parallel RCTs and 28 cross-over RCTs were included.

Characteristics and quality of studies

Parallel-group RCTs: characteristics

Characteristics of the populations, interventions and follow-up are shown in *Table 7*. The application of dual-chamber pacing was compared to ventricular pacing in four multicentre parallel randomised trials: Mode Selection Trial in Sinus Node Dysfunction (MOST),[48,51] Pacemaker Selection in the Elderly (PASE),[35] Canadian Trial of Physiological Pacing (CTOPP)[52] and UKPACE[45] (unpublished). MOST, UKPACE and CTOPP involved over 2000 participants each. PASE included 407 people. Overall, these trials randomised 3323 people to dual-chamber or 'physiological' pacing and 3683 to ventricular pacemakers. UKPACE has not been published or peer reviewed: the first draft of the trial report was obtained for this assessment.

Studies were either trials of device, in which participants were randomised to insertion of a dual- or single-chamber pacemaker, or trials of programming mode, in which a dual-chamber pacemaker was inserted but participants were randomised to have the pacemaker operating in single- or dual-chamber mode.

Interventions and comparators

Two parallel trials of programming mode compared dual-chamber rate-modulated pacing to ventricular rate-modulated pacing (MOST and PASE). CTOPP was a trial of device and compared physiological pacing to ventricular pacing. Physiological pacing means that atrioventricular synchrony was achieved by (a) use of a single-chamber atrial pacemaker where AV conduction was intact, or (b) use of a dual-chamber pacemaker where any degree of AVB was present. This is a potential source of heterogeneity when comparing the results of CTOPP to other trials.

UKPACE compared dual-chamber to ventricular devices. The trial also randomised rate-modulated or non-rate-modulated pacing in equal proportion in the ventricular arm. Ventricular pacing was compared to dual chamber overall and separately by rate modulation.

All pacemakers in the MOST and PASE trials were rate modulated. In CTOPP, 25% of pacemakers in the single-chamber ventricular arm were non-rate responsive.

Populations studied

The detailed characteristics of the study populations in the parallel RCTs are shown in *Table 8*. MOST included only people with sinus node abnormalities, with or without AVB. PASE and CTOPP included mixed populations of people with SSS, SSS with AVB and AVB with normal sinus node function. Mean age was similar in the three studies (73–76 years), as were the proportions of participants with a previous history of MI (one-quarter to a half). MOST included higher proportions of people with history of atrial fibrillation and hypertension. Similar proportions in MOST and PASE had a history of previous heart failure (one-fifth to one-quarter). A smaller proportion in CTOPP was classified as having abnormal left ventricular function (16–17%). Just over 80% of the MOST population and 70% of the PASE populations were classified as NYHA class I (no symptoms or limitation of activities) or II (slight, mild limitation of activity, comfortable at rest or with mild exertion). Corresponding data were not reported in CTOPP. [*Text describing the characteristics of patients enrolled in the UKPACE trial is commercial-in-confidence (CiC) and has been removed.*]

The duration of the parallel group trials was between 1.5[35] and 3.5[52] years [*CiC removed – duration of follow-up for UKPACE*].

TABLE 7 *Parallel RCTs: populations, interventions, comparisons, settings and follow-up*

Study	Population	Intervention	Comparison	Randomisation	Country	Recruitment	Centres	Author	Patients	Date	Follow-up
MOST[48,51]	SSS or SSS and AVB	DDDR	VVIR	Trial of programming	USA and Canada	September 1995 to October 1999	91	Lamas *et al.*	2010	2002	Programmed 5 years; average 33.1 months
PASE[35]	SSS, AV or both	DDDR	VVIR	Trial of programming	USA	February 1993 to September 1994 Ended June 1996	29	Lamas *et al.*	407	1998	550 days (min. 216, max. 996 days)
CTOPP[52]	SSS, AVB or both	Physiological pacing (AAIR DDD, DDDR)	VVIR or VVI	Trial of device	Canada	Over 3 years, dates not stated	32	Connolly *et al.*	2568	2000	Expected 3.5 years on average (min. 2, max. 5 years)
UKPACE[45]	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	Toff *et al.*	*2021*	*Un-published*	*CiC removed*

TABLE 8 *Detailed characteristics of participants: parallel RCTs*

	MOST[48]		CTOPP[52]		PASE[35]		*UKPACE*[45]	
Participant characteristics	**Dual chamber**	**Ventricular**	**Physiological**	**Ventricular**	**Dual chamber**	**Ventricular**	***Dual chamber***	***Ventricular***
Number of participants	1014	996	1094	1474	203	204	1012	1009
Age (mean)	74	74	73	73	76	76	*CiC removed*	*CiC removed*
Gender (male)	53%	52%	57%	60%	57%	62%	*CiC removed*	*CiC removed*
Hypertension	63%	61%	35%	35%	52%	51%	*CiC removed*	*CiC removed*
NYHA class I/II	81%	84%	–	–	70%	73%	*CiC removed*	*CiC removed*
Atrial fibrillation	47%	44%	21%	21%	–	–	*CiC removed*	*CiC removed*
Prior MI	28%	24%	26%	25%	33%	33%	*CiC removed*	*CiC removed*
Prior heart failure	22%	18%			26%	28%	*CiC removed*	*CiC removed*
Depressed EF	–	–	17%[a]	16%[a]	27%	25%	*CiC removed*	*CiC removed*
SA node disease	100%	100%	33%	34%	44%	42%	*CiC removed*	*CiC removed*
AV and SND	20% (4% CHB)	21% (5% CHB)	9%	8%	–	–	*CiC removed*	*CiC removed*
AV block	–	–	51%[b]	52%[b]	49%[b]	50%[b]	*CiC removed*	*CiC removed*
Other/unknown	–	–	8%	6%	7%	7%	*CiC removed*	*CiC removed*
Antiplatelet drugs	–	–	34%	35%	41%	37%	*CiC removed*	*CiC removed*
Anticoagulant drugs	–	–	12%	10%	6%	4%	*CiC removed*	*CiC removed*
Antiarrhythmic drugs	–	–	13%	12%	2–17%	1–23%	*CiC removed*	*CiC removed*
β-Blockers	–	–	–	–	9%	16%	*CiC removed*	*CiC removed*
ACE inhibitors	–	–	–	–	31%	27%	*CiC removed*	*CiC removed*
Diuretics	–	–	–	–	34%	36%	*CiC removed*	*CiC removed*

[a] Defined as abnormal left ventricular function.
[b] AVB only.
ACE, angiotensin-converting enzyme; EF, ejection fraction; SND, sinus node disease.

Imbalances in baseline characteristics were reported only for MOST. There were differences in prior heart failure, diabetes and ventricular tachycardia or fibrillation (higher in dual chamber) and in NYHA class I–II (higher in ventricular). In PASE there were no significant differences at baseline. Baseline characteristics were not tested in CTOPP.

Outcomes reported: parallel and cross-over studies

The outcomes reported in all included studies are described in *Table 9*. The outcomes considered in the cross-over trials were, as a consequence of the shorter study duration, more restricted than in the longer term parallel studies.

TABLE 9 *Outcomes reported in all RCTs included in the review*

	Studies	
Outcome	**Parallel RCTs**	**Cross-over trials**
All-cause deaths	3 *(4)* trials MOST,[48] CTOPP,[52] PASE[35]	–
Strokes, embolism	3 *(4)* trials MOST,[48] PASE,[35,53] CTOPP[52]	–
Atrial fibrillation	3 *(4)* trials MOST,[48,54] PASE,[35,53] CTOPP[52,55]	–
Progression to heart failure, rates of hospitalisation for heart failure	2 *(3)* trials MOST,[48,54] CTOPP[52,55]	–
Role of pacemaker dependency	2 trials: MOST,[56] CTOPP[57]	–
Exercise capacity	–	**21 trials:** Avery (1994),[58] Capucci (1993),[59] Channon (1994),[60] Davis (1985),[61] Deharo (1996),[62] Hargreaves (1995),[63] Jordaens (1988),[50] Kamalvand (1997),[64] Kenny (1986),[65] Kristensson (1985),[66] Linde-Edelstam (1992),[67] Menozzi (1990),[68] Mitsuoka (1988),[69] Oldroyd (1991),[70] Perrins (1983),[71] Rediker (1988),[72] Saner (1996),[73] Sulke (1991),[74] Sulke (1992),[75] Sulke (1994),[76] Yee (1984)[77]
Functional status	SAS: 3 trials MOST,[48] CTOPP,[52] PASE[35]	**SAS:** 7 trials Deharo (1996),[62] Kamalvand (1997),[64] Lau (1994),[78] Lau (1994),[79] Rediker (1988),[72] Sulke (1992),[75] Sulke (1994)[76] **Functional status questionnaire 2 trials:** Saner (1996),[73] Yee (1984)[77]
Pacemaker syndrome/ reimplantation rates and symptom scores	Pacemaker syndrome or reimplantation: 3 trials MOST,[48] PASE.[35] CTOPP (reimplant)[52] Symptoms scores 1 trial CTOPP[80]	**Symptom scores:** 22 trials Avery (1994),[58] Boon (1987),[81] Capucci (1993),[59] Channon (1994),[60] Davis (1985),[61] Deharo (1996),[62] Hargreaves (1995),[63] Heldman (1990),[34] Hoijer (2002),[49] Kamalvand (1997),[64] Kenny (1986),[65] Kristensson (1985),[66] Lau (1994),[78] Menozzi (1990),[68] Mitsuoka (1988),[69] Oldroyd (1991),[70] Perrins (1983),[71] Saner (1996),[73] Sulke (1991),[74] Sulke (1992),[75] Sulke (1994),[76] Yee (1984)[77]
Quality of life	3 trials MOST,[48] PASE,[35] CTOPP[80]	**16 trials:** Boon (1987),[81] Deharo (1996),[62] Hoijer (2002),[49] Kamalvand (1997),[64] Lau (1994),[78] Lau (1994),[79] Linde-Edelstam (1992),[82] Lukl (1994),[83] Menozzi (1990),[68] Mitsuoka (1988),[69] Perrins (1983),[71] Rediker (1988),[72] Saner (1996),[73] Sulke (1991),[74] Sulke (1992),[75] Sulke (1994)[76]
Cognitive function	–	**2 trials:** Linde-Edelstam (1992),[82] Hoijer (2002)[49]
Adverse events	3 *(4)* trials: MOST,[48,84] PASE,[35] CTOPP[52]	–
[CiC removed – outcomes of UKPACE]		

TABLE 10 *Summary of critical appraisal of parallel RCTs*

Item	MOST[48]	PASE[35]	CTOPP[52]	*UKPACE*[45]
Randomisation sequence generation	Adequate	Partial	Unknown	*CiC removed*
Concealment of allocation	Adequate	Unclear	Adequate	*CiC removed*
Similarity of groups at baseline	Reported	Reported, with important omissions	Reported	*CiC removed*
Eligibility criteria specified	Adequate	Adequate	Adequate	*CiC removed*
Blinding of assessors	Adequate for some outcomes	Unknown	Adequate	*CiC removed*
Blinding of care provider	Unknown	Unknown	Unknown	*CiC removed*
Co-intervention, equal at baseline	Unknown	Adequate	Adequate	*CiC removed*
Co-intervention, equal during follow-up	Unknown	Unknown	Partial	*CiC removed*
Participants blinded	Yes	Yes	Yes	*CiC removed*
Code break to participants	Unknown	Unknown	Unknown	*CiC removed*
Results for primary outcome measure	Adequate	Partial	Partial	*CiC removed*
ITT analysis	Adequate	Adequate	Adequate	*CiC removed*
Missing values	Unknown	Unknown	Unknown	*CiC removed*
Loss to follow-up	Adequate	Partial	Unknown	*CiC removed*

Parallel-group RCTs: methodological quality

Table 10 summarises the results of critical appraisal of the parallel-group RCTs. The remainder of this section considers the threats to validity arising from the methods used in these studies from selection, detection, performance and attrition biases. Finally, the external validity of the trials is addressed by considering the level of detail of reporting of participant characteristics and the extent to which the eligible and recruited populations represent the populations from which they were drawn.

Selection bias

Reporting of randomisation and allocation concealment was variable. In MOST and PASE randomisation was carried out in a central location. The method of random sequence generation was not reported in CTOPP. In PASE, envelopes containing the allocation schedule were opened at the time of implantation. In MOST, this step was carried out centrally with allocation to mode taking place following pacemaker insertion. In CTOPP, random allocation was carried out centrally 48 hours before pacemaker insertion with concealment using sealed envelopes, which were opened at the time of implant. *[CiC removed – information on the randomisation method used in UKPACE.]* The timelag could, theoretically, give rise to bias if outcomes occurred differentially in the period between allocation and intervention.

The allocation procedures in CTOPP and PASE may have given rise to some bias because allocation was carried out before suitability for dual-chamber pacing was assessed. During the insertion procedure, the adequacy of atrial sensing, that is, the ability of the pacemaker to sense atrial activity, is usually assessed. Where atrial capture is inadequate, a dual-chamber pacemaker is inappropriate. MOST addressed this issue by randomising after the assessment of atrial capture. In CTOPP, participants in the dual-chamber arm who were found to have inadequate atrial capture were implanted with a ventricular pacemaker. Such early cross-overs occurred in 5.6% in CTOPP, who mainly had atrial lead implantation difficulties or atrial fibrillation. In addition, 1.8% of people randomised to physiological pacing in CTOPP were reprogrammed to ventricular before discharge. *[CiC removed – cross-over in UKPACE.]* Corresponding data are not reported in PASE. The impact of this issue is likely to bias the comparison

against dual chamber pacing, although the magnitude is probably small.

All trials excluded people with chronic AF, defined using similar criteria across trials. However, MOST and PASE included a larger proportion of people found to have AF at the time of pacemaker implant. This may be due to the underlying indication for pacing in each trial, in that MOST included individuals with SSS only, whereas CTOPP and PASE included mixed populations with SSS and AVB. This may reduce the comparability of rates of AF as an outcome between the trials. It is unclear whether this factor also threatens the external validity of CTOPP since atrial fibrillation may be diagnosed more often in the USA, where MOST and PASE were conducted.

More important as a potential source of selection bias are baseline imbalances between the intervention arms in the MOST study. Patients assigned to dual-chamber pacing had, at baseline, higher rates of prior heart failure, prior ventricular tachycardia or fibrillation and diabetes. Correspondingly, patients assigned to single-chamber ventricular pacing were more likely to be in NYHA class II or I. Statistical analyses were appropriately adjusted for baseline differences, which did have an effect (i.e. there are differences between the adjusted and unadjusted results for the composite end-point of death, stroke or heart failure and for individual estimates of heart failure and atrial fibrillation), although the potential for residual, unrecognised confounding remains.

Detection bias

MOST, PASE and CTOPP were described as single blind (i.e. with blinding of participants). Investigators were generally not blinded, although all trials employed blinded outcome adjudication committees. *[CiC removed – Assessment Group comments on detection bias in the UKPACE study.]*

In PASE, quality of life was measured in telephone interviews at 3, 9 and 18 months, carried out by researchers blind to treatment allocation. Quality of life was also measured in cases where the device was reprogrammed from ventricular to dual pacing, which occurred in approximately 18% of cases before the planned 3-month assessment. It is not clear how quality of life was measured in these cases, although it may have been carried out in different circumstances to the scheduled assessments.

Independent measurement of outcomes is particularly important in assessing pacemaker syndrome given the subjective nature of the symptoms. MOST established strict criteria for diagnosing pacemaker syndrome, although details are lacking on whether measurement of this outcome was independent. Pacemaker syndrome was the most important reason for cross-over in the MOST trial.

Similar criteria were used in MOST and PASE for the definition of pacemaker syndrome, although no details are given about the independence or verification of diagnosis. Although adjudication by a blinded assessor may have been unpractical, the absence of independent measurement of this important outcome is a source of some concern.

Details of the measurement of pacemaker syndrome and the proportion of cross-overs for this reason were not reported for CTOPP, although as a trial of device, cross-overs were much less common than in PASE and MOST. *[CiC removed – methods for the assessment of pacemaker syndrome in the UKPACE trial.]*

Performance bias

CTOPP was a trial of physiological pacing, in which a small proportion of participants (approximately 5%) who were randomised to dual chamber received atrial pacing (i.e. individuals with a diagnosis of SSS and intact AV conduction). This is a potential source of bias, although it is difficult to determine direction and magnitude.

Types and programming of pacemakers varied between trials. MOST and PASE reported lower and upper limits of programming. These theoretically determine the total time spent in pacing. It may therefore limit generalisability of the analyses where this factor is relevant. However, variations in programming are unlikely to differ by pacing mode.

All trials allowed concomitant drug treatment for CVD. There were no significant differences in co-treatment between the pacing arms in PASE and CTOPP. No information is available for MOST. Overall there is no evidence to suggest the presence of significant performance bias in this group of trials.

Attrition bias

Loss to follow-up was not specifically reported in any of the parallel-group design trials. In PASE, around 90% of the study population had functional status measured at 18 months, suggesting that follow-up was good. Loss to follow-up was not reported in the main trial publications

of CTOPP or MOST. However, a subsequent publication[84] reported that 99% of follow-up was complete for MOST. *[CiC removed – Assessment Group comments on attrition bias in the UKPACE study.]*

All studies report their analyses as being based on the ITT principle. However, a large proportion of changes in pacing mode occurred from single to dual chamber in MOST (31.4%) and PASE (26%). Changes in mode occurred, to a lesser degree, in both directions in CTOPP (17% from dual to single, 4% from single to dual) *[CiC removed – rates of cross-over in UKPACE]*. These differences probably reflect differences in hardware or software randomisation. In MOST, clinical outcomes (death, stroke, heart failure and AF) were evaluated using survival analysis. It is likely that reprogramming was therefore taken into account, that is, participants were censored at the time of reprogramming.

In MOST and PASE, LOCF was used in the analyses where reprogramming or loss to follow-up occurred. This is a commonly used approach. However, the high proportion of early reprogramming may have led to an overestimation of the effect of dual chamber pacing on quality of life. In both studies, quality of life was measured at the time of reprogramming and these values were carried forward. The problem with this analysis is that it assumes that the measured quality of life just before reprogramming reflects the experience of this group over the remaining course of the trial, which may bias the analysis in favour of dual-chamber pacing. People who had their mode reprogrammed account for most of the difference in quality of life between the groups. The alternative, of using all quality of life data on these participants, would underestimate the effect of dual-chamber pacing since cases that crossed over to dual- from single-chamber pacing showed an improvement in quality of life. This issue is discussed further in the results section of this assessment (see section 'Quality of life assessed using single global questions', p. 32).

Statistical analysis

MOST reported a set of power calculations carried out for primary and secondary outcomes and quality of life based on the ability to detect a relatively large effect (25% difference between groups). CTOPP was powered to detect a 30% reduction in relative risk of stroke or death from cardiovascular causes. An additional power calculation was conducted for the CTOPP study on quality of life, taking into account a 25% loss to follow-up on this outcome. *[CiC removed – Assessment Group comments on the statistical power of UKPACE.]*

External validity

The parallel-group trials report inclusion criteria and baseline characteristics in detail. MOST and CTOPP recruited adults aged over 18 or 21 years, respectively. PASE was restricted to people aged over 65 years. However, in practice the mean age of participants in the three trials was similar (CTOPP 73,[52] 74[48] and PASE 76[35] years) and only slightly younger than the average age at pacemaker insertion in the UK (75.8 years) (see section 'Current pacemaker usage', p. 7). *[CiC removed – information on the mean age of patients in the UKPACE trial.]*

CTOPP reports the number of patients included in the trial as a proportion of total pacemaker implants during the study period. Fifty-eight per cent of people receiving first implant were eligible for the study and 57% of these gave consent. Physician preference was the most important reason for exclusion of eligible subjects (56%), followed by technical reasons (28%) and patient preference (16%). Eligible patients who were not enrolled were slightly younger than the trial population (mean age 71 versus 73 years), had slightly more sinoatrial node disease (35% versus 34%) and slightly less AVB (46% versus 50–52%) as the predominant underlying disorder, and had greater functional limitation (49% NYHA grade II or higher versus 37% and 41% in the trial arms).[52] These data indicate that the trial recruited a group of people reasonably similar to the overall clinical population from which the sample was drawn.

[CiC removed – UKPACE eligibility and exclusion.]

No details of the reference population are given in MOST and PASE.

The studies applied exclusion criteria based on a range of cardiovascular-related diseases, which may have resulted in the inclusion of patients with less severe disease than might be encountered in routine clinical practice. Patients with clinically overt heart failure were excluded from MOST and PASE. PASE had a higher proportion of people with a history of heart failure, which is reflected in the lower proportion in NYHA category I or II (70% versus 80%). Corresponding data for CTOPP are not given, only that around 60% were in NYHA class I. *[CiC removed – UKPACE exclusion criteria.]*

TABLE 11 *Characteristics of ancillary studies*

Study	Trial	Sample size	Outcomes considered
Skanes, 2001[55]	CTOPP	2568	AF
Newman, 2003[80]	CTOPP	1722 293	Quality of life
Tang, 2001[57]	CTOPP	2244	Pacemaker dependency
Stambler, 2003[53]	PASE	407	AF (predictors)
Sweeney, 2003[56]	MOST	1339	Baseline QRS
Glotzer, 2003[54]	MOST	312	Episodes of non-sustained AF
Greenspon, 2004[85]	MOST	2010	Predictors of stroke

All trials excluded patients with a previously confirmed diagnosis of chronic AF. In MOST and PASE, it was a requirement that the definition of confirmed AF was documented for 6 months. No such criterion on duration was stipulated in CTOPP.

MOST excluded individuals with malignancy expected to limit patients' life expectancy, while the CTOPP and PASE studies excluded individuals with limited life expectancy from non-cardiovascular causes.

Although it is difficult to compare the trials to each other and to routine practice, external validity appears reasonable, although MOST and PASE appear to include more severe populations than CTOPP. CTOPP excluded people with chronic AF, while the PASE and MOST studies included people with AF for less than 6 months. There were also differences in prevalence of hypertension (>60% in MOST, >50% in PASE and 35% in CTOPP). There may be reasons to believe that this applied perhaps to previous heart failure [26–28% in PASE, 18–22% in MOST and 16–17% (abnormal left ventricular function) in CTOPP]. *[CiC removed – information on the prevalence of medical conditions in UKPACE.]*

Ancillary studies and subgroup analyses

Several additional analyses and subgroup analyses have been reported from the data collected as part of the three published parallel trials of dual-chamber pacing. The results of these are presented later in this assessment. Six subgroup analyses were identified (*Table 11*).

Methodological features of the subgroup analyses are summarised in *Table 12*.

In general, the analysis and interpretation of subgroup analyses are controversial.[86] The main subgroup analyses were conducted by pacemaker dependency, presence or absence of AF and underlying disease (SSS and AVB). However, validity may be limited since post hoc classification was frequently used. In addition, predictors were measured with different methods and definitions.

In CTOPP, the end-point of AF was considered in subgroup analyses. In MOST, atrial high-rate episodes (AHRE: spontaneous atrial tachyarrhythmia and AF) were used as a proxy for AF. AHRE were defined as rates higher than 220 bpm detected by the pacemaker.[48] Participants in this substudy had pacemakers programmed to VDIR if randomised to ventricular pacing, for recording purposes.

In MOST, subgroup analyses were based on pacemaker functions,[56] with pacemaker dependency directly measured with samples of pacemaker recordings (proportion of cumulative ventricle paced) in individuals with normal QRS duration at baseline. In CTOPP, pacemaker dependency was indirectly assumed to be present in individuals with underlying spontaneous heart rate lower then 60 bpm during ventricular pacing and measured at baseline. The CTOPP substudy on pacemaker dependency[57] was invalidated by the exclusion of participants for whom end-points had occurred before measurement of underlying spontaneous heart rate. Conclusions from this study should be considered very cautiously.

Cross-over trials: characteristics

Twenty-eight cross-over studies were identified. All were trials of pacing mode. There were three comparisons:

- Ten trials compared dual-chamber and fixed rate ventricular pacing.

TABLE 12 *Methodological features of subgroup analyses*

Study	Subgroup analysed	Preplanned	Baseline equality between groups maintained	Blinding maintained/ objective outcomes	Subgroup analysis considered in power calculation	ITT maintained	Loss to follow-up
Skanes, 2001[55]	All individuals from main study	Yes	Yes	Yes	No	Yes	As in main trial
Newman, 2003[80]	All English-speaking individuals from main study 293 individuals selected from main study	Yes. Substudy: QoL collected at baseline (within 48 hours from implant) and at month 6 Main study: all patients interviewed at month 6	Baseline data are provided and tested with all *p*-values non-significant after correction for multiple comparisons; however, there is a large difference in proportions of patients with SSS and AV in the substudy compared with the parent study	Cannot tell	Only for the substudy	No, substudy (207 patients only analysed) ITT stated from main study	Numbers not stated
Tang, 2001[57]	Subselected group of the main study	Unclear. Definition of pacemaker dependency: presence of underlying rate of <60 bpm; for each patient, a point estimate of underlying heart rate was assessed during the first follow-up visit by setting the pacemaker to the VVI mode and a stable heart rate was recorded (UHR)	Baseline values are reported and tested for equality. Difference in the proportion of patients with rate-adaptive pacing in the two groups (characteristic not tested)	Cannot tell	No	Cannot tell	324 patients were excluded Primary outcome had already occurred (57 ventricular, 47 physiological) UHR not assessed at first follow-up visit (63 patients ventricular, 49 physiological) First follow-up visit not attended (52 ventricular, 56 physiological)

continued

TABLE 12 *Methodological features of subgroup analyses (cont'd)*

Study	Subgroup analysed	Preplanned	Baseline equality between groups maintained	Blinding maintained/ objective outcomes	Subgroup analysis considered in power calculation	ITT maintained	Loss to follow-up
Stambler, 2003[53]	All individuals from main study	Unclear. The only preplanned analysis mentioned is for SSS/AVB	Yes (however, unclear whether concealment was appropriate in the main paper)	Yes	No	No (LOCF in main study)	As in main study
Sweeney, 2003[56]	Subselected sample	Unclear. QRS values collected at baseline; however, no explanation provided for selection of sample	Unclear. Baseline values not tested, there might be differences in AF, prior MI, NYHA class perhaps prior atrial tachycardia	Cannot tell	No	Cannot tell	Cannot tell
Glotzer, 2003[54]	Subselected sample	Unclear. Investigator initiated study in approved centres. Participants with a recording-capable pacemaker were approached and enrolled after entry to the main study	Differences at baseline were not reported by pacing mode. The prevalence of prior supraventricular arrhythmia was higher than in the main study	Not stated. Outcomes from pacemaker recordings	The study reaches significant conclusions, so it has power to detect differences in effect	Cannot tell. Mentions data analysed per initial randomisation	Cannot tell
Greenspon, 2004[85]	All individuals from main study	Reanalysis of trial data	Yes	Yes	No	Yes	As in main study

UHR, unpaced heart rate.

TABLE 13 *Characteristics of cross-over trials*

Study	Country	Population				Intervention	Comparator	Duration
		Indication	*n*	M:F	Mean age (year)			
Avery, 1994[58]	UK	AVB	13	7:6	79	DDD	VVI	1 month
Boon, 1987[81]	UK	AVB or SSS	15	13:2	69	DDD	VVI	4 weeks
Capucci, 1993[59]	Italy	AVB, SSS or both	14	12:2	66	DDD, DDDR	VVI	1 month
Channon, 1994[60]	UK	AVB	16	8:8	81	DDD	VVI	7 days
Davis, 1985[61]	Australia	AVB	14	10:4	65	VDD	VVI	3 weeks
Deharo, 1996[62]	France	AVB	18	14:4	70	DDD	VVIR	1 month
Hargreaves, 1995[63]	UK	AVB	20	14:6	80	DDD	VVI, VVIR	2 weeks
Heldman, 1990[34]	USA	AVB, SSS or both	40	23:17	68	DDD, DDI	VVI	1 week
Hoijer, 2002[49]	Sweden	AVB or SSS	19	13:6	76	DDDR	VVIR	8 weeks
Jordaens, 1988[50]	Belgium	AVB	18	12:3[a]	74	DDD	VVI	48 hours
Kamalvand, 1997[64]	UK	AVB, SSS or both	48	28:20	64	DDDR (+/– mode switching)	VVIR	4 weeks
Kenny, 1986[65]	UK	AVB, SSS or both	10	4:6	70	DDD (two fixed rates used)	VVI	1 month
Kristensson, 1985[66]	Sweden	AVB	44	22:22	68	VDD	VVI	3 weeks
Lau, 1994[78]	Hong Kong	SSS	15	?	66	DDDR	AAIR, VVIR	4 weeks
Lau, 1994[79]	Hong Kong	AVB or SSS	33	?	66	DDD, DDDR	VVIR	8 weeks
Linde-Edelstam; 1992[82] Linde-Edelstam, 1992[67]	Sweden	AVB	17	13:4	64	DDD	VVIR	2 months
Lukl, 1994[83]	Czech Republic	AVB or SSS	21	?	68	DDD	VVIR	2 weeks
Menozzi, 1990[68]	Italy	AVB	14	4:10	72	DDD	VVIR	6 weeks
Mitsuoka, 1988[69]	UK	AVB or SSS	16	14:2	AVB: 64 SSS: 63	DDD	VVI	1 month
Oldroyd, 1991[70]	UK	AVB	10	7:3	56	DDD	VVIR	1 month
Perrins, 1983[71]	UK	AVB	13	9:4	65	VDD	VVI	1 month
Rediker, 1988[72]	USA	AVB or SSS	19	15:4	70	DDD	VVI	6 weeks
Saner, 1996[73]	Swiss	AVB or SSS	12	7:5	68	DDD	VVIR	6 weeks
Sulke, 1991[74]	UK	SSS and AVB	22	9:13	52	DDD, DDDR	VVIR	4 weeks
Sulke, 1992[75]	UK	AVB or AVB+SSS	16	11:5	67	DDD	VVI	4 weeks
Sulke, 1994[76]	UK	AVB or AVB+SSS	10	6:4	53	DDDR	VVIR	4 weeks
Yee, 1984[77]	Canada	AVB	8	4:4	59	VDD	VVI	3 months

[a] Provided only for individuals analysed.
F, female; M, male.

- Fourteen trials compared dual-chamber with rate-modulated ventricular pacing.
- Four trials compared VDD pacing (dual-chamber sensing, but ventricular pacing) with ventricular pacing.

One trial, by Hargreaves and colleagues[63] included a comparison of dual-chamber with both fixed rate and rate-modulated ventricular pacemakers. Two trials[73,74] included a comparison of single-chamber ventricular with both fixed rate and rate-modulated dual-chamber pacing.

Table 13 shows the main characteristics of the cross-over studies and is an extended version of the table of study characteristics published in the review by Dretzke and colleagues.[43] The participants in cross-over trials were younger than

those in the parallel-group trials (unweighted mean = 68 years, versus 73–76 years), with a higher proportion of males (64% versus 57%).

The cross-over trials were much smaller than the parallel-group studies, with an average of only 19 participants (range 8–48, total studied 515), and follow-up was considerably shorter (range 2 days to 3 months). Patients in the cross-over trials were slightly younger than those in the parallel studies (average age 68 years), with a wider age range studied (range of average ages = 52–82 years). One trial included only people with SSS, 14 included a population with either SSS or AVB or both, and 13 included only people with AVB. Reporting of co-morbidity and concomitant treatment in the study populations was variable.

The intervention in the cross-over trials was predominantly dual-chamber pacing (24/28, 86%). In the remaining four studies, the intervention pacing mode was VDD. In three cases, dual-chamber pacing, both rate modulated and non-rate modulated, was studied. In one case,[34] DDD and DDI were considered together. In this mode, both chambers are sensed, but only the ventricle is paced. Atrial sensing aims to maintain atrioventricular synchrony. In a further four trials the intervention was rate-responsive dual-chamber pacing. In all of these cases, the comparator was also rate responsive, although in a further eight studies the comparator mode was rate responsive while the intervention was not. In one study DDDR mode was compared with single-chamber atrial (AAIR) and ventricular (VVIR) pacing (*Tables 14–16*).

Cross-over trials: methodological quality

Tables 14–16 give an overview of the methodological features of the cross-over trials according to the comparisons undertaken. Some of the features used to appraise the quality of parallel-group RCTs have a slightly different meaning in the context of cross-over studies (e.g. ITT analysis), where it is not participants that are randomised, but the order of treatments within participants.

Selection bias

Selection bias is systematic error that arises in a measurement comparing two groups because of significant differences between the groups that also relate to the outcome, that is, it is confounding. Cross-over studies do not have two groups in the same sense as in a parallel design. There are two groups of measurement, but these have been taken in the same individuals. The data are therefore paired. Selection bias may still arise if there is a systematic difference in relation to the ordering of the treatment periods. Random allocation of this is likely to reduce the risk of error arising through secular effects, such as progression or recovery in the underlying condition. Spontaneous improvement is unlikely in the population with bradycardia, although progression is possible. The duration of study is therefore important and trials were therefore brief: treatment periods were, on average, 4–5 weeks long. Therefore, it is unlikely in most cases that progression will have given rise to substantial bias, although this cannot be measured empirically.

Only one study[50] had a treatment period of less than 1 week (2 days). Although outcomes in this study were chosen to permit measurement shortly after intervention, it remains possible that this study was insufficiently long to demonstrate the effects of the intervention.

A second important problem for cross-over trials (although not restricted to them[87]) is carry-over, whereby the effects of the intervention given in the first treatment period have an effect during the second treatment period. A washout period is sometimes used in cross-over trials of drugs to address this problem. In the case of pacing modes, a washout period is not required as carry-over effects would not be expected.

Concealment of allocation is important in parallel trials, where the investigator should be unaware of the next allocation in the sequence at the time of enrolling the next patient. In cross-over studies the situation different is and the reviewers think that this factor is likely to be less important as a source of bias (although they are not aware of any empirical evidence that considers the impact of this factor). The key distinction is that knowledge of the allocation schedule will not have an impact on the treatment received, but only on the order in which treatments are received. No cross-over studies reported allocation concealment.

Detection bias

Most trials include accounts of reasonable attempts to blind participants and assessors to pacing mode. The procedures used to blind participants and assessors were not tested in any of the trials. In some trials,[59,61,62,81] outcome assessment was not carried out blind to mode allocation and this may give rise to detection bias.

In general, the measures used in the cross-over trials had not been validated before their use. In most cases, outcome measures were adapted from

TABLE 14 *Cross-over trials of dual-chamber compared with fixed rate ventricular pacing*

Study	Randomisation sequence generation	Concealment of randomisation	Eligibility criteria specified	Blinding of assessors	Blinding of care provider	Participants blinded	Co-intervention, equal at baseline	Co-intervention, equal during follow-up	Results for primary outcome measure	Loss to follow-up?	Losses accounted for?
Avery, 1994[58]	?	?	No	Adequate	?	Adequate	?	?	Adequate	Yes	No
Boon, 1987[81]	?	?	Yes	No	?	Adequate	?	?	Adequate	Yes	Yes
Capucci, 1993[59]	Randomisation table	?	Yes	No	?	Adequate	?	?	Adequate	Yes	Yes
Channon, 1994[60]	?	?	Yes	Adequate	?	Adequate	Adequate	?	Adequate	Yes	Yes
Heldman, 1990[34]	?	?	No	?	?	Adequate	?	Adequate	Adequate	No	–
Jordaens, 1988[50]	?	?	Yes	?	?	?	?	?	Adequate	Yes	Yes
Kenny, 1986[65]	?	?	No	Adequate	?	Adequate	Adequate	Adequate	Adequate	No	–
Mitsuoka, 1988[69]	?	?	No	Adequate	?	Adequate	Adequate	?	Adequate	No	–
Rediker, 1988[72]	?	?	No	Adequate	?	?	?	?	Adequate	Yes	No
Sulke, 1992[75]	Randomisation table	?	Yes	Adequate	?	Adequate	?	?	Adequate	No	–

TABLE 15 *Cross-over trials of dual-chamber compared with rate-modulated ventricular pacing*

Study	Randomisation sequence generation	Concealment of randomisation	Eligibility criteria specified	Blinding of assessors	Blinding of care provider	Participants blinded	Co-intervention, equal at baseline	Co-intervention, equal during follow-up	Results for primary outcome measure	Loss to follow-up?	Losses accounted for?
Deharo, 1996[62]	?	?	Yes	No	?	? Yes	?	?	Adequate	Yes	Yes
Hargreaves, 1995[63]	?	?	Yes	Adequate	?	Adequate	?	?	Adequate	No	–
Lau, 1994[79]	?	?	No	Adequate	?	Adequate	?	?	Adequate	No	–
Linde-Edelstam, 1992[82]	?	?	No	Adequate	?	Adequate	Adequate	Adequate	Adequate	No	–
Linde-Edelstam, 1992[67]	?	?	No	Adequate	?	Adequate	Adequate	Adequate	Adequate	No	–
Menozzi, 1990[68]	?	?	Yes	Adequate	?	Adequate	?	?	Adequate	No	–
Oldroyd, 1991[70]	?	?	Yes	Adequate	?	Adequate	?	?	Adequate	No	–
Lukl, 1994[83]	?	?	No	Adequate	?	Adequate	?	?	Adequate	No	–
Saner, 1996[73]	Randomisation table	?	No	?	?	?	?	?	Adequate	No	–
Sulke, 1991[74]	Randomisation table	?	No	Adequate	?	Adequate	?	?	Adequate	?	?
Hoijer, 2002[49]	?	?	?	Adequate	?	Adequate	?	?	Adequate	?	?
Kamalvand, 1997[64]	Randomisation table	?	No	Adequate	No	Adequate	?	?	Adequate	Yes	Yes
Lau, 1994[78]	?	?	Yes	Adequate	?	Adequate	Adequate	Adequate	Adequate	Yes	No
Sulke, 1994[76]	Randomisation table	?	No	Adequate	?	?	?	?	Adequate	No	–

TABLE 16 *Cross-over trials of VDD compared with fixed rate ventricular pacing*

Study	Randomisation sequence generation	Concealment of randomisation	Eligibility criteria specified	Blinding of assessors	Blinding of care provider	Participants blinded	Co-intervention, equal at baseline	Co-intervention equal during follow-up	Results for primary outcome measure	Loss to follow-up?	Losses accounted for?
Davis, 1985[61]	?	?	Yes	No	?	Adequate	?	?	Adequate	Yes	–
Yee, 1984[77]	?	?	Yes	?	?	Adequate	?	?	Adequate	No	–
Kristensson, 1985[66]	?	?	No	Adequate	No	Adequate	Adequate	Adequate	Adequate	No	–
Perrins, 1983[71]	?	?	No	Adequate	No	Adequate	No	Adequate	Adequate	No	–

other instruments or developed specifically for the study.

Performance bias

Details on baseline medications and co-morbidity are available for few studies. Therefore, it is not possible to draw conclusions on differences in concomitant treatments in the two periods. However, these are unlikely to be important since the trials were of short duration.

Attrition bias

Attrition in cross-over trials presents particular problems. Where a participant drops out of the study before the start of the second (or any subsequent) treatment period the planned comparison cannot be made and the data are unusable. Where a participant drops out after starting but before completing a treatment period, LOCF or some other method for imputation may be used. Such methods may allow greater use of available data, but may also give rise to bias in the comparison of treatment periods, particularly where dropout is related to outcome.

In six of the studies comparing dual-chamber with ventricular pacing, there were stated losses to follow-up.[50,58–60,72,81] Of these, most provided some account of the reasons for dropout. Loss to follow-up was reported in four further studies.[61,62,64,78] Only two studies reported loss to follow-up of greater than 20%.[58,78]

Statistical analysis

No power calculations were provided in any cross-over trial. Although few patients were included, because the analysis of such trials is based on a comparison of effect within individuals rather than between them (and within-subject variance is generally much less than between subjects), smaller studies are required to demonstrate a similar effect.[88]

The methods used in the analyses of results of the mode-randomised trials were in general appropriate. Results were adequately reported in most studies (i.e. expressed numerically with some indication of precision).

Dual-chamber versus single-chamber ventricular pacing: summary of quality of evidence

- Four large parallel-group RCTs (including the unpublished UKPACE study) and 28 small cross-over trials were included (total $n = 7006$). UKPACE data were included in the meta-analysis of trials where possible.
- In general, the quality of the parallel-group trials (PASE, MOST and CTOPP) was good. PASE and MOST were trials of programming mode. CTOPP and UKPACE were trials of device.
- All parallel studies were randomised and, in the larger trials (CTOPP and MOST), concealment was adequate.
- Baseline differences in MOST were handled appropriately in the statistical analysis, although the potential for confounding by unknown factors remains.
- Completeness of follow-up was good in all studies, although there is some potential for attrition bias in quality of life measurement.
- Three of the large parallel studies were single blind (participants). Efforts were made in all studies to ensure independent verification of most outcomes. However, the methods for verification of pacemaker syndrome in PASE and MOST are uncertain. There is also uncertainty about the independence of measurement of quality of life in the event of patients switching pacing mode in PASE and MOST.
- External validity was good. The eligibility criteria for CTOPP were applicable to nearly 60% of people undergoing first implantation in the study centres and around 60% of these were recruited. The populations in MOST and PASE were similar to those in CTOPP.
- Five subgroup and ancillary studies were identified from the three large published parallel studies. Such analyses are prone to bias and the effects of chance. Only two were definitely preplanned and methodological details of the others are limited. The CTOPP substudy of pacemaker dependency should be viewed with particular caution.
- The 28 cross-over trials included in the review were carried out in much smaller populations (total $n = 493$), contained fewer methodological details and were of much shorter duration, although the higher power intrinsic to this design should be noted. In light of the larger body of longer term evidence from the parallel design trials they are currently less useful as a basis for policy making.

Dual-chamber versus single-chamber ventricular: results

The main outcomes considered for dual-chamber pacing were:

- mortality
- atrial fibrillation

TABLE 17 *Mortality: RCTs of dual-chamber versus ventricular pacemakers*

	All-cause death				Cardiovascular deaths			
Study	**Dual chamber**	**Ventricular**	**Effect**	**95% CI**	**Dual chamber**	**Ventricular**	**Relative effect**	**95% CI**
PASE[35]	32/203 (16%)	34/204 (17%)	RR = 0.94	0.8 to 1.59	–	–	–	–
MOST[48]	200/1014 (19.7%)	204/996 (20.5%)	HR = 0.97 Adj HR = 0.95	0.8 to 1.18 0.78 to 1.16	8.5%	9.2%	HR = 0.93 Adj HR = 0.87	0.69 to 1.24 0.65 to 1.18
CTOPP[52]	69/1094 (6.3%)	97/1474 (6.6%)	RR reduction 0.9%	–18.1 to 16.8	–	–	–	–
UKPACE[45]	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*

Adj HR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; RR, relative risk.

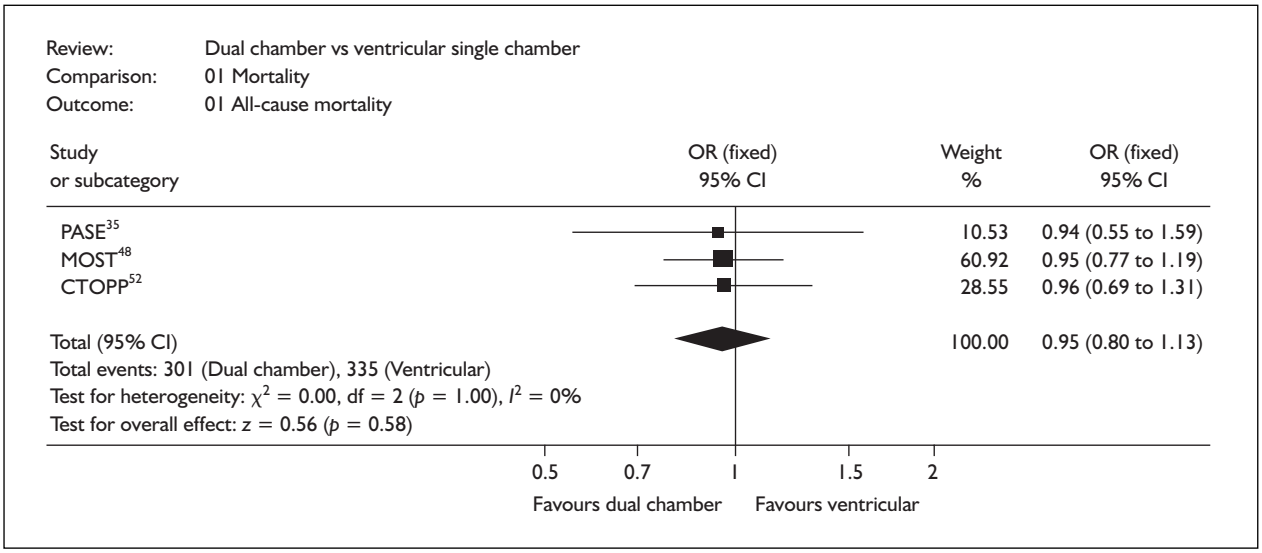


FIGURE 7 *Forest plot: odds ratio, mortality*

- stroke
- heart failure
- exercise capacity
- quality of life.

Results are presented by outcome, including results reported in publications other than the main trial reports, and subgroup analyses. In addition to tabulation of results from literature, pooled estimates were calculated for the main outcomes considered and are presented using forest plots. As UKPACE has not been published and results are unpublished and confidential, meta-analyses were carried out with and without this study. Results of parallel and cross-over trials are discussed in relation to each outcome.

Mortality

Total deaths reported were 13% (301/2311) for individuals with dual-chamber pacemakers and 12.5% (335/2674) for individuals with ventricular pacemakers. No individual trial showed a significant difference in all-cause or cardiovascular mortality (*Table 17*), nor is the pooled estimate significant [odds ratio (OR) = 0.95, $p = 0.58$] (*Figures 7* and *8*). *[CiC data from the UKPACE study have been excluded.]*

Death rates were higher in MOST and PASE than in CTOPP, reflecting differences in the study populations that are greater than might be expected according to a comparison of the baseline characteristics. *[CiC removed – death rates in the UKPACE trial.]*

FIGURE 8 *Forest plot: odds ratio, mortality including UKPACE*

[This figure has been excluded owing to the confidential nature of the UKPACE study]

Subgroup analyses of effects on mortality were carried out according to:

- pacemaker dependency in CTOPP[57]
- episodes of transient AF in MOST[54] and PASE[53]
- underlying diagnosis (SSS or AVB) in PASE[35]
- *[CiC removed – subgroup analysis undertaken in the UKPACE trial.]*[45]

In CTOPP, pacemaker dependency was defined as the presence of an underlying spontaneous heart rate of less than 60 bpm.[57] A significant increased risk of death was found in pacemaker-dependent individuals paced with ventricular pacemakers (7.8%) compared with physiological pacing (4.6%), a relative risk reduction of 38% (95% CI 18 to53%, $p < 0.001$), but an absolute risk reduction of 3.2%, corresponding to a number needed to treat (NNT) of 31. Mortality in non-pacemaker-dependent individuals was not significantly different. A similar pattern was found for cardiovascular deaths. Two factors are important in understanding the biological plausibility of the subgroup and considering the potential for confounding as a reason for the finding. First, the subgroup was defined at first follow-up, which took place 2–8 months after recruitment, and excluded people who had experienced any outcome up to that point. Second, pacemaker dependency was defined according to underlying natural heart rate and did not, for example, take chronotropic incompetence into account.

The occurrence of episodes of transient AF was a risk factor for total mortality in MOST (HR 2.48, 95% CI 1.25 to 4.91, $p = 0.009$). In PASE, mortality was higher in individuals with AF (relative risk of death 1.35, CI not reported), but this relationship was not significant ($p = 0.39$).

No significant differences in mortality by pacing mode were found in PASE according to underlying diagnosis (AVB or SSS). In individuals with SSS, there was 12% mortality on dual-chamber pacing and 20% in ventricular mode ($p = 0.09$). The corresponding proportions for AVB were 17% on dual-chamber pacing and 15% in ventricular mode ($p = 0.41$).

[CiC removed – detailed information on subgroup analysis conducted in the UKPACE trial.]

Stroke

A small proportion of individuals suffered strokes during the parallel RCTs: a total of 2.4% (56/2311) of individuals with dual-chamber and 2.7% (72/2674) with ventricular pacemakers (*Table 18*). *[CiC data from the UKPACE study have been excluded.]*

There was no significant difference in incidence of stroke in individual trials. The pooled odds ratio of stroke was in favour of dual-chamber pacing but was not statistically significant (OR = 0.81, 95% CI 0.57 to 1.16, $p = 0.25$) (*Figure 9*).

FIGURE 10 *Pooled odds ratio, stroke, TIA or thromboembolism, including UKPACE*

[This figure has been excluded owing to the confidential nature of the UKPACE study]

The study by Greenspon and colleagues[85] analysed predictors of stroke in MOST. The main predictors identified were: prior stroke or TIA, Caucasian race, hypertension, prior systemic embolism and NYHA functional class III or IV ($p < 0.05$). This study found that AF was a risk factor for stroke after adjustment for these predictors (HR = 1.68, 95% CI 1.02 to 2.76, $p = 0.042$), while pacing mode remained non-significant after adjustment.

Subgroup analyses were conducted on stroke by pacemaker dependency in CTOPP[57] and by

TABLE 18 *Incidence of stroke: RCTs of dual chamber versus ventricular pacemakers*

	Dual chamber	Ventricular	Relative measure of effect	95% CI	*p*-Value
MOST[48]	4%	4.9%	HR = 0.82 Adj HR = 0.81	0.54 to 1.25 0.54 to 1.23	0.36 0.33
PASE[35]	4/203 (2%)[a]	7/204 (3.4%)[a]	RR = 0.57	–	0.54
CTOPP[52]	11/1094 (1%)	16/1474 (1.1%)	RR = 0.96	–	–
UKPACE[b]	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*

[a] From Stambler *et al*.[53]
[b] Composite of stroke, TIA or thromboembolism.

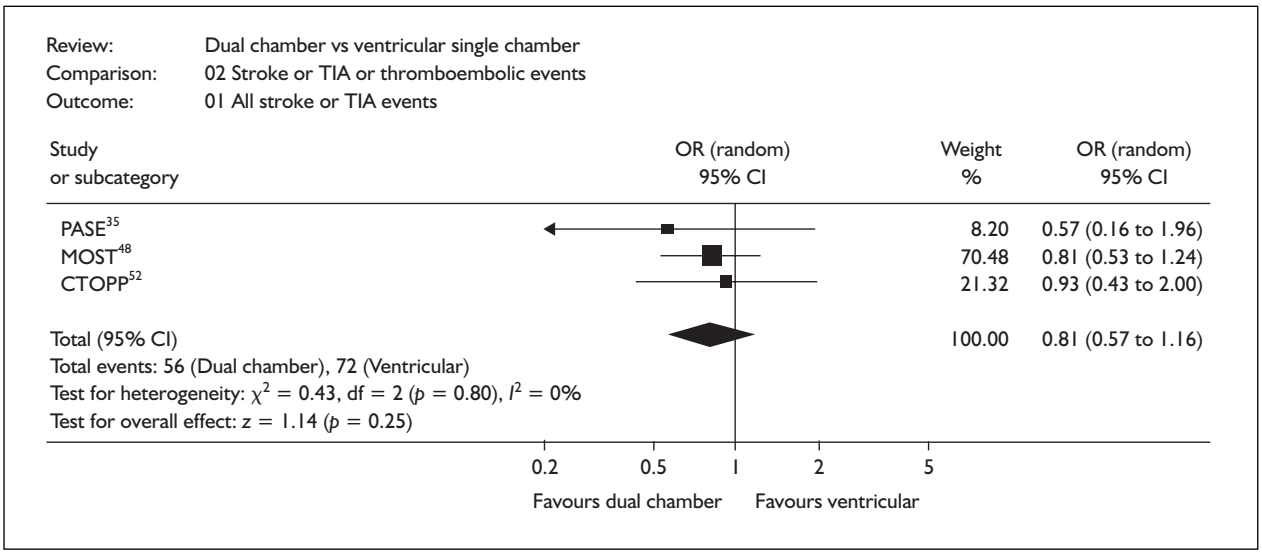


FIGURE 9 *Pooled odds ratio, stroke. TIA, transient ischaemic attack*

TABLE 19 *Incidence of atrial fibrillation: RCTs of dual-chamber versus ventricular pacemakers*

Trial	Dual chamber	Ventricular	Relative measure of effect	95% CI	*p*-Value
MOST[48]	21.40%	27.10%	HR = 0.79 Adj HR = 0.77	0.66 to 0.94 0.64 to 0.92	0.008
CTOPP[52]	58/1094 (5.3% annual rate)	97/1474 (6.60% annual rate)	RR reduction –18%	0.3 to 32.6	< 0.05
PASE[35]	35/203 (17%) 17% (cumulative incidence, KM)	38/204 (19%) 18% (cumulative incidence, KM)	–	–	0.8
UKPACE[45]	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*

KM, Kaplan–Mayer.

underlying disease (SSS or AVB) in PASE.[35] In CTOPP, no difference was found according to pacemaker dependency, with strokes occurring in 1% of pacemaker-dependent participants on physiological and 0.9% on ventricular pacing. In non-pacemaker-dependent individuals, stroke occurred in 0.7% (physiological) and 0.9% (ventricular).

No difference in rates of stroke was found by underlying disease in PASE, with 1% of individuals paced with dual chamber reporting stroke and 2% in ventricular pacing. Rates for individuals with AVB were similar, 1% in dual-chamber pacing and 3% in ventricular pacing.

Atrial fibrillation

AF was most frequently observed in MOST and least often in CTOPP (*Table 19*).

AF was significantly reduced with dual-chamber pacing in MOST and CTOPP. No significant reduction was reported in PASE. Overall, the incidence of AF was significantly lower with dual-chamber (13.4%, 310/2311) than with ventricular pacemakers (15.1%, 405/2674). The odds ratio for AF was 0.76 (95% CI 0.65 to 0.90), (*Figure 11*), favouring dual-chamber pacing ($z = 3.19$, $p = 0.001$). *[CiC data from the UKPACE study have been excluded.]*

[CiC removed – detailed information on the incidence of AF in the UKPACE trial.]

The long-term follow-up on CTOPP[89] was published after the initial searches for this report. The short-term findings were confirmed, with significantly reduced AF in the dual-chamber arm. The reduction was reported in people with AVB and SSS.

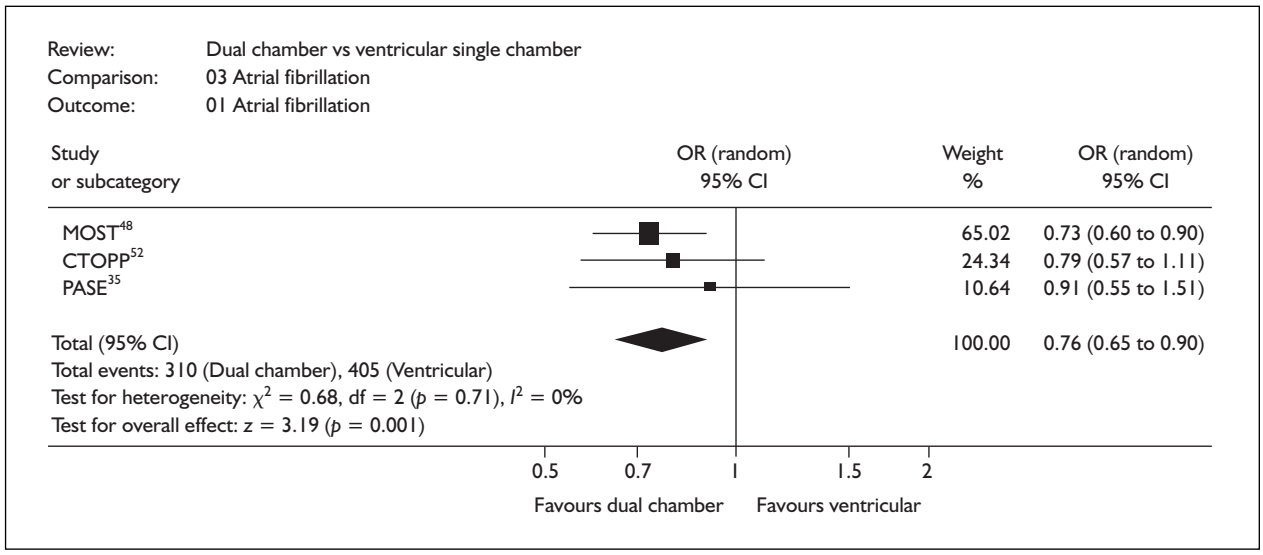


FIGURE 11 *Pooled odds ratio, atrial fibrillation*

The detection of significantly decreased rates of AF for dual chamber in MOST compared with the other trials may be explained by:

- A type II error in the other trials. MOST had more power to detect a change than PASE.
- Previous history of AF. MOST had a higher proportion of people with a previous history of AF and therefore higher risk of experiencing AF in future than CTOPP.
- Underlying cause of bradycardia. Risk of AF may be higher where the conduction in the atrium is preserved. MOST included only people with SSS, while 60–70% of people in CTOPP and PASE *[CiC removed – data from the UKPACE trial]* had AVB.

It is likely that all of these factors are likely to be operating. Other prognostic factors, such as degree of atrial dilation, may also be important, but information is lacking in the trial reports considered in this assessment.

In conclusion, dual-chamber pacing reduces AF during a period of 3 years after initial implant. However, sustained benefit in the longer term is uncertain and may be difficult to assess in the elderly. This is because long-term comparison may be affected by high loss to follow-up, and in addition by higher expected rates of mortality in these recipients.

FIGURE 12 *Pooled odds ratio, atrial fibrillation including UKPACE*

[This figure has been excluded owing to the confidential nature of the UKPACE study]

Predictors for chronic AF were investigated in CTOPP by Skanes and colleagues.[55] Their study was based on a reanalysis of data from all participants, classified according to whether they developed chronic AF during follow-up, and concluded that physiological pacing significantly reduces the burden of chronic AF, with a relative risk reduction of 27.1% (annual rate). The study looked at the main predictors of chronic AF in individuals paced for SSS and AVB. These were ventricular mode (annual rate 3.84% versus 2.8% physiological, $p = 0.016$) presence of sinoatrial node (SAN) disease (annual rate 5.66% versus 1.86% individuals without SAN, $p < 0.001$) and prior AF (annual rate 9.64% versus 2.04% individuals without AF, $p < 0.001$). Age failed to reach significance (3.83% individuals ≥ 74 years old versus 2.95% <74, $p = 0.057$). Annual rates of chronic AF did not differ by other characteristics of participants (prior MI, hypertension, diabetes and left ventricular function).

There is conflicting evidence on the direction of benefits by underlying cause of bradycardia. In PASE there was a non-significant difference in AF among those on ventricular pacing according to underlying diagnosis (28% SSS versus 11% AVB). In the dual-pacing arm a smaller and also non-significant difference was shown (19% SSS versus 16% AVB). *[CiC removed – comment on the UKPACE trial removed.]* However, AF is reduced in both SSS and AVB subgroups in CTOPP.

Sweeney and colleagues[56] examined the characteristics of individuals with AF by pacemaker dependency in MOST. The number of

TABLE 20 *Incidence of heart failure: RCTs of dual-chamber versus ventricular pacemakers*

Trial	Dual chamber	Ventricular	Effect	95% CI	*p*-Value
MOST[48]	10.30%	12.30%	HR = 0.82 Adj HR = 0.73	0.63 to 1.06 0.56 to 0.95	0.13 0.02
CTOPP[52]	34/1094 (3.1% annual rate)	52/1474 (3.50% annual rate)	RR reduction –7.9%	18.5 to 28.3%	0.52
UKPACE[45]	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*

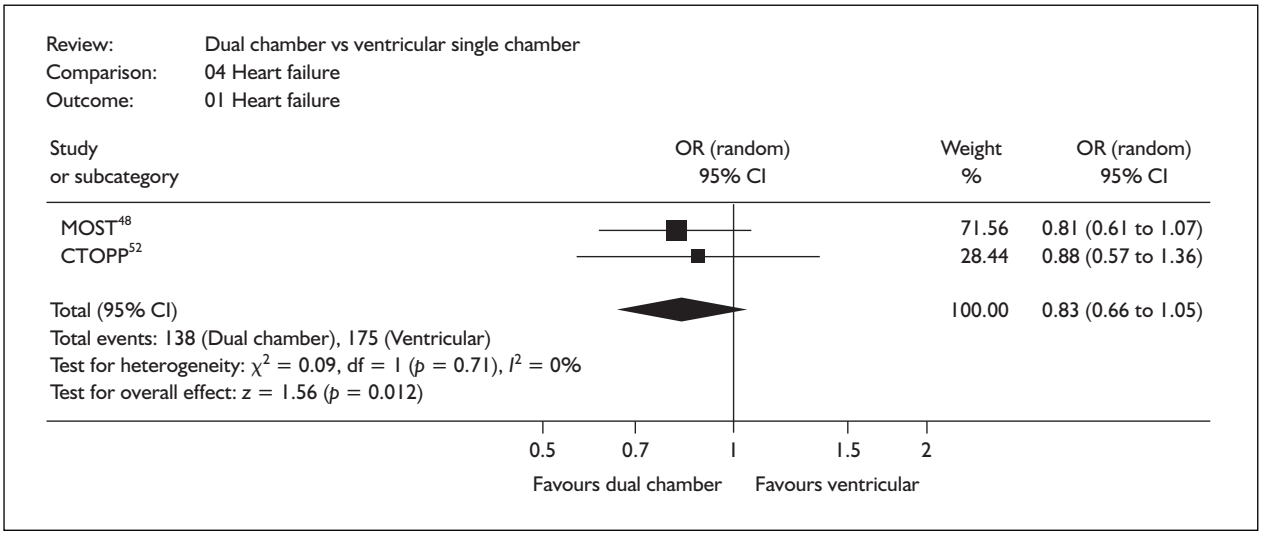


FIGURE 13 *Pooled odds ratio, heart failure*

people with continuous pacing was higher in dual-chamber (50% were paced in the ventricle for 90% of the time or more) than in ventricular mode (20%). The risk of AF was increased in individuals paced up to 80–85% of the beats. AF increased by 1% (95% CI 0.2 to 1.8%, $p = 0.01$) for dual-chamber and 0.7% for ventricular (95% CI 0 to 1.4%, $p = 0.04$) for each increase of 1% in cumulative percentage ventricle beats paced.

In the same trial, Glotzer and colleagues[54] found that the presence of any episode of transient AF was an independent predictor of AF (HR = 5.93, 95% CI 2.88 to 12.2, $p < 0.001$).

Tang and colleagues[57] (CTOPP) investigated the impact of pacemaker dependency on AF. AF was higher in ventricular pacing, both in individuals dependent on pacemakers (7.3% annual rate) and in non-pacemaker-dependent individuals (5.2% annual rate), compared with 4.6% in physiological pacing regardless of pacemaker dependency. Physiological pacing was associated with a risk reduction of 35.3% (95% CI 12 to 53%) in pacemaker-dependent individuals and of 16.2% (95% CI –22 to 43%) in non-pacemaker – dependent individuals. However, these differences were non-significant ($p = 0.22$).

Heart failure

Heart failure was reported in MOST and CTOPP (*Table 20*). These trials reported hospitalisation rates. *[CiC removed – information on the reporting of heart failure in UKPACE.]*

The overall incidence of heart failure was 6.5% (138/2108) for dual-chamber and 7.1% (175/2470) for ventricular pacing. MOST was the only study to detect significant differences in heart failure by mode (adjusted HR = 0.73). *[CiC data from the UKPACE study have been excluded.]* However, pooled results did not reveal differences by mode (OR = 0.83, 95% CI 0.66 to 1.05, $z = 1.56$, $p = 0.118$).

FIGURE 14 *Pooled odds ratio, heart failure, including UKPACE*

[This figure has been excluded owing to the confidential nature of the UKPACE study]

Sweeney and colleagues[56] looked at the impact of pacemaker dependency on progression to heart failure in MOST. Heart failure increased with the proportion of beats paced. For non-dependent

individuals (paced for less than 40% of beats) dual chamber was a risk factor for heart failure (HR = 1.54, 95% CI 1.01 to 2.36, $p = 0.046$). The risk increased with dependency (HR = 2.6, 95% CI 1.05 to 6.47, $p = 0.04$) for individuals paced for 40–80% of total beats. For individuals paced for more than 80% of beats, the risk of developing heart failure with dual-chamber pacing was constant, whereas it was increased for ventricular pacing (HR = 2.5, 95% CI 1.44 to 4.36, $p < 0.0012$).

Tang and colleagues[57] found no differences in the incidence of heart failure by pacemaker dependency in CTOPP. Rates of heart failure were similar for individuals with heart rate lower or higher than 60 bpm (lower, 2.8% for both modes, RR reduction = 0.9, 95% CI –51 to 35; higher, physiological 2.6% versus ventricular 2.4%, RR difference = –13.3, 95% CI –88 to 32, $p = 0.71$).

Composite outcomes

The four parallel-group RCTs also considered composite outcomes. Studies may have higher power to detect differences by pacing mode using such outcomes, owing to a higher incidence of events. In this context composite outcomes may provide additional information on the validity of single outcomes. However, one study, CTOPP, was powered on the composite outcome of cardiovascular deaths and stroke, reported in this section and in *Table 21*.

MOST and PASE considered combined all-cause death, first non-fatal stroke, first hospitalisation for heart failure, and a second composite outcome for all-cause death and stroke. CTOPP considered combined cardiovascular deaths and stroke. *[CiC removed – data on composite outcomes considered in UKPACE.]*

In MOST, the main composite end-point was significantly better for dual-chamber pacing (HR = 0.85, 95% CI 0.72 to 1, $p = 0.05$). This result was largely driven by heart failure, which occurred in 12.3% (ventricular) and 10.3% (dual chamber). The composite outcome of death and stroke was non-significant (Adj HR = 0.91, 95% CI 0.75 to 1.1, $p = 0.32$). Death occurred in 20% and stroke in 4% of the total population in this trial.

In PASE, 27% and 22% of the population reached the primary composite end-point with dual-chamber and ventricular pacing, respectively. There was no difference in the composite incidence of death and stroke (19% dual and 17% ventricular, $p = 0.75$). PASE was probably underpowered to detect significant differences in single clinical end-points, since its main power calculation was conducted on quality of life.

MOST provided a series of subanalyses of combined end-points by pacing mode. Participant characteristics considered were gender, age, race and history of supraventricular tachycardia. No significant differences were reported for any of the subgroups studied (*Table 21*).

Subgroup analyses were conducted by underlying pacing indication in PASE, with higher total incidence of deaths, heart failure, AF or stroke for ventricular pacing. The difference was greater for people with SSS, but not statistically significant. The composite of death and stroke was higher in ventricular mode for the SSS group only, with no differences reported for the AVB group. These differences were also not statistically significant.

There were no differences in combined cardiovascular deaths and stroke in CTOPP (4.9% dual versus 5.5% ventricular). The relative risks of reaching the composite end-point by pacing mode were calculated for subgroups defined by age, gender, presence of MI or documented coronary artery disease (CAD), left ventricular function, SAN disease, AV node block, third degree heart block, prior AF or prior stroke, anticoagulants and antiarrhythmic therapy. All differences were non-significant (*Table 21*).

[CiC removed – UKPACE results of composite outcomes.]

Exercise and effort tolerance

Effort tolerance was measured in 20 cross-over trials. None of the parallel group trials reported this outcome. Measurement of physical performance and exercise capacity was reported in 19 cross-over trials. In addition, six trials reported a measure of subjectively perceived effort tolerance.

Effort was measured in conducting ordinary activities such as walking, climbing stairs and bicycle riding, with the use of instruments including the 6-minute walking test, symptom-limited bicycle ergometer, stair climbing, treadmill and chair stand-up tests. Treadmill and bicycle ergometer tests were conducted under maximal performance, with participants asked to exercise until symptoms intervened and tests had to be stopped. At this point, resistance (exercise duration) was recorded. In some trials, effort was measured in workload or energy units obtained. In other studies, a measure of performance was

TABLE 21 *Composite end-points: RCTs of dual-chamber versus single-chamber ventricular pacemakers*

End-point	Subgroups	MOST[48]				CTOPP[52]			PASE[35]			*UKPACE*[45]	
		Dual chamber	Ventricular	Relative measures of effect	95% CI	Dual chamber	Ventricular	*p*-Value	Dual chamber	Ventricular	*p*-Value	*Dual chamber*	*Ventricular*
Combined all-cause death, first non-fatal stroke, first hospitalisation for heart failure	All sample	27.6%	29.9%	HR = 0.9 Adj HR = 0.85	0.77 to 1.06 0.72 to 1				44 (22%)	56 (27%)	0.18		
	SSS								18/90 (20%)	26/85 (31%)	0.07		
	AVB								21/99 (21%)	27/102 (26%)	0.49		
	Men (n = 1055)			0.91	0.73 to 1.15								
	Women (n = 955)			0.89	0.71 to 1.13								
	≥ 75 years (n = 987)			0.97	0.79 to 1.21								
	<75 years (n = 1023)			0.83	0.65 to 1.07								
	White (n = 1704)			0.88	0.73 to 1.05								
	Non-white (n = 306)			1	0.68 to 1.46								
	History of supraventricular tachycardia (n = 1059)			0.92	0.74 to 1.14								
	No history of supraventricular tachycardia (n = 951)			0.88	0.69 to 1.13								
Combined all-cause death and stroke	All sample	21.5%	23%	0.93 0.91	0.78 to 1.13 0.75 to 1.1				35 (17%)	39 (19%)	0.75		
	SSS								12 (13%)	19 (22%)	0.11		
	AVB								18 (18%)	18 (18%)	0.69		
Combined cardiovascular death and stroke	All sample (%)					4.9%	5.5%						
	Subgroups					HR	HR						
	Age, <74 or ≥ 74					0.65	1.00	0.054					
	Gender, M/F					0.98	0.84	0.52					
	MI or documented CAD, Y/N					0.89	0.91	0.9					
	LVF, normal/abnormal					0.93	0.84	0.61					
	SAN disease, Y/N					1.09	0.78	0.1					
	AV node block, Y/N					0.82	1.02	0.29					
	AF, Y/N					0.97	0.89	0.72					
	Stroke, Y/N					0.74	0.94	0.38					

continued

TABLE 21 *Composite end-points: RCTs of dual-chamber versus single-chamber ventricular pacemakers (cont'd)*

End-point	Subgroups	MOST[48]				CTOPP[52]			PASE[35]			*UKPACE*[45]	
		Dual chamber	**Ventricular**	**Relative measures of effect**	**95% CI**	**Dual chamber**	**Ventricular**	***p*-Value**	**Dual chamber**	**Ventricular**	***p*-Value**	***Dual chamber***	***Ventricular***
	Anticoagulant therapy, Y/N					0.79	0.92	0.6					
	Antiarrhythmic therapy, Y/N					0.81	0.92	0.66					
	Third degree heart block, Y/N					0.87	0.94	0.74					
Cardiovascular deaths, resuscitated cardiac arrest, AF, hospitalisation for heart failure, MI or angina, stroke, reoperation												*CiC removed*	*CiC removed*

LVF, left ventricular function; N, no; Y, yes.

TABLE 22 *Instruments and measurement of exercise capacity, dual-chamber versus ventricular pacing*

Study	Instrument	Exercise capacity, indicators
Avery, 1994[58]	6-minute walking test	Total distance, number of stops, reasons for stopping
	Stair climbing	Time taken to climb two flights
Capucci, 1993[59]	Bicycle ergometer, symptom limited	Workload achieved in last completed step
Channon, 1994[60]	6-minute walking test	Total distance (25 m per slot)
	Stair climbing	Time taken to climb one flight (26 steps)
	Borg score, 6 (no difficulty) to 20 (very hard)	Perceived exertion
Davis, 1985[61]	Treadmill exercise, maximal, Bruce protocol	Exercise duration
Deharo, 1996[62]	Treadmill exercise, maximal, Haughton protocol	Exercise duration, maximum workload
Hargreaves, 1995[63]	6-minute walking test	Total number lengths (25 m) or number lengths walked before stopping
	Stair climbing	Time taken to climb two flights (26 steps each)
	Borg score, 6 (no difficulty) to 20 (very hard)	Perceived exertion
	Chair stand-up	Number of ups and downs
Jordaens, 1988[50]	Bicycle ergometer, symptom limited	Exercise duration
Kamalvand, 1997[64]	VAS, treadmill, graded exercise	Perceived exercise capacity, exercise duration
Kenny, 1986[65]	Bicycle ergometer, symptom limited	Exercise workload (kpm)
Kristensson, 1985[66]	Bicycle ergometer, symptom limited	Exercise workload
	Borg score, 6 (no difficulty) to 19 (very hard)	Perceived exertion
Linde-Edelstam, 1992[67]	Treadmill exercise, submaximal	Exercise time to Borg score 5
	Borg score, 6 (no difficulty) to 19 (very hard)	Perceived exertion
Menozzi, 1990[68]	Bicycle ergometer, symptom limited	Total workload (observer not blinded in this test)
Mitsuoka, 1988[69]	Bicycle ergometer, symptom limited	Exercise workload (W)
Oldroyd, 1991[70]	Treadmill exercise, maximal	Exercise duration
Perrins, 1983[71]	Bicycle ergometer, symptom limited	Exercise workload (kpm)
Rediker, 1988[72]	Exercise study (not specified), symptom limited	Exercise duration (data for patients unable to exercise were excluded)
Saner, 1996[73]	Treadmill exercise, maximal	Exercise duration
Sulke, 1991[74]	VAS, treadmill, graded exercise	Perceived exercise capacity, exercise duration
Sulke, 1992[75]	VAS, treadmill, graded exercise	Perceived exercise capacity, exercise duration
Sulke, 1994[76]	VAS	Perceived exercise capacity
Yee, 1984[77]	Treadmill exercise, maximal, Bruce protocol	Exercise duration

VAS, visual analogue scale.

obtained for activities carried out by participants with effort below maximum possible strain, within an allotted time for the exercise (number of stairs climbed, distance walked). The instruments are described in *Table 22*. *Table 23* shows the results from trials.

A meta-analysis was conducted for results reported in all trials. Dual-chamber pacing was associated with a standardised mean improvement in exercise performance of 0.35 (95% CI 0.17 to 0.52, $p < 0.0001$) (*Figure 15*).

However, some (non-statistically significant) heterogeneity was found across studies ($p = 0.16$). An exploration of the possible sources of variation was conducted, with stratification by pacing mode, age of recipients and outcome measure used.

TABLE 23 *Exercise capacity: cross-over studies of dual-chamber versus ventricular pacemakers*

	6-Minute test		Stair climbing		Bicycle ergometer		Chair stand-up		Treadmill		Perceived exercise capacity	
	Dual chamber	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**
Avery, 1994[58]	360 ± 65	327 ± 69	127 ± 65	132 ± 56								
Capucci, 1993[59]					DDDR 12.6 ± 3.1 DDD 11 ± 2.9	11 ± 2.9						
Channon, 1994[60]	18.7 (SE 3.95)	16.43 (SE 5.68)	16.18 (SE 3.7)	13.71 (SE 3.45)			35.29 (SE 11)	28.9 (SE 15.7)			Borg score 37 ± 6	Borg score 42 ± 7
Davis, 1985[61]									8.4 ± 3	7.2 ± 3		
Deharo, 1996[62]									Workload 59.3 ± 37.8 Duration 10.1 ± 3.6	Workload 60 ± 33.4 Duration 10.1 ± 3.8		
Hargreaves, 1995[63]	VVI 20 (SE 1), VVIR 20 (SE 1)	VVI 18 (SE 2), VVIR 20 (SE 1)	VVI 14 minutes (SE 1), VVIR 14 minutes (SE 1)	VVI 15 minutes (SE 1), VVIR 15 minutes (SE 1)			VVI 44 (SE 5), VVIR 44 (SE 5)	VVI 36 (SE 4), VVIR 43 (SE 6)			Borg score VVI 34 (SE 2), VVIR 34 (SE 2)	Borg score VVI 37 (SE 1), VVIR 37 (SE 1)
Jordaens, 1988[50]					6.2 ± 2.3	5.5 ± 2.6						
Kamalvand, 1997[64]									128 ± 20	116 ± 21	VAS 56 ± 27%	VAS 43 ± 26% $p = 0.08$
Kenny, 1986[65] (D_{100} mode)					DDD_{100} 2312 (SE 1035) DDD_{150} 1194 (SE 1178)	2246 (SE 1321)						
Kristensson, 1985[66]					Workload 100 ± 30 W	Workload 88 ± 28 W $p < 0.01$					Borg score 18.9 (SE 0.9)	Borg score 16.6 (SE 2.8), $p < 0.01$
Linde-Edelstam, 1992[67]									10.1 ± 5.5 ns; leg fatigue no difference	10.5/4.7		
Menozzi, 1990[68]					70 ± 18 W per minute	68 ± 15 W per minute						
Mitsuoka, 1988[69]					681 (SE 363) W	659 (SE 353) W						
Oldroyd, 1991[70]									489 (SE 31)	477 (SE 32)		
Perrins, 1983[71]					VDD 3250 ± 1676 (SE kpm)	2542 ± 1269 (SE kpm)						

continued

TABLE 23 *Exercise capacity: cross-over studies of dual-chamber versus ventricular pacemakers (cont'd)*

	6-Minute test		Stair climbing		Bicycle ergometer		Chair stand-up		Treadmill		Perceived exercise capacity	
	Dual chamber	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**	**Dual chamber**	**Ventricular**
Saner, 1996[73]									DDD 935 ± 387 s, DDDR 1087 ± 383s	VVIR 753 ± 349 s, $p = 0.001$	VAS DDD 81 ± 16%, DDDR 88 ± 12%	VAS 58 ± 25% $p = 0.008$
Sulke, 1991[74]									DDIR 10.15 ± 3.4, DDD 10 ± 3.2, DDDR 11.3 ± 3.4, $p < 0.01$	10.2 ± 3.6	VAS (all dual) 70.1 ± 15.4%	VAS 47.9 ± 23.8%
Sulke, 1992[75]									DDD 10.9 ± 1 minutes, DDI 9.5 ± 1.1 minutes	9 ± 1.2 minutes	VAS DDD 4.6% (SE 0.2%), DDI 4.3% (SE 0.4%), ns	VAS 3.9 % (SE 0.4%)
Sulke, 1994[76]											VAS 85.8 ± 12.2%	VAS 49.9 ±23.7%
Yee, 1984[77]									6.9 ± 3.1	5.3 ± 2.9, ns		
Rediker, 1988[72]	Exercise duration (SE instrument not specified) DDD 2.2 ± 1.2 minutes, VVI 0.6 ± 1.4 minutes, $p = 0.03$											

ns, not significant.

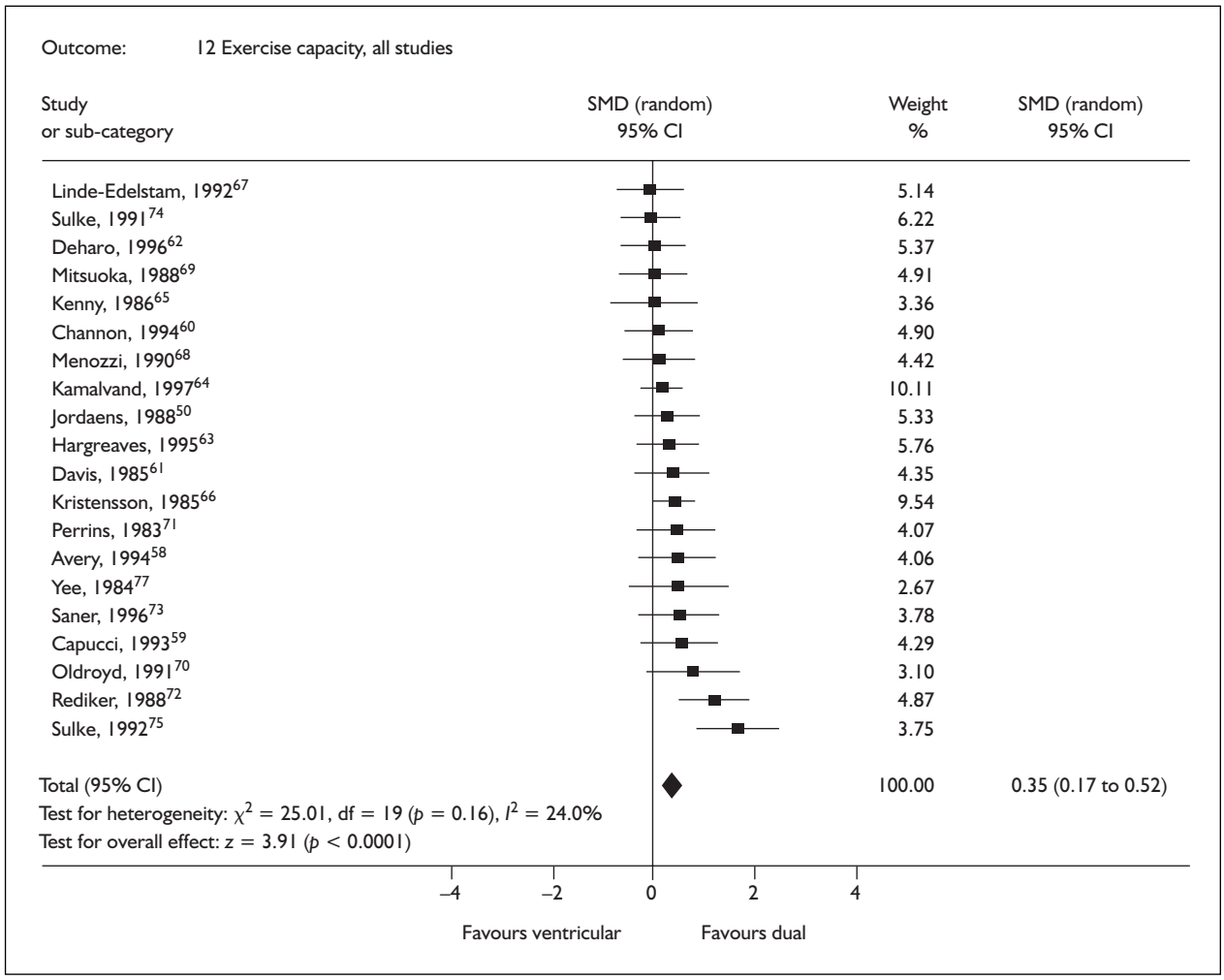


FIGURE 15 *Meta-analysis of exercise capacity: cross-over trials*

There were variations in the type of ventricular pacing mode (seven studies included rate response[62,63,67,68,70,73,76]) and in the type of dual-chamber pacing mode considered, with four studies of rate-modulated dual-chamber[59,64,73,74] and four of VDD pacemakers.[61,66,71,77] Three studies[63,73,74] compared ventricular pacing to two dual-chamber modes and were included in more than one group.

The overall effect was driven by the inclusion of non-rate-modulated pacemakers, with significant gains in dual-chamber pacing compared with VVI pacing (0.49, 95% CI 0.10 to 0.89, $p = 0.01$). However, this was the only group where significant heterogeneity remained after stratification ($p = 0.02$). No benefit was apparent from the comparison of dual-chamber pacing to VVIR (+0.11, 95% CI –0.15 to 0.37, $p = 0.41$). In addition, there was a significant benefit for recipients of VDD pacemakers (+0.42, 95% CI 0.11 to 0.74, $p = 0.009$) and for DDDR (0.33, 95% CI 0.04 to 0.61, $p = 0.02$) compared with VVI (*Figure 16*).

There was wide variation in age, with the mean age of recipients between 52 and 82 years. Seven studies included participants with mean age older than 75 years.[50,58,60,62,63,65,68]

Exercise tolerance was significantly improved in younger patients (0.45, 95% CI 0.15 to 0.72, $p = 0.001$), but significant heterogeneity remained in this group of studies ($p = 0.03$) (*Figure 17*).

For outcome measures used, differences were found in the use of tests by age, with the 6-minute walking test being used in studies with elderly participants (79 years or more).[58,60,63] The treadmill test was equally used in studies with participants of younger and intermediate ages, and the bicycle ergometer was predominantly used in studies with individuals older than 65 years. The use of the bicycle or treadmill test was not associated with differences in

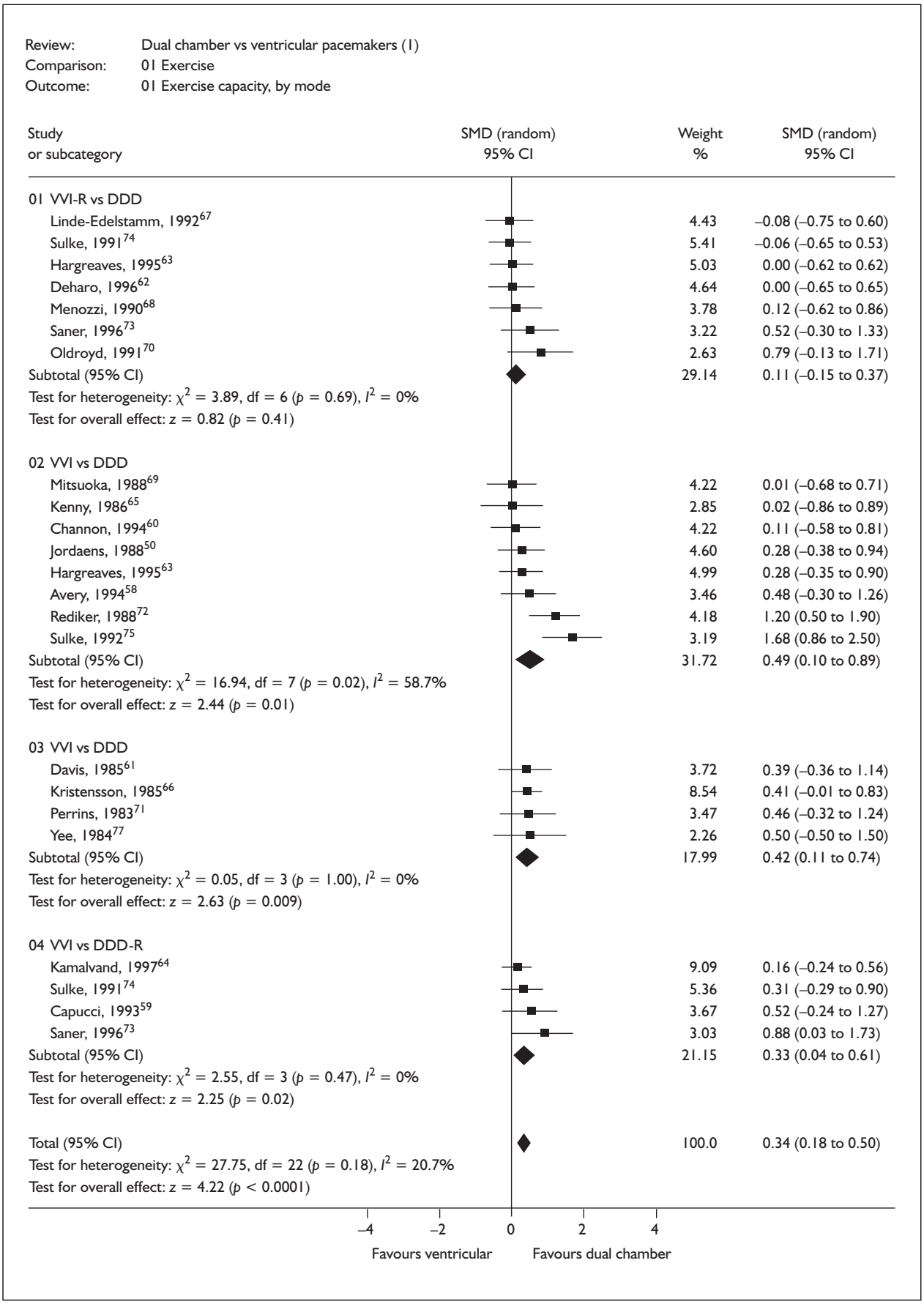


FIGURE 16 *Meta-analysis of exercise capacity stratified by pacemaker type: cross-over trials*

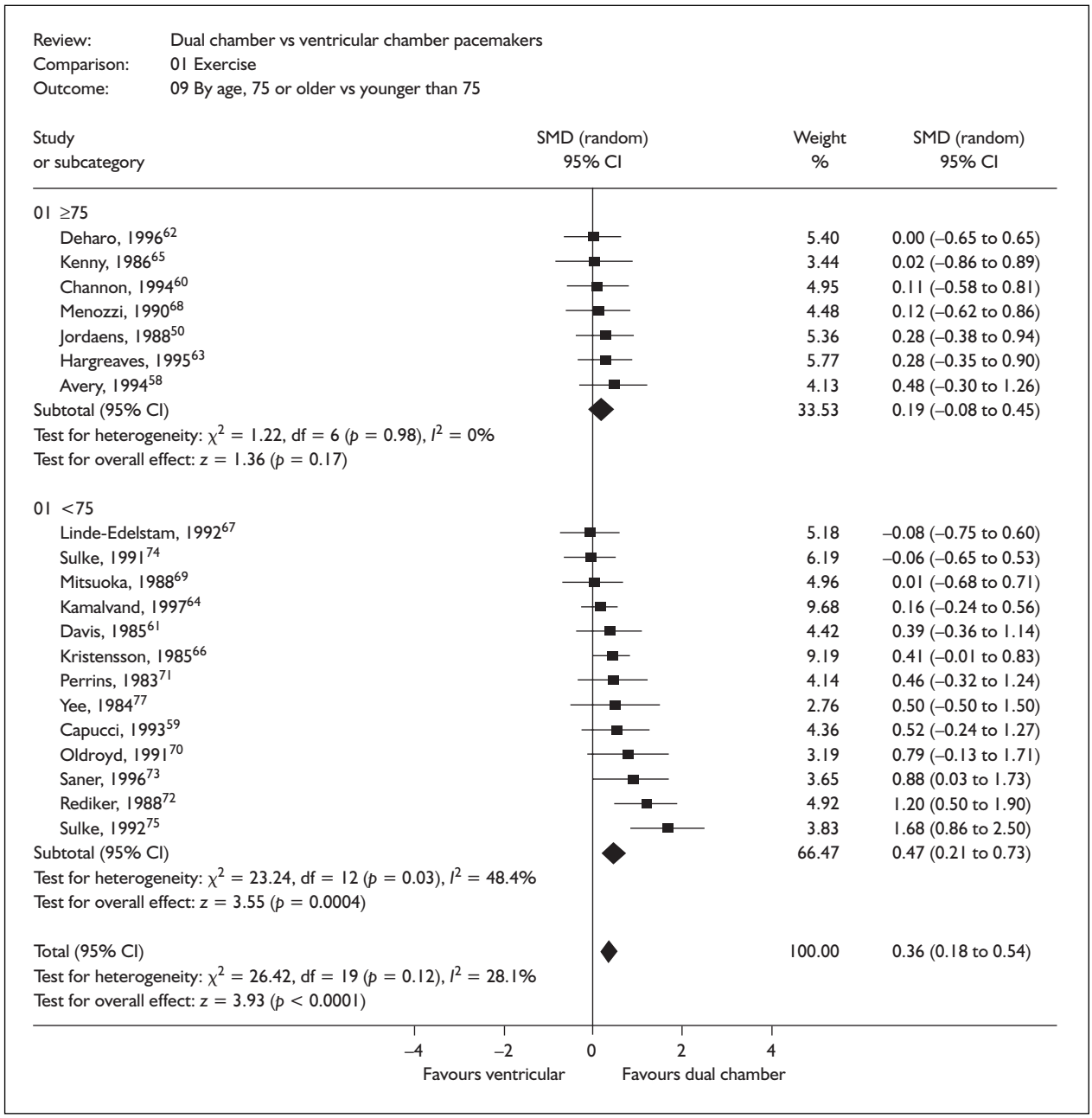


FIGURE 17 *Meta-analysis of exercise capacity stratified by age: cross-over trials*

reporting benefits, and with both instruments a benefit was found for dual-chamber pacemakers. Conversely, studies that used the 6-minute walking test reported no additional benefit for dual-chamber pacing. In conclusion, the use of different exercise performance tests between elderly and younger participants may introduce a source of confounding, with the possibility that elderly individuals may be unlikely or fail to use the potential additional effort capacity made available by dual-chamber in comparison to ventricular pacing.

In six studies participants were asked to rate their perceived effort or resistance on a graded scale (Borg score) or visual analogue scale (VAS). There was a significant increase in perceived exercise capacity with dual-chamber pacing, with evidence of increased benefit occurring in younger and older ages alike (*Figure 18*).

Overall, dual-chamber pacing was associated with better exercise performance. However, this conclusion is not robust, since there were several sources of heterogeneity. There were some

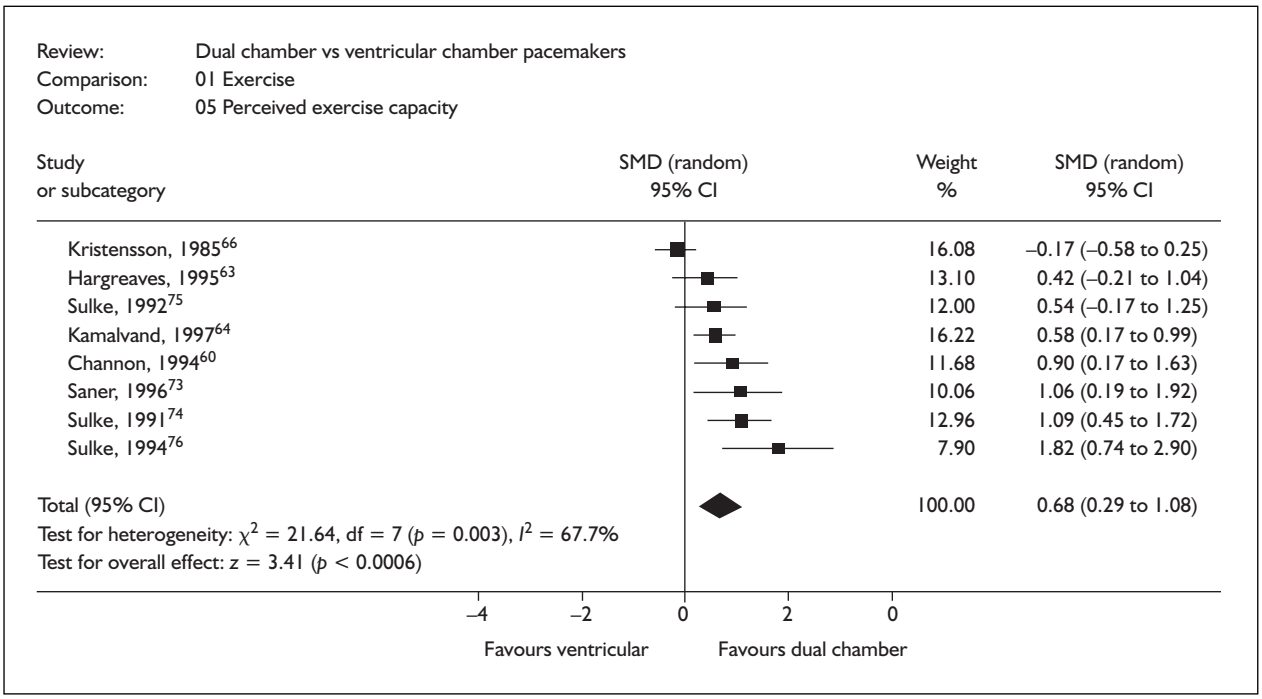


FIGURE 18 *Meta-analysis of perceived exercise capacity: cross-over trials*

TABLE 24 *Assessment of functional class, SAS scores, dual-chamber versus ventricular pacemakers*

	SAS scores (SD)		
Study	**DDD**	**VVI**	***p*-Value**
Deharo, 1996[62]	1.3 (0.46)	1.3 (0.46)	ns
Kamalvand, 1997[64]	2.2 (1.9)	2.5 (1)	0.05
Lau, 1994[79]	1.5 (0.3)	1.5 (0.2)	ns
Lau, 1994,[78]	1.8 (0.1)	1.7 (2)	?
Rediker, 1988[72]	1.6 (0.7)	1.8 (0.9)	ns
Sulke, 1991[74]	1.3 (0.54)	1.73 (0.63)	<0.05
Sulke, 1992[75]	Data are not presented separately		ns
Sulke, 1994[76]	1.2	1.6	ns
MOST[48]	2.1 (SD not stated)	2.17 (SD not stated)	ns
PASE[35]	1.375 (1.479)	1.376 (1.473)	ns
CTOPP[52]	2.3 (1.16)	2.2 (1.17)	ns

Higher score = worse status.

indications that this may be due to rate responsiveness, suggesting that chronotropic incompetence may be an important factor in this comparison. However, this factor was insufficiently reported in the trials.

Finally, it is unclear whether improved exercise capacity contributes to improved well-being.

Functional status

Functional status was studied in eight cross-over trials and three parallel trials (MOST, PASE and CTOPP). These studies included an assessment of functional class with the SAS[90] (*Table 24*), described in Chapter 2 (section 'Impact: disability and quality of life', p. 5).

In a meta-analysis of these studies (*Figure 19*) there were no significant improvements in functional class associated with dual-chamber pacing (–0.04, 95% CI –0.18 to 0.09, $p = 0.53$) (*Figure 19*). These results were largely driven by the larger parallel trials. The pooled analysis did not incorporate results from MOST as no estimate of the standard

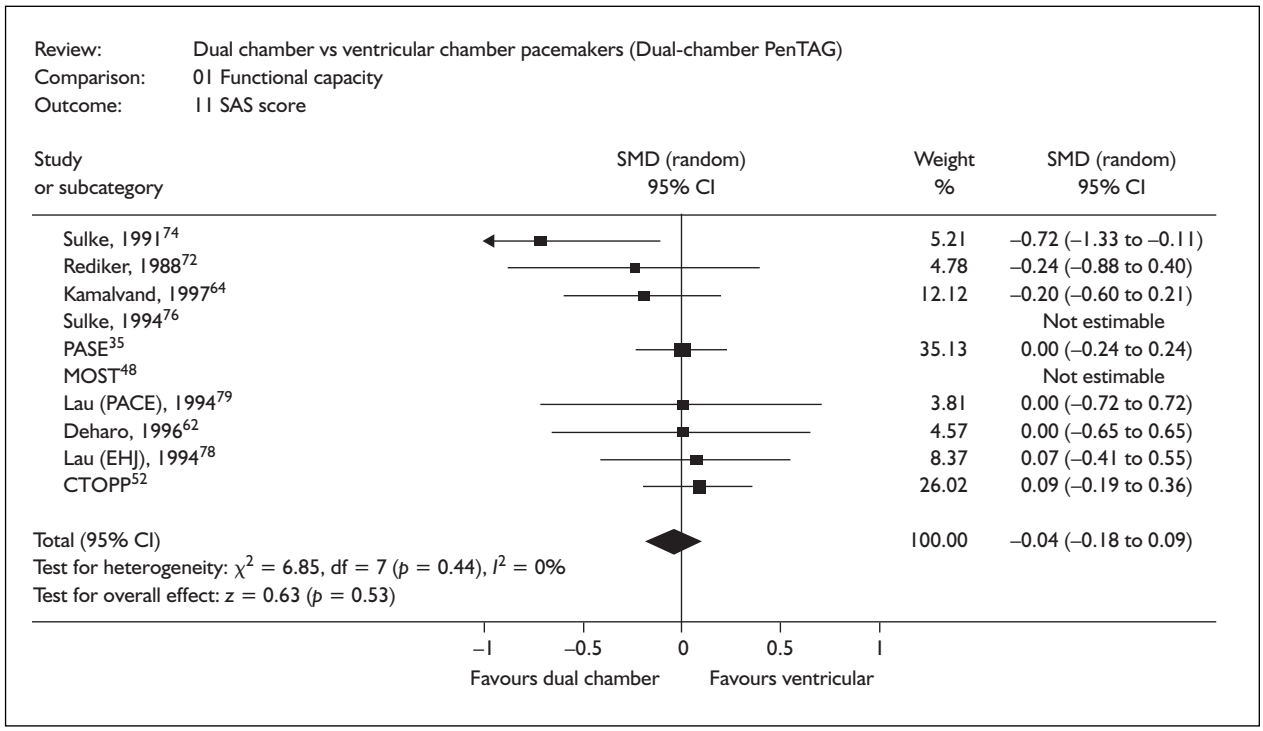


FIGURE 19 *Meta-analysis of SAS scores: cross-over trials*

deviation was available. However, this is unlikely to change overall results since the SAS scores in MOST were equal for the two pacing modes.

Quality of life

Quality of life was studied in three RCTs (MOST, PASE and CTOPP) and in 13 cross-over studies.

Twelve studies used a single global measure of general well-being.

Nine studies reported measures of quality of life obtained from multidimensional quality of life questionnaires. The resulting picture is difficult to summarise, both because of the use of disparate and non-comparable and non-validated instruments, and also owing to the use of questionnaires that included symptom scores, with substantial overlap with other outcomes assessed in this report.

QOL assessed using single global questions

General well-being was measured in 12 cross-over studies. Seven studies used a VAS. The recipient was asked to indicate a measure of current well-being as a point on a line between 0 (worst health) and 1 (best health).

Three studies used categorical measures of well-being[68] or change in well-being.[69,71] Deharo and colleagues[62] used "recipients' comments" to evaluate well-being. One study[72] did not report the measure used. The results for general well-being scores are summarised in *Table 25*.

Meta-analysis (*Figure 20*) shows a significant improvement in quality of life associated with dual chamber pacing: on average by 1.56 SD units ($p < 0.001$). However, the pooled analysis did not include all studies, since three[62,68,81] did not report the mean or standard deviation for this particular outcome. More importantly, significant heterogeneity was found across studies. The meta-analysis was explored by stratification by pacemaker mode (*Figure 21*). Significant heterogeneity remained in the analysis of the largest group of trials. The cross-over trials therefore show a consistent direction of effect on quality of life, but a summary measure of the size of this effect cannot be estimated with confidence.

Multidimensional measures of quality of life

Parallel group

Three RCTs (MOST, PASE and CTOPP) measured quality of life using the SF-36, a generic measure. Results were calculated as differences between mean scores reported for each pacing mode group (*Table 26*). Two comparisons were provided, between baseline and follow-up (benefit of pacing) and between types of pacemakers (benefit of dual-chamber pacing).

TABLE 25 *General well-being*

Study	Instrument	Results
Boon, 1987[81]	VAS, 10 cm	DDD median 96%, (IQR 84.5–100%), VVI median 71.70%, (IQR 55–90%)
Deharo, 1996[62]	Recipients' comments	No difference noted in general well-being, data not reported
Kamalvand, 1997[64]	VAS, 15 cm	DDDR with mode switching 69 ± 21%, DDDR 60 ± 25%, VR 51 ± 27%, $p < 0.02$
Lau, 1994[78]	VAS, 10 cm	DDDR: 71.3 ± 6.3, VVIR 50.2 ± 10.2
Menozzi, 1990[68]	Subjective score 1 fine, 2 fair, 3 poor, 4 bad	DDD 1.57, VVIR 2.36 (SD not stated), $p = 0.02$
Mitsuoka, 1988[69]	Subjective score: 1 much worse, 2 little worse, 3 no change, 4 little improved, 5 much improved	DDD 3.38 ± 0.78, VVI 2.06 ± 0.66
Perrins, 1983[71]	Subjective score: 1 much worse, 2 little worse, 3 no change, 4 little improved, 5 much improved	VDD 3.54 ± 0.8, VVI 1.72 ± 0.6
Rediker, 1988[72]	Undefined	Dual chamber 48 ± 8, ventricular 52 ± 5, $p = 0.01$
Saner, 1996[73]	VAS, 10 cm	VVIR 62 ± 29%, DDD 88 ± 12%, DDDR 88 ± 12%, $p = 0.02$ (DDD vs DDDR ns)
Sulke, 1991[74]	VAS, 10 cm	VVIR 46.3 ± 23.1%, dual, all 70.3 ± 14.7%, $p < 0.001$
Sulke, 1992[75]	VAS, 10 cm	DDD 91 ± 2.2%, VVI 71 ± 3.5, $p < 0.01$
Sulke, 1994[76]	VAS, 10 cm	DDDR 84.6 ± 10.7%, VVIR 52.5 ± 26.1%, $p < 0.05$

IQR, interquartile range.

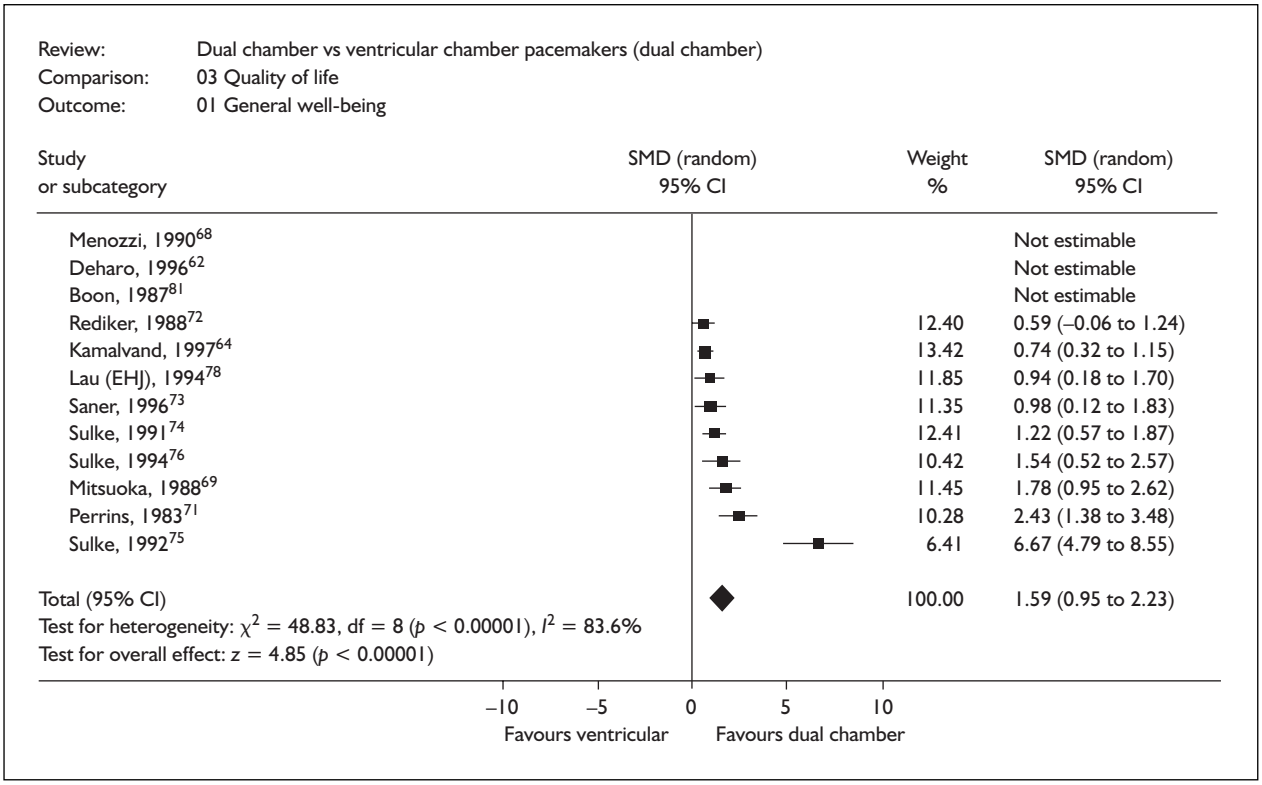


FIGURE 20 *Meta-analysis of general well-being: cross-over trials*

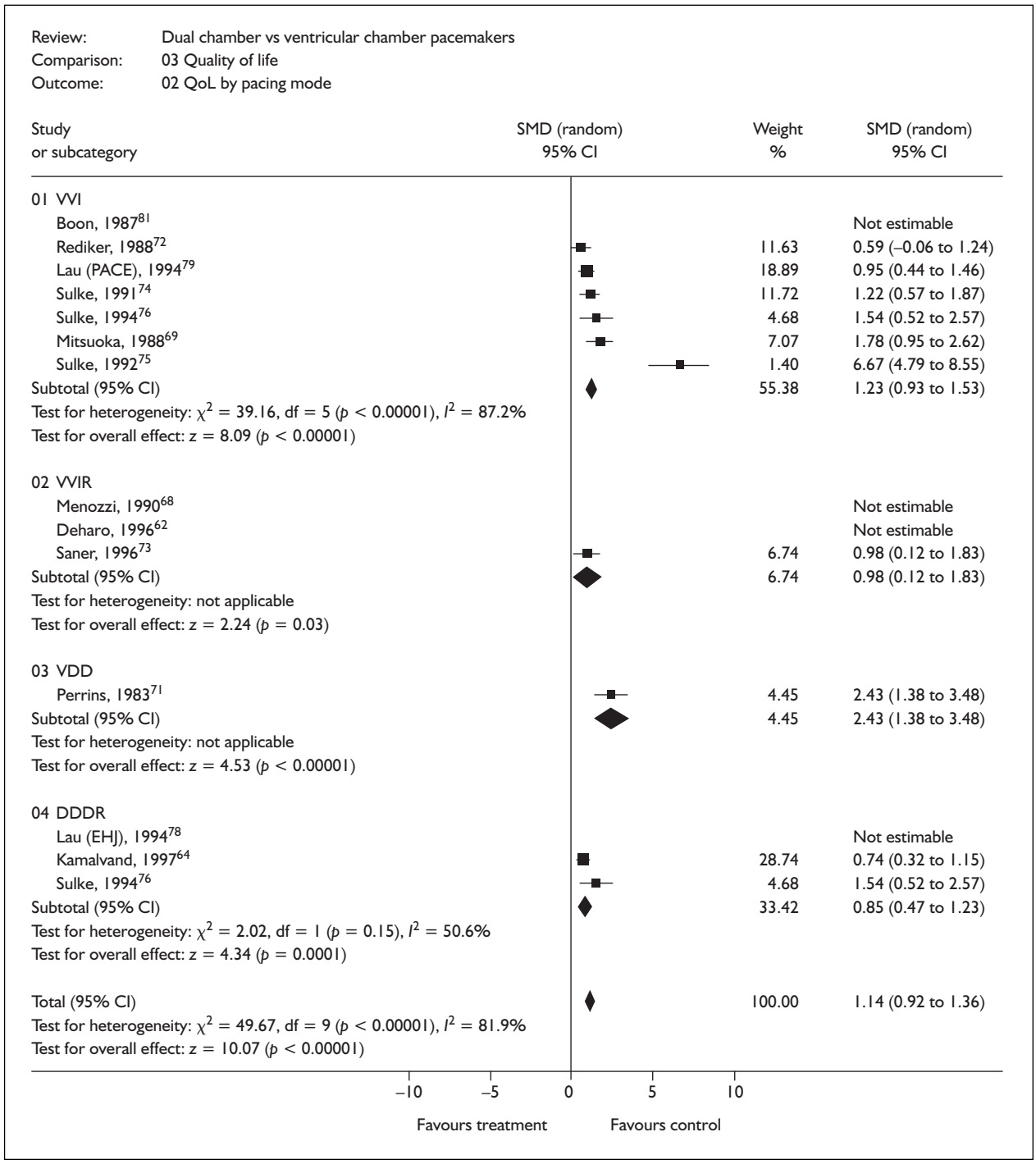


FIGURE 21 *Meta-analysis of quality of life stratified by pacing mode: cross-over trials*

All trials showed significant improvement of quality of life over baseline in both arms (i.e. pacing of any type improved quality of life).

The comparison between pacing modes showed significantly better results for dual-chamber pacing in MOST only (*Table 27*) Advantages were reported in physical function, physical role, social function, energy and emotional role. Three scores (mental health, pain and general health) were not significantly different. Summary scores for the mental and physical components were both significantly better with dual-chamber. It should be emphasised that these scores were calculated with LOCF for individuals who were reprogrammed from ventricular to dual pacemakers, that is, quality of life was evaluated before reprogramming and imputed as the score for the remaining follow-up. The authors report no difference in scores between dual-chamber and ventricular pacing if

TABLE 26 *Changes in quality of life scores between baseline and latest follow-up, SF-36, RCTs*

	Ventricular			Dual chamber		
Differences between baseline and follow-up	**CTOPP[a]**	**MOST[b]**	**PASE[c]**	**CTOPP**	**MOST**	**PASE**
Physical function	7	–3.2	5.5	5	–0.1	4
Physical role	28	18	20.3	27	26.7	19.2
Social function	20	6.4	6.7	17	9.8	6.5
Energy	11	3.6	6.2	10	5.2	7.8
Mental health	2	4.7	0	6	4.6	4.6
Emotional role	11	4.8	5.5	17	12.3	13.4
Pain	11	6.9	0.9	8	5.1	4.5
General health	1	–3.5	–2	–2	–2.5	–4.1

[a] All differences were significant ($p < 0.05$), with the exception of general health, and of physical function for dual chamber only.
[b] Significant differences for social function, physical role, emotional role, mental health and energy, ($p < 0.001$).
[c] All differences were significant ($p < 0.05$), with the exception of health score.

TABLE 27 *Differences in quality of life scores between dual-chamber and ventricular pacing at latest follow-up, SF-36, RCTs*

	CTOPP[a]	**PASE[a]**	**MOST**
	Month 6	Month 18	Month 48
Physical function	–2	–1.5	+ 1.9, $p = 0.04$
Physical role	–1	–0.2	+ 8.6, $p < 0.01$
Social function	–1	–1.1	+ 2.5, $p < 0.01$
Energy	6	7.9	+ 4.1, $p < 0.01$
Mental health	+4	4.6	+ 1.2, $p = 0.05$
Emotional role	–3	1.6	+ 3.6, $p < 0.01$
Pain	–3	3.6	+ 0.5, $p = 0.57$
General health	–3	–2.1	+ 1.1, $p = 0.09$
Mental component summary			+ 1.1, $p < 0.01$
Physical component summary			+ 1.2, p <0.01

[a] All scores are non-significant.

actual quality of life scores after reprogramming were included. This suggests that quality of life reaches a low before reprogramming and improves after reprogramming. As a consequence, the use of LOCF may bias the difference in measures of quality of life in favour of dual chamber.

PASE reports that differences became significant during follow-up for mental health at month 9 ($p = 0.03$) and in the shorter term, for social function, physical role, emotional role, mental health and energy (all $p < 0.001$). However, these benefits were transient, and for this reason, the finding may have been in association with pacemaker syndrome, since this was shown to occur early in this trial.

In contrast, CTOPP did not show differences in quality of life between pacing modes on any dimension of the SF-36.

In CTOPP, quality of life was also analysed by subgroups: (a) pacemaker dependency and (b) assignment to rate-modulated device. Quality of life was not significantly different by pacing mode for individuals who were dependent on pacing (with underlying heart rate <60 bpm), nor was a difference in quality of life reported when results for individuals with rate-modulated pacing only were analysed.

In addition to the SF-36, CTOPP measured quality of life with two other instruments, the SF-6, a reduced version of the SF-36, and the QLAP questionnaire.

Scores for the QLAP questionnaire were significantly better at month 6 for activity, physical and social score, and for the total summary score, with no differences reported for the psychological score.

The SF-6 questionnaire includes six items on general health, activity limitation, difficulty with work, emotional problems, social activity and bodily pain. Significant improvement was reported only in general health at month 6. Scores were also analysed by age (younger or older than 70 years). Younger recipients reported a small benefit from dual-chamber pacing (0.2 SD units) in activity, general health and work difficulty. An interaction test was performed, with no significant benefits associated with age in combination with pacemaker dependency.

In summary, transient improvements in quality of life were reported in MOST and in PASE, limited to some outcomes. In CTOPP, some benefit was apparent when the SF-6 and QLAP questionnaires were used, but not with the SF-36.

Although apparent differences in results are reported, these findings have some common features. In relation to the duration of the trials, it is possible that differences may have emerged at the time when pacemaker syndrome occurred. In PASE, there was evidence of this effect in the short term, but benefits disappeared with reprogramming. MOST showed better quality of life with dual-chamber pacing when scores calculated at reprogramming (i.e. when pacemaker syndrome occurred) were carried over. However, since this effect disappeared when ITT analysis was carried out, it can be concluded that improvements in quality of life were transient, as in PASE. In CTOPP, reprogramming was relatively rare. Finally, in relation to the instrument used it is possible that the SF-36 was inadequate to detect changes in benefits. However, improvements found with other disease-specific validated questionnaires were limited to some outcomes and in the short term, with no longer term benefit reported.

[CiC removed – information on the quality of life measures in the UKPACE trial.]

Cross-over trials

Five cross-over trials used multidimensional questionnaires of quality of life. Significant results are summarised in this section (*Table 28*), with comparisons between studies that used the same instruments.

Two trials, by Linde-Edelstam and colleagues[82] and Hoijer and colleagues,[49] used the Karolinska questionnaire (see section 'Impact: disability and quality of life', p. 5). These studies reported significant improvements for dual-chamber pacing in breathlessness. In addition, the trial by Linde-Edelstam and colleagues[82] reported benefits in chest pain, dizziness, memory and palpitations. Hoijer and colleagues reported significant improvements for mood in relation to activity.[49]

The trials by Lau and colleagues[78,79] used an instrument adapted from the Bradford Somatic Inventory. Lau and colleagues[78] reported improvements with DDDR compared with VVIR for dyspnoea, temperature intolerance, epigastric pain and palpitations. No significant differences were found between DDD and VVIR. The second trial[79] considered DDDR only and reported significant differences for a range of social interactions.

Lau and colleagues[78] also used a 12-item general health questionnaire, which showed no differences in scores for DDDR compared with VVIR.

Lau and colleagues[79] measured quality of life using the Illness Perception Score and a 48-item generic quality of life measure. Significant improvements detected by the first questionnaire were associated with DDDR only: volition, diet, concentration and work. Differences in contentment were found only between DDD and VVIR. On the generic quality of life questionnaire, the benefits of dual-chamber pacing were significant for stress, mobility, illness impact and worries, and for the total score.

The study by Lukl and colleagues[83] used a 19-item generic quality of life score, and reported improvements on dual-chamber mode for breathlessness during exertion, dizziness, fatigue, overexertion, palpitations and sweating. The study also reported benefits for dual-chamber pacing in subgroups defined by chronotropic incompetence and underlying diagnosis (SSS or heart block). Significant advantages were reported for dual-chamber pacing compared with VVIR for individuals within each group considered separately.

Pacemaker syndrome

This section reports the occurrence of pacemaker syndrome in individuals implanted or programmed in ventricular mode. It is assumed that symptomatic intolerance to pacing did not occur in any of the participants with dual-chamber pacemakers.

Pacemaker syndrome has been described as including a wide range of symptoms of mild heart failure (*Table 29*). It has been suggested that pacemaker syndrome may be equated to 'intolerance to ventricular pacing' and therefore

TABLE 28 *Quality of life scores, cross-over trials*

Study	Results, items showing significant improvement (dual chamber)	Results, items showing no difference between dual-chamber and ventricular pacing
Hoijer, 2002[49]	Karolinska questionnaire: dyspnoea, mood (active/deactivated)	
Linde-Edelstam, 1992[82]	Karolinska questionnaire: breathlessness ($p = 0.02$), dizziness ($p = 0.04$), memory ($p < 0.001$), palpitations ($p = 0.03$)	Karolinska questionnaire: activity, alertness, calmness, chest pain, concentration, decision making, depressive score, physical ability, pleasantness, self-perceived health A, self-perceived health B, sleep, social participation
Lau, 1994[78]	Bradford Somatic Inventory: social interaction, range $p < 0.02$	General Health Questionnaire, 12 items: total score Bradford Somatic Inventory: total score, activities of daily living, emotional adjustment, social Interactions, frequency, social interaction, quality, work adjustment, sleep, fatigue, appetite
Lau, 1994[79]	Physical malaise score (41 items, from Bradford Somatic Inventory): 4/41 scores, only for DDDR: dyspnoea ($p < 0.01$), temperature intolerance ($p < 0.01$), epigastric pain ($p < 0.05$), palpitations ($p < 0.01$) Illness perception score (43 items): diet ($p < 0.01$), volition ($p < 0.01$), concentration ($p < 0.05$), work ($p < 0.05$), contentment (DDD vs VVIR $p < 0.05$) QoL (48 items): total score ($p < 0.003$), stress ($p < 0.018$), mobility ($p < 0.01$), illness impact ($p < 0.05$), worries ($p < 0.002$)	No significant differences between DDD and VVIR
Lukl, 1994[83]	QoL (19 items): breathlessness during exertion ($p < 0.02$), dizziness ($p < 0.05$), fatigue ($p < 0.02$), overexertion ($p < 0.01$), palpitations ($p < 0.05$), sweating ($p < 0.05$) Chronotropic incompetence ($n = 9$): VVI 16.56/32/17.75; without chronotropic incompetence: 23.5/15.8 vs 36.92/17–69 ($p < 0.05$) SSS: $n = 8$ 23.25/12.16 vs 36.25/14.68 ($p < 0.05$) CHB: 18.85/16.67 vs 33.92/19.47 ($p < 0.01$)	Breathlessness, oedema, memory, sleep, tightness in chest
Saner, 1996[73]	Emotional well-being	

any symptoms associated with the haemodynamics of pacing may be attributed to pacemaker syndrome. It may not be possible to classify the symptoms of pacemaker syndrome into a precise diagnostic entity.

This difficulty is reflected in the variation in items included in the definition of the syndrome, with symptoms of dyspnoea, dizziness, palpitations, pulsations and chest pain included in the majority of scoring systems. However, other symptoms may also be included (*Table 30*). These scores have been included in meta-analysis, showing a significant effectiveness of dual-chamber pacing in reducing symptoms associated with intolerance to pacing. This suggests that reduction of symptoms is achieved with reprogramming.

The incidence of pacemaker syndrome was reported in two parallel trials, MOST (182/996,

TABLE 29 *Instruments for measuring symptoms and pacemaker syndrome*

Study	Instrument
Avery, 1994[58]	Minnesota Living with Heart Failure. 11 questions and ability to perform activities of daily living. Scores 0–5: 0 no effect on performance, 5 very much affects performance. Total score 55
Boon, 1987[81]	VAS 10 cm. Results expressed as median and IQR
Capucci, 1993[59]	Partial scores 1–5, for either symptom frequency or degree of discomfort (highest score for worst). Total score: sum of partial scores
Channon, 1994[60]	Severity of each symptom graded 0–5: 0 not at all, 1 very mild, 2 mild, 3 moderate, 4 quite severe, 5 very severe. Max. score 75. Symptoms in bold are included in Pacemaker syndrome subscore
Davis, 1985[61]	Total number of episodes
Deharo, 1996[62]	Frequency of symptoms expressed in scores 0–3: 0 no symptoms, 1 rare symptoms, 2 frequent, 3 very frequent
Hargreaves, 1995[63]	Severity of each symptom graded 0–5: 0 not at all, 1 very mild, 2 mild, 3 moderate, 4 quite severe, 5 very severe. Max. score 75.
Heldman, 1990[34]	Each symptom graded 0–10: 0 absent, 10 very severe. Grading of change: mild (total <16, with no difference in symptoms >5), moderate (increase in range from 17 to 32, with no score >8) or severe (total symptom score >32, or at least one score >8, or early request for reprogramming)
Hoijer, 2002[49]	Karolinska questionnaire, subscores
Kamalvand, 1997[64]	Specific Symptoms prevalence questionnaire (11 symptoms, scores 1–5: min. score 0, max. 84). Scores >25 indicate possible pacemaker syndrome
Kenny, 1986[65]	Daily frequency of symptoms and change between period 1 and 2: scores 1–5: 1 much worse, 2 little worse, 3 no change, 4 little improved, 5 much improved
Kristensson, 1985[66]	VAS 1–10, areas on the VAS are marked 0 no symptoms, 1–3 slight, 4–6 moderate, 7–9 severe, 10 extreme
Lau, 1994[78]	Incidence and frequency of symptoms. Specific Symptoms prevalence questionnaire (11 symptoms, scores 1–5: 1 all the time, 2 most of the time, 3 some of the time, 4 occasionally, 5 never). Scores are weighted and summed, min. score 0, max. 84. Scores >25 indicate possible pacemaker syndrome
Menozzi, 1990[68]	Frequency of symptoms, 0 no symptoms, 1–3 slight/occasional, 2 slight/frequent, 3 severe/occasional, 4 severe/frequent, 5 severe/nearly persistent
Mitsuoka, 1988[69]	Diary of frequency of symptoms, subjective score at the end of each month, with scores 1 much worse, 2 little worse, 3 no change, 4 little improved, 5 much improved. No summary score calculated
Oldroyd, 1991[70]	VAS 100 mm for each symptom, with total score = sum of scores. MacMaster questionnaire
Perrins, 1983[71]	Diary of frequency of symptoms, subjective score at the end of each month: 1 much worse, 2 little worse, 3 no change, 4 little improved, 5 much improved. No summary score calculated. It is unclear whether scores are reported only for shortness of breath
Saner, 1996[73]	Incidence and frequency of symptoms, total number of symptoms indicated
Sulke, 1991[74]	Specific Symptoms prevalence questionnaire (11 symptoms, scores 1–5: 1 all the time, 2 most of the time, 3 some of the time, 4 occasionally, 5 never). Scores are weighted and summed, min. score 0, max. 84. Scores >25 indicate possible pacemaker syndrome
Sulke, 1992[75]	Specific Symptoms prevalence questionnaire (11 symptoms, scores 1–5: 1 all the time, 2 most of the time, 3 some of the time, 4 occasionally, 5 never). Scores are weighted and summed, min. score 0, max. 84. Scores >25 indicate possible pacemaker syndrome
Sulke, 1994[76]	Specific Symptoms prevalence questionnaire (11 symptoms, scores 1–5: 1 all the time, 2 most of the time, 3 some of the time, 4 occasionally, 5 never). Scores are weighted and summed, min. score 0, max. 84. Scores >25 indicate possible pacemaker syndrome
Yee, 1984[77]	Presence and frequency of symptoms: 0 severe limitations, 60 absence of symptoms/limitations in function. No structured instrument was used. Individuals were asked to indicate differences in well-being between pacing modes. There is unclarity as to whether the instrument measures symptoms in combination with functional capacity

TABLE 30 *Symptoms and pacemaker syndrome measurement, cross-over studies*

Study	**Breathlessness**	**Pulsations**	**Dizziness**	**Blackout**	**Wheeze**	**Fatigue**	**Palpitations**	**Cough**	**Fainting**	**Headache**	**Blurred vision**	**Chest pain**	**Diarrhoea**	**Vomiting**	**Apprehension/mood disturbance**	**Leg cramps**	**Memory**	**Cough**	**Light-headedness**	**Dysuria**	**Concentration**	**Orthopnoea**	**Choking**	**Confusion**	**Lower limb oedema**	**Tachycardia**	**Chest congestion**	**Diaphoresis**	**Disturbed sleep**	**Fluttering eyes**	**Syncope**
Avery, 1994[58]	Minnesota Living with Heart Failure score																														
Boon, 1987[81]	×		×			×								×																	
Capucci, 1993[59]	×	×	×				×		×			×																			
Channon, 1994[60]	**×**	**×**	**×**	**×**	**×**	**×**			×		×	×	×	×	×		×		×												
Davis, 1985[61]	×	×	×				×				×	×															×		×		
Deharo, 1996[62]		×	×				×					×																	×		
Hargreaves, 1995[63]	**×**	**×**	**×**	**×**	**×**	**×**	**×**	**×**		×		×	×	×	×	×		×		×											
Heldman, 1990[34]	×	×	×			×	×	×		×		×			×			×				×	×	×	×	×	×	×			
Hoijer, 2002[49]	×		×				×					×																			
Kamalvand, 1997[64]	×	×	×			×	×	×									×		×		×	×			×						
Kenny, 1986[65]			×				×					×																			
Kristensson, 1985[66]	×	×	×				×					×																		×	×
Lau, 1994,[78]	×	×	×				×					×																			
Menozzi, 1990[68]	×	×	×				×					×																			
Mitsuoka, 1988[69]	×		×				×					×																			
Oldroyd, 1991[70]	×					×									×																
Perrins, 1983[71]	×		×				×					×																			×
Saner, 1996[73]	×		×				×				×																				
Sulke, 1991[74]	×	×	×			×	×	×									×		×		×	×			×						
Sulke, 1992[75]	×	×	×			×	×	×									×		×		×	×			×						
Sulke, 1994[76]	×	×	×			×	×	×									×		×		×	×			×						
Yee, 1984[77]	×											×[a]							×												

[a] Includes symptoms of angina.
Symptoms indicated in bold are included in the Pacemaker syndrome definition used in the paper, when separate scores are computed.

18.3%) and PASE (53/203, 26.1%). CTOPP reports that 63/1474 (4.3%) participants randomised to ventricular pacing subsequently had a dual-chamber pacemaker implanted, although pacemaker syndrome is not specifically reported. *[CiC removed – proportion of pacemaker syndrome in UKPACE trial.]*

There is therefore uncertainty around the proportion of cross-overs that may be attributed to pacemaker syndrome in trials of device. Pacemaker syndrome was the most important reason for cross-over in MOST, at the end of which 31.4% of devices randomised to ventricular pacing had been reprogrammed to dual-chamber pacing. Of these, 58% were due to severe pacemaker syndrome requiring permanent reprogramming. However, the uncertainty associated with this diagnosis is demonstrated by the fact that only two-thirds of this group met the strict criteria established a priori for pacemaker syndrome.

Therefore, the overall number of cross-overs from ventricular to dual-chamber pacing has been illustrated under two scenarios, assuming that all or no individuals who had a reimplant in CTOPP also had pacemaker syndrome. This illustrates the unstable nature of this estimate and shows the inappropriateness of using pooled estimates of the incidence of pacemaker syndrome.

Under the first scenario, the total number of individuals with pacemaker syndrome was 298/2674, with an average incidence of cross-overs from ventricular to dual-chamber pacing of 11%. In the alternative scenario, the overall average is

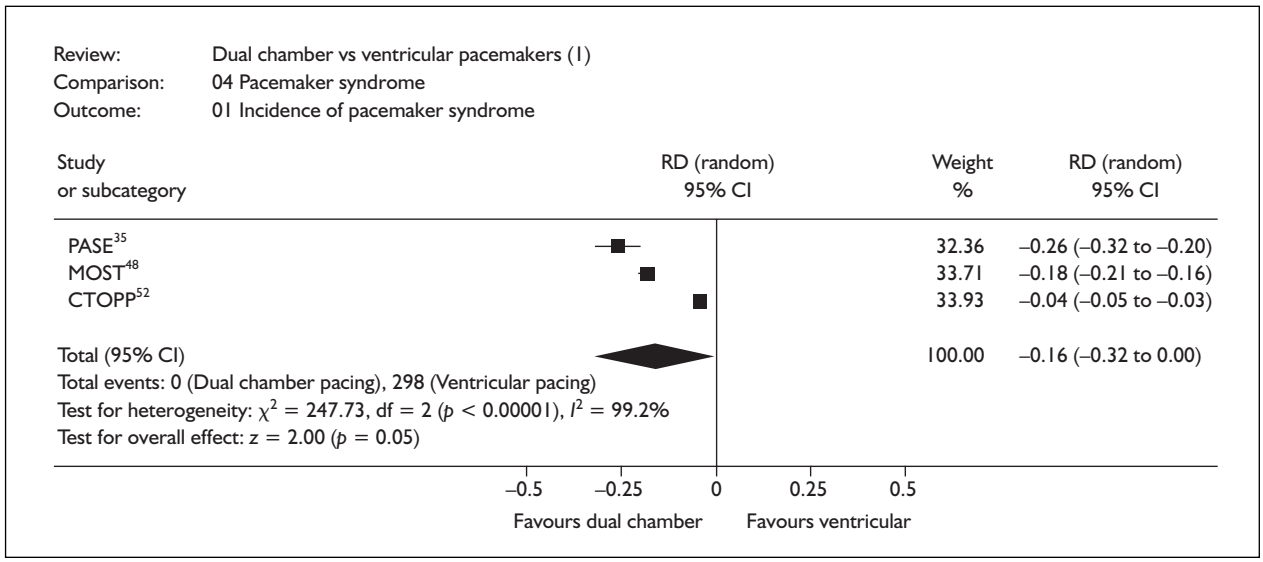


FIGURE 22 *Meta-analysis of pacemaker syndrome: scenario I (all patients with reimplant in CTOPP had pacemaker syndrome)*

8.8%. The meta-analyses shown in *Figures 22–24* indicate that a pooled analysis would suggest a difference in risk of 16% (95% CI 0 to 32%) in scenario I, favouring dual-chamber pacing. Scenario II represents the worst case scenario for dual-chamber pacing, with no reduction in risk in CTOPP. The risk of pacemaker syndrome is reduced by 15%, with a large increase in the uncertainty of the estimate (95% CI –124 to 0.95%) and the loss of statistical significance ($p = 0.79$). It should also be noted that the confidence interval includes an impossible value for the proportion with pacemaker syndrome (–124%). *[CiC removed – results of pooled estimates which included data from the UKPACE trial.]*

FIGURE 23 *Meta-analysis of pacemaker syndrome: scenario I, including UKPACE (all patients with reimplant in CTOPP and UKPACE had pacemaker syndrome)*

[This figure has been excluded owing to the confidential nature of the UKPACE study]

In both scenarios, heterogeneity was extremely high ($I^2 = 98.8$ to 100%, $p < 0.001$). The existence of genuine differences underlying these estimates is clear. Possible explanations include the following.

1. There is uncertainty around the boundaries between pacemaker syndrome and symptoms of heart failure and no evidence of what diagnostic techniques are available and used to diagnose pacemaker syndrome.
2. In relation to point 1, there may be misclassification of pacemaker syndrome and heart failure symptoms in trials. In this case, individuals with mild heart failure would be misclassified as having pacemaker syndrome in the ventricular arm, but not in dual chamber, since that diagnostic option does not exist. In addition, there would be more cases of symptoms of heart failure in dual chamber. That would suggest a bias against ventricular pacing for 'pacemaker syndrome' and against dual chamber for heart failure. Lack of blinding of assessors may have a role in misclassification of symptoms. There is indirect evidence to help to assess the existence or direction of such misclassification. The very similar rates of heart failure with ventricular or dual-chamber pacing are based on 'hospitalisations' for heart failure, and this outcome is not equivalent to symptoms of heart failure. CTOPP[80] reports that symptoms of dizziness or fainting are significantly less in physiological than in ventricular (31% dual, 38% ventricular, $p < 0.05$), while other symptoms of pacemaker syndrome (palpitations, pulsation or pounding) are equally frequent in both arms, suggesting that a high proportion of individuals report symptoms that may be misclassified.
3. There is uncertainty on the lead-time to pacemaker syndrome. It is likely that most cases will occur relatively soon after implantation. The RCTs provide indirect estimates of time to pacemaker syndrome, approximated by time to cross-over. In MOST, 69% of reprogramming occurred by month 3 and 73% by month 6, with similar times in PASE (44% by month 1 and 77% by month 6). CTOPP showed slower progression to upgrade, with cumulative cross-

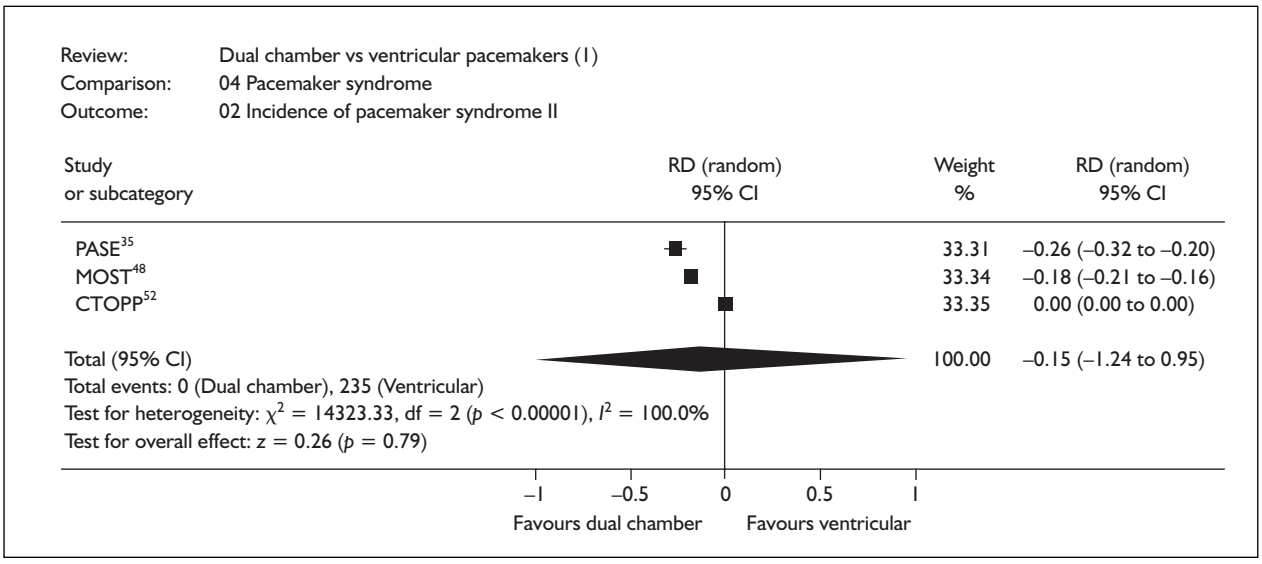


FIGURE 24 *Meta-analysis of pacemaker syndrome: scenario II (no patients with reimplant in CTOPP had pacemaker syndrome)*

over of 2.1% at year 1, 2.7% at year 3 and 4.7% at year 3, corresponding to 49% of the total by year 1 and 63% by year 2.

4. There is uncertainty around the degree of severity of pacemaker syndrome. One cross-over study, by Heldman and colleagues,[34] reported that different degrees of symptoms severity occur. Heldman estimated that 45% of individuals have severe pacemaker syndrome, 34% moderate and 22% mild.
5. There is disagreement on whether symptoms of pacemaker syndrome warrant the risk associated with reimplantation or upgrade. A potential advantage of dual-chamber pacemakers is avoiding this risk at the onset of pacing. For this reason, differences between trials of mode and trials of device are crucial.

FIGURE 25 *Meta-analysis of pacemaker syndrome: scenario II, including UKPACE (no patients with reimplant in CTOPP and UKPACE had pacemaker syndrome)*

[This figure has been excluded owing to the confidential nature of the UKPACE study]

Individual symptoms

All cross-over studies measured the intensity or severity of symptoms. However, the results show heterogeneity across studies, with the exception of the single score for fatigue (Appendix 7) (*Figures 26* and *27*)

Adverse effects of implantation

Four trials reported the short-term and long-term incidence of complications related to pacemaker implants. These were reported by mode in CTOPP. In MOST and PASE, complications apply to dual-chamber pacing only since all participants were implanted with a dual-chamber device and thereafter randomised to programming. For this reason, complications were not reported by mode in MOST and PASE. In the following analysis, the total rate of complications in MOST and PASE was compared with the rate for dual chamber only in CTOPP, since in the two former trials all participants received dual-chamber hardware. *[CiC information from the UKPACE study has been excluded.]*

Perioperative mortality

In PASE there were 0.25% deaths at the time of implantation. No deaths were reported in MOST. In the latter study, 14 deaths occurred (0.7%) during the month after implant. Perioperative deaths were not reported in CTOPP.

Non-fatal complications

The perioperative rate of complications was 6% in CTOPP,[52] 6.1% in PASE[29] and 4.8% in MOST[84] *[CiC data from the UKPACE study have been excluded]* (*Table 31*). In MOST, there was an additional 2.7% risk of subsequent complications, with a total rate of 7.5% over the course of the trial. Later complications occurred at an approximately constant rate in MOST.[84]

The most frequent perioperative complications were atrial lead dislodgement (1.9% MOST, 0.5% PASE), ventricular lead dislodgement or failure (1.1% MOST, 1.7% PASE) and pneumothorax

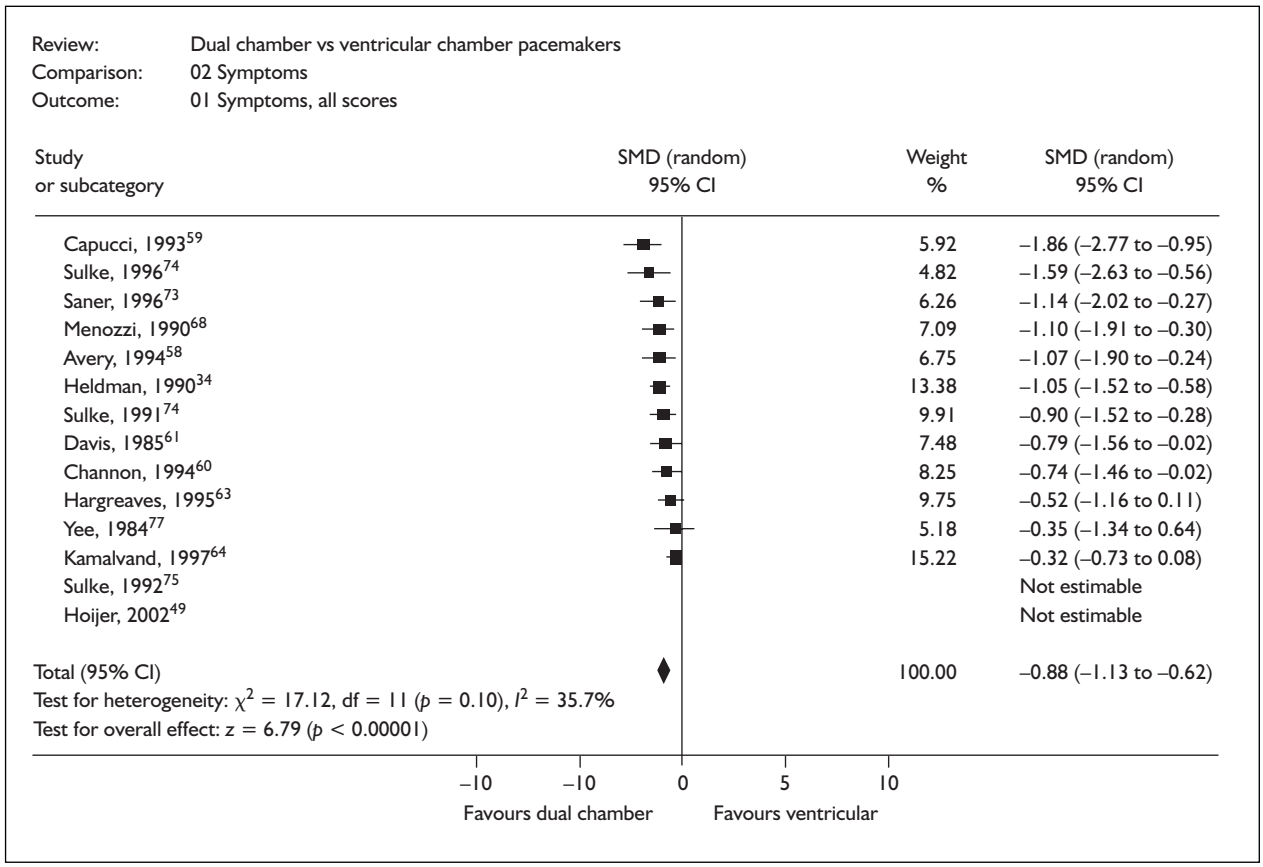


FIGURE 26 *Meta-analysis of symptomatic change: cross-over trials*

(1.5% MOST, 2% PASE) (*Table 31*). Cardiac perforation was reported in 1% in PASE. Perioperative infections (0.2% in both trials) or other complications (0.1% MOST, 0.75% MOST) were rare. There was no significant predictor for complications in PASE. In MOST an association with gender was reported, with women showing a 6% 30-day complication rate compared with 3.8% in men (HR = 1.4, 95% CI 0.98 to 1.99, $p = 0.06$).[84]

In CTOPP, dual-chamber pacing was associated with more perioperative complications: 9% for dual-chamber compared with 3.8% for ventricular pacing. This difference was significant ($p < 0.001$). However, it should be noted that inadequate atrial sensing was a reason for exclusion of recipients from MOST. When this cause of complications is excluded from the total in CTOPP, the overall rate of complications is very similar in PASE and CTOPP (6.1% versus 6.8% dual and 3.3% ventricular) and lower in MOST (4.8%).

The majority of complications in CTOPP were due to lead dislodgement (higher in dual-chamber) and pneumothorax (similar proportions for dual-chamber and ventricular pacing). Other complications included inadequate sensing and inadequate pacing. These were significantly higher for the dual-chamber arm. A small number of implants were affected by haemorrhage and device malfunctioning. These complications were similar in dual and ventricular pacing. *[CiC removed – reasons for complications in the UKPACE trial.]* The incidence of lead dislodgement was similar in MOST (3%) and CTOPP (2.6% average) and slightly lower in PASE (2.2%).

Dual-chamber versus single-chamber ventricular pacing: summary of effectiveness

- Dual-chamber pacing was not associated with significant improvement in mortality in any individual trial. The pooled analysis strengthens this conclusion. *[Comment about the CiC UKPACE trial removed.]*
- Dual-chamber pacing was not associated with improvements in incidence of stroke.
- Dual-chamber pacing significantly reduced the incidence of AF in two large parallel trials. *[Comment about the CiC UKPACE trial removed.]* The pooled odds ratio was 0.76 (95% CI 0.65 to 0.9). The differences in findings for AF between

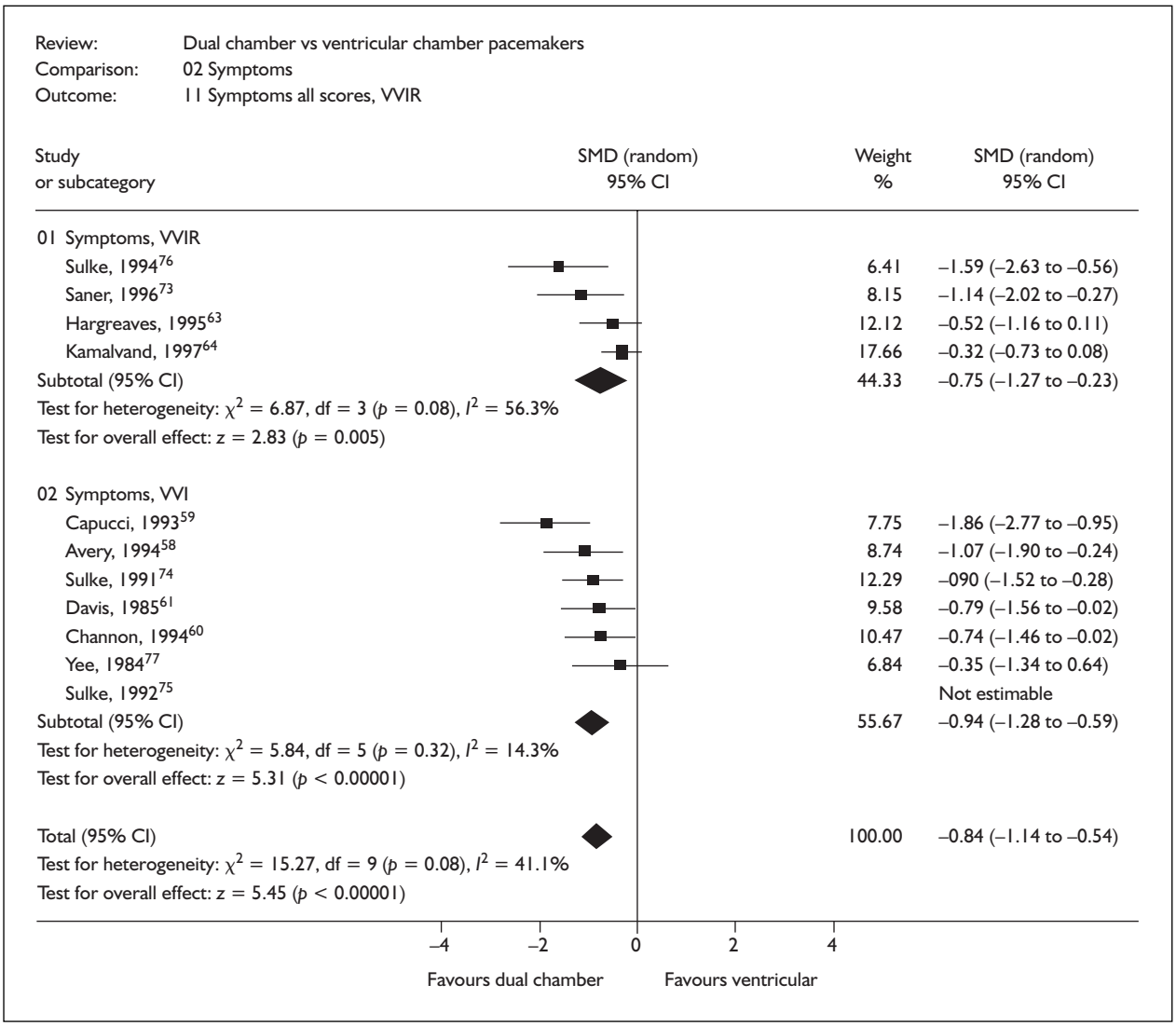


FIGURE 27 *Meta-analysis of symptomatic change stratified by pacemaker type: cross-over trials*

TABLE 31 *Perioperative complications*

	CTOPP[52]			*UKPACE*[45]			MOST[48]	PASE[35]
Type of complication	**Dual *n* = 1084**	**Ventricular *n* = 1474**	***p*-Value**	**Dual *n* = 1012**	**Ventricular *n* = 1009**	***p*-Value**	**Dual**	**Dual**
Any	9.0%	3.8%		*CiC removed*	*CiC removed*	<0.001	4.8%	6.1%
Pneumothorax	1.8%	1.4%	<0.001	_	_	_	1.5%	2%
Haemorrhage	0.2%	0.4%	0.42	_	_	_	–	–
Inadequate pacing	1.3%	0.3%	0.32	_	_	_	–	–
Inadequate sensing	2.2%	0.5%	0.002	_	_	_	–	–
Device malfunctioning	0.2%	0.1%	<0.001	_	_	_	–	–
Lead dislodgement	4.2%	1.4%	0.4	_	_	_	Atrial 1.9%, ventricular 1.1%	Atrial 0.5%, ventricular 1.7%
Subclavian vein thrombosis	–	–	<0.001	–	–	–	–	1.5%
Erosion	–	–	–	–	–	–	–	0.25%
Infection	–	–	–	–	–	–	–	0.25%
Cardiac perforation	–	–	–	–	–	–	–	1%

trials are difficult to explain and may be due to differences in the underlying causes of bradycardia.
- Heart failure was significantly reduced in MOST only. A pooled analysis did not support this finding (OR = 0.83, 95% CI 0.66 to 1.05).
- There was significant improvement in effort tolerance with dual-chamber pacing measured in cross-over trials, although the pooled analyses demonstrate heterogeneity between studies and suggest that improvements may be confounded by rate responsiveness.
- No differences by age were found in exercise capacity. However, this may be due to the measurement instruments used in the elderly, who are not tested under maximal effort.
- No significant difference in functional capacity was shown in a meta-analysis of cross-over and parallel-design trials using the SAS measure.
- Subgroup analyses from the large parallel studies have not shown consistent and robust evidence of differential effects of dual-chamber pacing in identifiable patient groups.
- Quality of life was assessed in 17 studies, including the four parallel-group RCTs and 13 cross-over studies using a wide range of measures.
- Results are variable, with some evidence of improvement associated with dual-chamber pacing, particularly in cross-over studies. MOST and PASE showed small improvements in quality of life using SF-36, but CTOPP did not. Improvements in quality of life were short term in PASE and, as a result of the method of analysis, MOST.
- It seems likely that pacemaker syndrome accounts for much of the difference in quality of life seen in the larger studies.
- A wide range of symptoms was used to support the diagnosis of pacemaker syndrome between studies and there are no widely accepted diagnostic criteria.
- The incidence of pacemaker syndrome varied between 4% (inferred) and 26%. The time to development of pacemaker syndrome is uncertain, owing to difficulties in diagnosis. Incidence was higher in trials of programming, suggesting that ease of upgrade is important to the diagnostic threshold.
- Dual-chamber pacing significantly relieves symptoms of pacemaker syndrome when these occur. Symptoms were improved with dual-chamber pacing compared with both ventricular fixed rate and rate-modulated pacing.
- The majority of complications occurred perioperatively. Dual-chamber pacing was associated with higher rates of lead dislodgement (4.2% versus 1.4% for ventricular pacing and inadequate pacing (1.3% versus 0.3%). Other complications were similar by mode, including pneumothorax, infections, haemorrhage and device malfunctioning.

Clinical effectiveness of dual-chamber versus single-chamber atrial pacing

Number of studies

The literature search revealed one RCT, by Nielsen and colleagues,[91] and two cross-over trials, by Schwaab and colleagues[92] and Lau and colleagues[78]) comparing dual-chamber with atrial pacing. All studies compared dual-chamber, rate-modulated pacemakers with atrial chamber, rate-modulated pacemakers in people with SSS without AVB. This is the only population eligible to receive a single-chamber atrial pacemaker.

Study characteristics

Populations

The parallel-group RCT by Nielsen and colleagues[91] randomised 177 patients with symptomatic bradycardia and sinus pause, 123 to dual chamber and 54 to atrial pacing. Cross-over studies by Lau and colleagues[78] and Schwaab and colleagues[92] were smaller and included 15 and 19 individuals, respectively. The study by Schwaab and colleagues included individuals with brady–tachy syndrome and chronotropic incompetence.

The average age was 74 years for participants in the trial by Nielsen,[91] with younger populations included in the trial by Lau[78] (average 66 years) and Schwaab[92] (average 70 years) (*Table 32*).

CAD was present in 68/177 (38.5%) of people in the trial by Nielsen[91] and six (50%) in the trial by Lau.[78] Schwaab and colleagues reported no further details on the population.[92]

Intervention and comparison

Nielsen and colleagues[91] included two options for the dual-chamber mode: with short-rate adaptive atrioventricular delay (DDDR-s) and with fixed, long atrioventricular delay (DDDR-l) (*Table 33*). In addition, all DDDR pacemakers had a mode-switching function whereby as AF was sensed in the atrium, the pacemaker mode was automatically switched to ventricular pacing. This feature reduces the occurrence of high ventricular rates caused by tracking AF or other atrial tachyarrhythmias.

TABLE 32 *Summary of population characteristics*

	Nielsen, 2003[91]			Lau, 1994[78]	Schwaab, 2001[92]
	DDDR-s[a] (*n*)	**DDDR-l[a] (*n*)**	**AAIR (*n*)**	**(n)**	**(n)**
n	60	63	54	15	19
Mean age (years)	79 ± 9	74 ± 9	74 ± 9	66 ± 2	70 ± 7
Gender (male)	26/60	24/63	23/54	5/15	11/19
NYHA class I/II	60/60	60/63	50/54	15	
CAD	25/60	22/60	21/54	6	
Prior (symptoms of) heart failure	2	5	1	Not stated	
History of syncope	26	24	19	9	
Dizzy spells (symptoms)	32	34	34	2	
Antiplatelet drugs	40	36	35		
Anticoagulant drugs	5	11	5		
Antiarrhythmic drugs	9	11	11	8	19

[a] DDDR-s, short-rate adaptive atrioventricular delay; DDDR-l, fixed, long atrioventricular delay (see also following section).
n, Number of individuals.

TABLE 33 *Studies of dual-chamber compared with single-chamber atrial pacemakers*

	Parallel study	Cross-over studies	
Study	**Nielsen, 2003[91]**	**Lau, 1994[78]**	**Schwaab, 2001[92]**
Population	SSS	SSS	Brady–tachy syndrome
Intervention	DDDR	DDDR	DDDR
Comparison	AAIR	AAIR	AAIR
Randomisation	Device	Mode	Mode
Recruitment	December1994 to March 1999; follow-up interrupted in 2000	Not stated	Not stated
Participants	Total: 177 DDDR-s: 60, DDDR-l: 63, AAIR: 54	12	19
Number of centres	2	1	1
Average follow-up	2.9 ± 1.1 Years	4 weeks	6 months
Date	2003	1994	2001
Country	Denmark	Hong Kong	Germany

Nielsen's study[91] was a trial of devices. Cross-over studies[78,92] were trials of mode.

Outcomes

Lau and colleagues[78] used the SAS score of functional capacity. The trial by Schwaab and colleagues[92] also used the SAS score, in addition to perceived effort tolerance. Symptom scores were reported in both trials by Schwaab and Lau. Quality of life was scored with a VAS measuring general well-being. In addition, Schwaab and colleagues[92] used a questionnaire of self-perceived health status and the Karolinska questionnaire.

The role of pacemaker dependency was not studied in any of the trials. Outcomes from these studies are summarised in *Table 34*.

Quality of studies

See *Table 35*.

Selection bias

Randomisation procedures were not detailed in any of the trials. Baseline characteristics were reported to be similar in the trial by Nielsen and colleagues.[91] No conclusion can be drawn on baseline values in the two cross-over trials since

TABLE 34 *Summary of outcomes*

Outcome	Number of studies	
	Group RCTs	**Cross-over RCTs**
All-cause deaths	Nielsen[91]	–
Strokes, embolism	Nielsen[91]	–
Atrial fibrillation	Nielsen[91]	–
Progression to heart failure	Nielsen[91]	–
Exercise capacity	Functional status: Nielsen[91]	Effort tolerance: Schwaab[92] SAS: Schwaab,[92] Lau[78]
Cognitive function	–	Schwaab[92]
Adverse events	Nielsen[91] (changes in pacing mode)	–
Quality of life	–	QoL: Schwaab,[92] Lau[78]

TABLE 35 *Summary of critical appraisal, RCTs and cross-over studies of atrial versus dual chamber pacemakers*

Item	Nielsen, 2003[91]	Lau, 1994[78]	Schwaab, 2001[92]
Randomisation sequence generation	Unknown	Unknown	Unknown
Concealment of randomisation	Unknown	Unknown	Unknown
Similarity of groups at baseline	Adequate	Unknown	Unknown
Eligibility criteria specified	Adequate	Adequate	Adequate
Blinding of assessors	No	Adequate	Adequate
Blinding of care provider	Unknown	Unknown	Unknown
Participants blinded	Unknown	Adequate	Adequate
Code break to participants	Unknown	Unknown	Unknown
Co-intervention, equal at baseline	Adequate	Adequate	Adequate
Co-intervention, equal during follow-up	Adequate	Adequate	Adequate
Results for primary outcome measure	Adequate	Inadequate	Adequate
ITT	Adequate	No	No
Missing values	Unknown	Inadequate	Inadequate
Loss to follow-up	Adequate	Adequate	Adequate
Checklist from CRD Report 4.[37]			

they are not detailed for the start of the second period. Similar considerations apply to the likelihood of changes in baseline characteristics of recipients that were discussed for cross-over trials of dual versus ventricular pacing. However, the study by Lau and colleagues[78] was potentially longer than the other studies in this review. Although small, some progression towards AVB may have occurred in some individuals.

The trials by Nielsen and colleagues[91] and by Lau and colleagues[78] included people with SSS with normal AV conduction and no bundle branch block. Nielsen and colleagues carried out an AV conduction test at implantation, (i.e. after randomisation), and all individuals with evidence of impaired AV conduction (Wenckebach block at a rate <100 bpm) received dual-chamber pacing. This affected two individuals who were randomised to atrial but received dual-chamber pacing. The limit set for the Wenckebach test was low compared to practice in the UK, where a Wenckebach point of around 130 bpm would be used. The limit used by Nielsen and colleagues may have been too low to identify individuals with 'subclinical' AVB, that is, AVB block that may become manifest at high rates. For this reason, the estimate of subsequent progression to AV block may have been too high.

Schwaab and colleagues[92] included individuals with spontaneous or drug-induced symptomatic sinus bradycardia and with a diagnosis of chronotropic incompetence according to clearly specified criteria. It is unclear whether a history of at least two episodes of paroxysmal atrial

tachycardia was also a necessary condition for recruitment. Individuals with bundle branch block, bifascicular block and PQ interval >240 ms, second or third degree AVB and valvular heart disease were excluded. People with chronic AF were excluded by Nielsen and colleagues.

AVB is important in this context, as the development of AV conduction problems leading to symptoms may require upgrade to dual-chamber pacing. Details of AV conduction in the trials were poorly reported. The study by Schwaab and colleagues[92] reports that a high proportion of participants developed AV conduction prolongation and second degree AVB in the course of the trial (24% at rest and 39% during exercise).

Detection bias
In the trial by Nielsen and colleagues,[91] recipients were blinded to the intervention. No steps were taken to validate outcomes rated by investigators, although objective measurement of primary end-points was attempted, including ECG for atrial fibrillation, standard definitions for stroke and cause of death from death certificates. The cross-over trials by Schwaab[92] and Lau[78] were double blinded, with investigators and recipients unaware of pacing mode.

Performance bias
All trials allowed concomitant drug treatment for CVD. The study by Lau and colleagues[78] allowed digoxin, antiarrhythmic drugs and ACE inhibitors. In Schwaab and colleagues[92] all patients were treated with antiarrhythmic medications or β-blockers. Medications were unchanged during both cross-over trials. Reimplantation was required in six participants in Nielsen and colleagues,[91] although no details are provided of the reasons.

Attrition bias
Nielsen and colleagues[91] reported complete follow-up. Both cross-over trials analysed data only on individuals who completed the trials. Data for two recipients were excluded from the analysis in the Schwaab trial[92] (one developed AF and one died) and for three recipients in the Lau study[78] (two because of pacemaker failure and one because of non-compliance, with no further details).

In the trial by Nielsen and colleagues,[91] three individuals in the AAIR arm were implanted with dual-chamber pacemakers, and three were upgraded during follow-up (11% in total), because of the development of AVB (1), lead malfunction (1) and inadequate atrial capture (1). As in trials of ventricular versus dual-chamber pacemakers, this may result in a dilution of any underlying differences in effect.

Statistical analysis and power calculation
Statistical methods were appropriate in all trials.

The trial by Nielsen and colleagues was underpowered since it was suspended before reaching the target number of participants. The trial was a pilot for a larger study currently being conducted, the DANPACE trial.[93] No details of power calculation were reported for the two cross-over trials.

Intention-to-treat analysis
This approach was used in the parallel-group trial by Nielsen and colleagues.[91] In the cross-over trials[78,92] the analysis was restricted to individuals who completed both treatment periods.

External validity
Nielsen and colleagues[91] recruited participants from patients who presented consecutively. They provide a detailed description of exclusion. Individuals with chronic, non-cardiovascular morbidity and high risk of death (cerebral disease including dementia or cancer) were not included. In addition, underlying indications for pacing such as cardiomyopathy, carotid sinus syndrome, prior heart transplant, major non-cardiac surgery, bradycardia and ventricular tachycardia were reasons for exclusion. No details are provided in the cross-over trials[78,92] apart from the inclusion and exclusion criteria discussed above.

Dual-chamber versus single-chamber atrial pacing: summary of quality of evidence

- One small parallel-group RCT and two small cross-over trials were included (total $n = 211$).
- The quality of the parallel-group trial was reasonable, with methodological features similar to trials of dual versus ventricular pacing. However, the trial was small and was interrupted. This was a trial of device.
- The parallel trial was randomised and concealment was adequate, with no significant imbalance at baseline. Completeness of follow-up was good and well detailed.
- In the parallel-group RCT, investigators were not blinded. However, outcomes were objectively defined for most outcomes. The trial reported changes in pacing mode.
- External validity was good. The eligibility criteria were applicable to all potential participants and reasons for exclusion are clearly detailed.

- The cross-over trials were carried out in a small population (total $n = 33$), contained fewer methodological details and were of much shorter duration.

Dual-chamber versus single-chamber atrial pacing: results

Mortality, stroke, atrial fibrillation and heart failure

Nielsen and colleagues[91] report all-cause and cardiovascular mortality, AF, stroke and heart failure (using consumption of diuretics as a proxy measure). There were three arms in this trial comparing ventricular to dual-chamber pacing with long or short programming delay. The two dual-chamber arms have been combined where possible in the following analysis. Where this was not possible, results for the DDDR-l are reported since this mode was presented by the authors as the usual standard.

All-cause mortality was not significantly different between pacing modes. The annual death rate was 8% for dual-chamber pacing with slight variations for the two types of programming (8% for DDDR-s and 8.4% for DDDR-l). Mortality for atrial pacing was 5.4%. No significant differences in cardiovascular mortality were reported, with 7.4% for atrial pacing and 11.7% (DDDR-s) or 14.3% (DDDR-l) for dual-chamber pacing.

Dual-chamber pacing was not associated with a decreased risk of stroke or heart failure.

A small number of participants reported cardiovascular events. Stroke was reported in three people (5.6%) in the atrial pacing arm and in 11 (8.9%) in the two dual-chamber pacing arms ($p = 0.32$).

Progression to heart failure, measured by increased consumption of diuretics, was reported in 28% of participants receiving atrial pacing and 26% receiving dual-chamber pacing ($p = 0.34$).

The only outcome where a benefit was found was AF, with a higher incidence during dual-chamber pacing compared with atrial pacing. Four recipients (7.4%) in the atrial pacing arm and 25 (20%) in the dual-chamber arm reached this end-point ($p = 0.03$).

The cumulative rates (Kaplan–Mayer estimates) for AF with atrial pacing were 2% (year 1), 4% (year 2), 5.5% (year 3), 9.5% (year 4) and 10% (year 5). The cumulative incidence for dual-chamber pacing was 5% (year 1), 8% (year 2), 13.7% (year 3), 19.5% (year 4) and 22.8% (year 5). (These estimates were calculated for the DDDR-l mode.) There was a slightly steeper cumulative incidence for the DDDR-s mode.

Exercise tolerance

Schwaab and colleagues[92] reported exercise duration tested with a bicycle ergometer, maximal effort test. Exercise duration was significantly higher with atrial pacing (423 seconds, SD 127 seconds) than with dual-chamber pacing (402 seconds, SD 102 seconds) ($p < 0.05$), although the size of the effect is small and its clinical importance and impact on quality of life may not be significant. The total workload was also significantly improved with atrial compared with dual-chamber pacing (103 W, SD 31 W atrial; 96 W, SD 27 W dual, $p < 0.05$).

Functional status

Functional status was studied in the two cross-over studies. All individuals in the study by Lau[78] were in NYHA functional class II or I throughout the study. No details are reported for Schwaab.[92]

Neither cross-over study found a significant difference between modes for improvement in functional class. Results for the SAS score (standardised mean difference) were pooled but showed no significant benefit (*Figure 28*).

In the trial by Nielsen, 31% of participants randomised to atrial and 38% of individuals with dual-chamber pacing worsened by at least one functional class ($p = 0.17$).

Quality of life

Quality of life was studied in a very small group of recipients in the two studies by Lau and colleagues[78] and Schwaab and colleagues.[92] The former had four types of measures for quality of life, including validated and non-validated questionnaires. Schwaab and colleagues used three questionnaires.

Dimensions of quality of life considered were general well-being, symptoms and more general multidimensional constructs for quality of life.

Single global assessment of well-being

General well-being was evaluated in both cross-over studies with a 10-cm VAS anchored to worse and best possible health states.

Both studies reported values for well-being of around 70% of best possible health during follow-

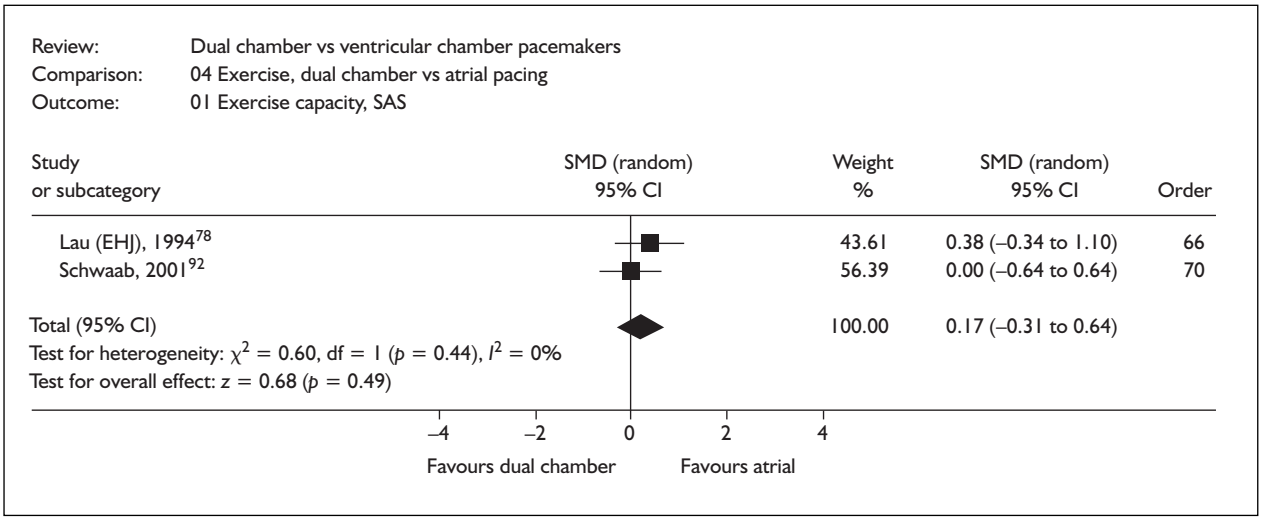


FIGURE 28 *Meta-analysis of SAS scores: atrial versus dual chamber*

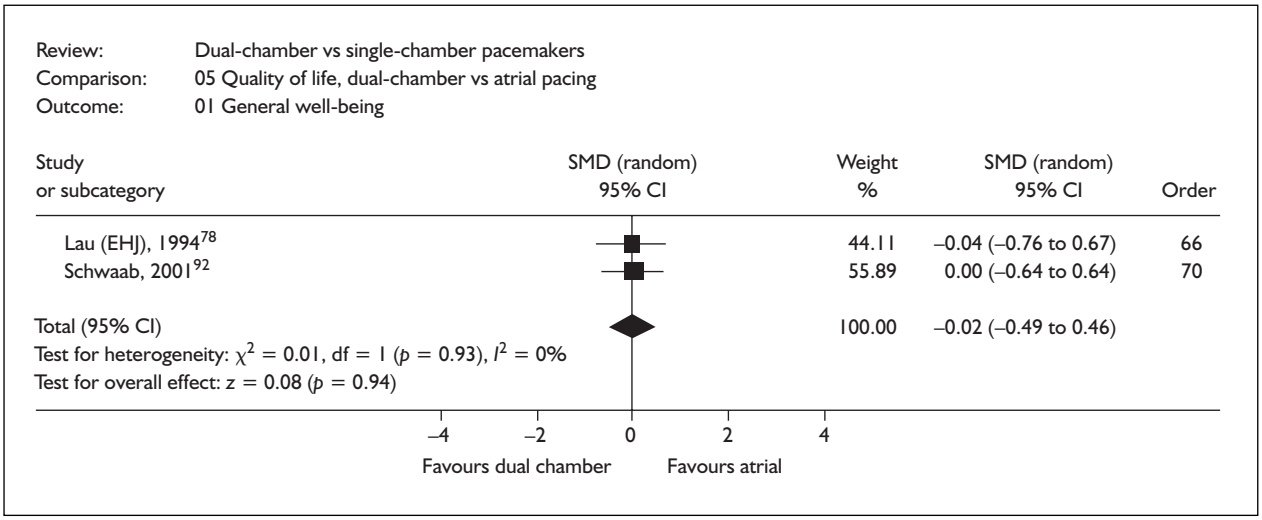


FIGURE 29 *Meta-analysis of quality of life (general well-being): atrial versus dual chamber*

up. Overall, there was no benefit from dual-chamber pacing (*Figure 29*). The overall pooled estimate for benefit was a reduction of 0.02 SD units; a minimal, non-significant difference.

Multidimensional measures of quality of life

Lau and colleagues[78] included two multidimensional measures of quality of life: the General Health Questionnaire (12 items) and a questionnaire for the assessment of physical malaise including 41 items adapted from the Bradford Somatic Inventory.

None of the scores reported was better for dual-chamber pacing, with 9/10 scores reporting slightly better values for atrial pacing (*Table 36*, from Lau[78]). Differences were non significant.

Schwaab and colleagues[92] used two multidimensional measures of quality of life. The first was a measure of self-perceived health status, using four dimensions: general well-being, physical functioning, emotional functioning and cognitive functioning. All comparisons were non-significant.

The second questionnaire investigated symptoms using the symptoms components of the Karolinska questionnaire. These are reported in the next section, on symptoms.

Symptoms

Lau and colleagues[78] and Schwaab and colleagues[92] reported symptom scores (dyspnoea, palpitations, dizziness and chest pain). Lau and

TABLE 36 *Multidimensional measures of quality of life: single-chamber atrial versus dual-chamber pacing*

General Health Questionnaire	DDDR 14.3 (SD 2.2), AAIR 15.2 (SD 2.1)
Somatic Inventory	Total score (range 41–82): DDDR 71.5 (SD 3.3), AAIR 70.2 (SD 3.5) Activities of daily living: DDDR 31.2 (SD 2), AAIR 32.8 (SD 2.1) Emotional adjustment: DDDR 24.2 (SD 1.7), AAIR 23.2 (SD 1.8) (lower score better) Social interactions, frequency: DDDR 11.3 (SD 1.1), AAIR 11.8 (SD 1.2) Social interaction, range: DDDR 2.1 (SD 0.2), AAIR 2.2 (SD 0.3) Social interaction, quality: DDDR 21.5 (SD 1.2), AAIR 22.4 (SD 1.1) (lower score better) Work adjustment: DDDR 0.4 (SD 0.1), AAIR 0.3 (SD 0.1) (lower score better) Sleep: DDDR 0.3 (SD 0.1), AAIR 0.3 (SD 0.1) (lower score better) Fatigue: DDDR 1.6 (SD 0.1), AAIR 0.6 (SD 0.1) (lower score better) Appetite: DDDR 1.2 (SD 0.1), AAIR 0.1 (SD 0.1) (lower score better)

colleagues measured presence of symptoms as an average of individuals' scores, ranging from 1 (always) to 5 (never). Schwaab and colleagues used a VAS (the Karolinska questionnaire), with 0 for worse status and 100 for best status (absence of symptoms).

Forest plots for standardised mean difference in scores are shown in *Figure 30*. No benefit was found for dual-chamber pacing in the total score for each symptom considered.

In addition, Lau and colleagues[78] reported scores for sleep disturbance and neck pulsations. No differences were found between AAIR and DDDR in pulsations, with both scores equal to score for best status (never had pulsations). No differences were found for sleep disturbances (AAIR 4.6, SD 0.25; DDDR 4.3, SD 0.35).

Schwaab and colleagues[92] reported a total score for symptoms of pacemaker syndrome, although the type and number of symptoms included are not reported. A five-point categorical scale similar to that used by Lau[78] was used. The total score did not differ between dual and atrial pacing (atrial 3.6, SD 0.64; dual 3.5, SD 0.6).

Progression to AVB

All trials provide information on the development of AVB during follow-up in atrial pacing.

Nielsen and colleagues[91] reported the annual incidence of development of high-degree AVB as 1.9%. Schwaab[92] reported that three individuals (16%) developed AVB after exercise and in seven (37%) second or third degree AVB was present during Holter recordings carried out during follow-up. Lau and colleagues[78] did not find any AV conduction block or prolongation. However, they also acknowledge that the occurrence may be potentially limited by the short duration of the study.

Dual-chamber versus single-chamber atrial pacing: summary of effectiveness

- Dual-chamber pacing was compared with atrial pacing in one parallel-group RCT and two cross-over RCTs, reporting mortality, stroke, heart failure, exercise tolerance, functional status and quality of life.
- All-cause mortality was not significantly different by pacing mode, with an annual death rate of 8% for dual-chamber and 5.4% for atrial pacing.
- The only outcome where a benefit was found was AF, with a higher incidence during dual-chamber pacing compared with atrial pacing. Four recipients (7.4%) in the atrial pacing arm and 25 (20%) in the dual-chamber arm reached this end-point ($p = 0.03$).
- A small, statistically significant effect on exercise duration was shown in favour of atrial pacing (423 seconds, SD 127 seconds) compared with dual-chamber pacing (402 seconds, SD 102 seconds) ($p < 0.05$). There were no effects of either mode on functional class.
- No additional benefits were achieved with dual-chamber pacing for quality of life and symptoms.
- Atrial pacing showed a potential benefit in symptoms and exercise, and a significant benefit in AF. However, all trials showed the potential for AVB to develop with time. This progression may make atrial pacing unsuitable in some patients. All trials were of short duration, with little potential for capturing the impact of progressive AVB on outcomes measured. Caution suggests that these trials are weak grounds for concluding the superiority of atrial pacing.

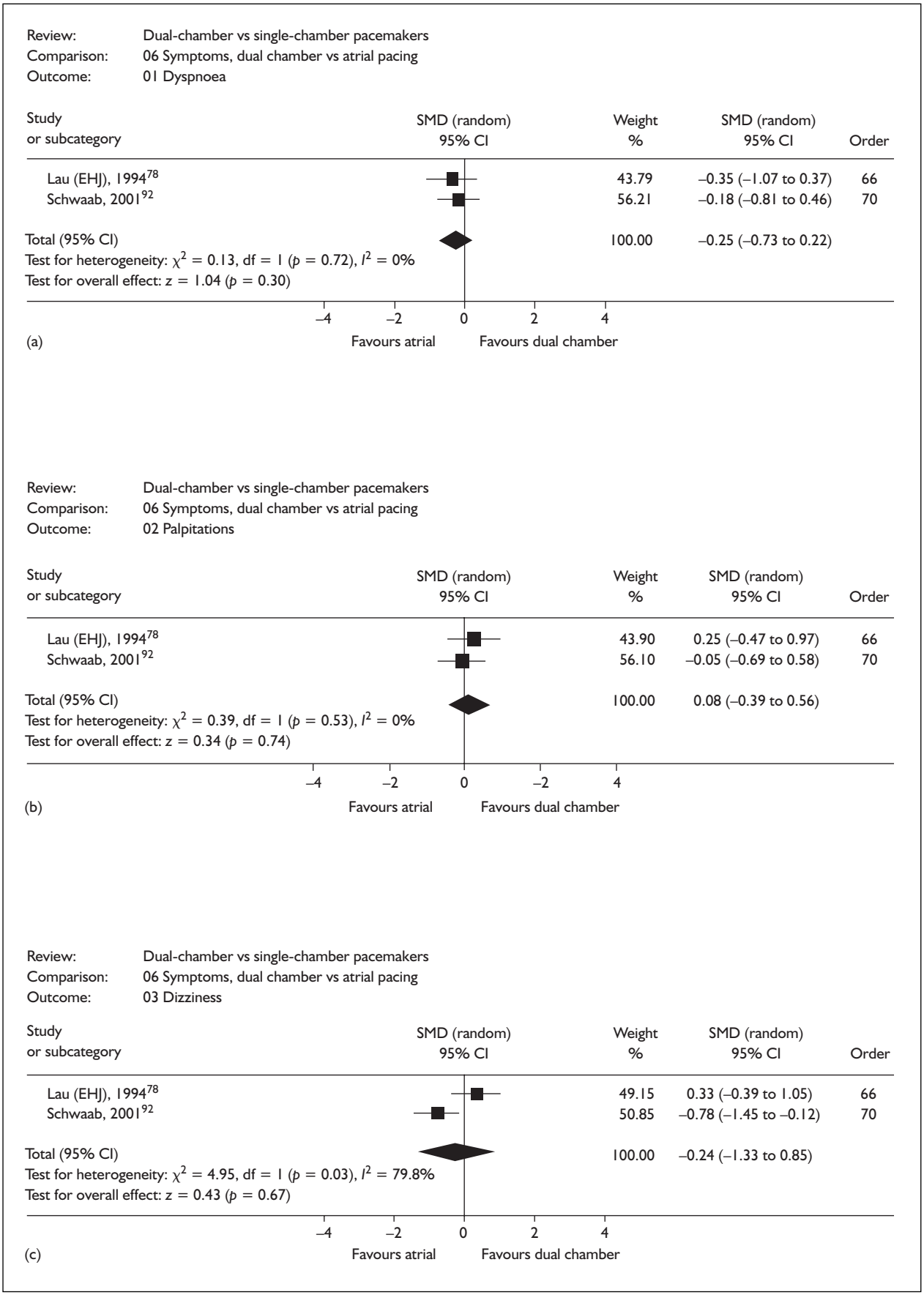


FIGURE 30 *Symptom scores, atrial versus dual-chamber pacing: (a) dyspnoea; (b) palpitations; (c) dizziness; (d) chest pain*

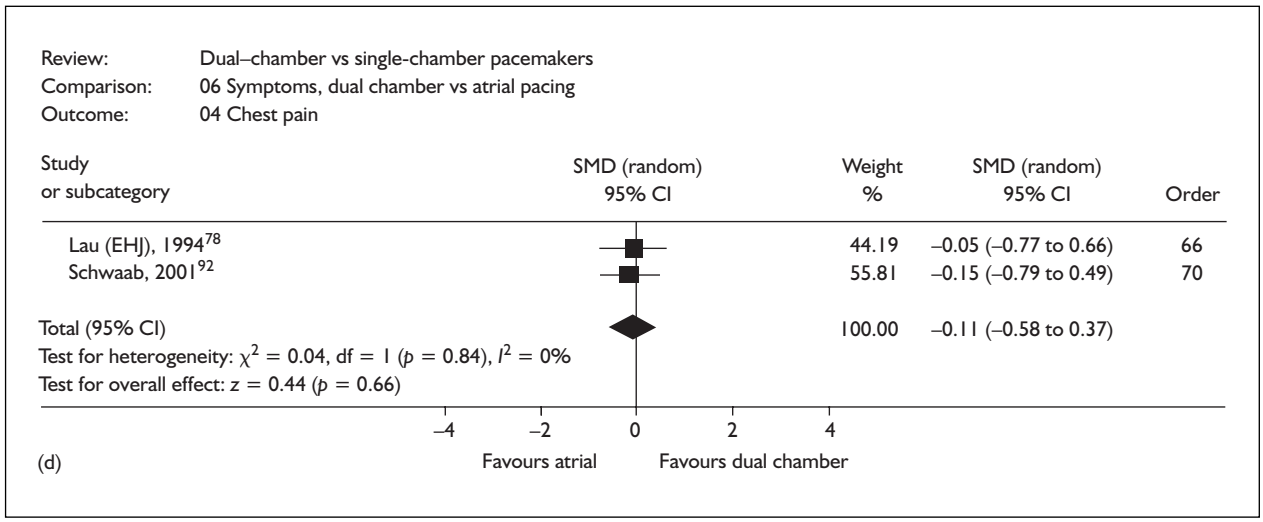


FIGURE 30 *Symptom scores, atrial versus dual-chamber pacing: (a) dyspnoea; (b) palpitations; (c) dizziness; (d) chest pain (cont'd)*

Chapter 5

Cost-effectiveness of dual-chamber pacing

Review of existing economic analyses

Published economic analyses

The searches identified no economic evaluations published since the previous systematic review of dual-chamber pacing carried out by the Birmingham Health Technology Assessment Group.[43]

The Birmingham review[43] was informed by searches of appropriate electronic sources [MEDLINE, EMBASE, NHS Economic Evaluations Database (EED), NHSCRD, Bandolier] and citation searching. Explicit inclusion criteria were applied by two reviewers. The review considered costing studies as well as cost-effectiveness studies. In view of the fact that no further studies have been published thereafter, that the relevance of published studies is limited and that the previous review is of good quality, this section draws on the findings of the Birmingham review.

Sixteen potentially relevant papers were identified, of which only four were considered suitable for inclusion. The other papers examined issues not directly relevant to the comparison of single- and dual-chamber pacing (five studies), assessed the potential budget impact of different pacing strategies (three studies) or were reviews of economic evaluations (three studies). One of the five remaining studies identified for the review was not obtained by the authors within the time-frame for completion of the review. This was a short report presented by Medtronic, a manufacturer of pacing devices, by Mahoney.[94] Methodological details are extremely scant, consisting of unreferenced citation of a meta-analysis of 35 published studies comparing single- and dual-chamber pacing. No methods are reported on how this meta-analysis was carried out or how the results were related to estimates of resource consumption to reach the conclusion that dual-chamber pacemakers would be cost saving. The absence of methodological details means that it is not possible to judge the validity of the conclusions and the study was appropriately excluded from further consideration.

None of the four studies included in the Birmingham review was a full economic analysis (i.e. related differences in costs to differences in outcome). The studies considered different populations: one each considered SSS, SSS/AVB, unspecified bradycardia and "all candidates for single/dual chamber pacemakers". Period of follow-up varied from 1 to 12 years. There were variations in the types of costs considered in each, and this partly accounts for the divergent conclusions shown. Two studies[95,96] concluded that overall costs for dual-chamber were greater than single-chamber pacing and two[97,98] reached the opposite conclusion.

The published economic literature is of limited relevance to the current assessment for several reasons. Most importantly, none of the published economic analyses draws on the evidence now available from large parallel-group RCTs. Estimates for the incidence of key events were taken from case series and are therefore more prone to selection and other biases. Second, three of the four studies considered in the Birmingham review were set in the USA. The generalisability of economic studies is more limited than for clinical effectiveness studies, principally because of differences in service organisation and therefore resource consumption, as well as differences in resource valuation and discounting conventions. Third, none of the studies included in the original Birmingham review was published after 1996 and generator technology may have developed since then, for example with respect to generator battery life in dual-chamber devices. Finally, none of the published analyses related differences in costs to differences in clinical outcomes measured using preference-based instruments.

The authors concur with the conclusions of the Birmingham review that "there is an urgent need for further economic evidence and, in particular, a UK based full economic evaluation (i.e. both costs and outcomes) of single versus dual chamber pacemakers".[43] This is addressed in the following sections, which report on economic analyses carried out by sponsors of dual-chamber pacing for the NICE appraisal process and by the authors of this assessment.

Sponsor submissions to NICE

Three economic evaluations were included in the sponsor submissions to NICE:

- Association of British Healthcare Industries (ABHI), carried out by Caro Research
- Guidant Medical, carried out by the York Health Economics Consortium (YHEC)
- St Jude Medical, carried out by Abacus International.

Each evaluation was critically appraised using two frameworks (Drummond and Jefferson,[41] a generic framework for the appraisal of economic evaluations; and Sculpher and colleagues,[40] a framework for appraising economic evaluations based on decision-analytic modelling studies). The following sections report the results and comment on the methodological quality of each of the evaluations contained within sponsor submissions. Tables reporting the appraisal of each study in detail are shown in Appendix 8 (section 'Economic evaluation studies', p. 232).

Association of British Healthcare Industries

The authors were not supplied with an electronic version of this model and so were unable to test varying the assumptions. In general, the ABHI evaluation is of good quality.

The model estimates the cost–utility of dual- versus single-chamber pacing. It was developed by an independent research consultancy (Caro Research) using a discrete event simulation (DES) approach, implemented in proprietary software (ARENA®). The researchers reportedly had complete intellectual freedom in carrying out the analysis. The model adopts a fairly simple overall structure. Mortality is assumed to be identical between pacing modes and heart failure is not included. The model runs for 5 years with appropriate discounting of costs and benefits.

The results suggest that dual-chamber pacing is likely to be considered acceptable value for money. Differences in benefits are very small [0.09 quality-adjusted life-years (QALYs) over the 5-year time horizon, i.e. 1 month]. Although initial implantation costs are higher for dual-chamber pacing, these are offset by two main factors: the development of AF and the cost of its treatment and reimplantation following the development of pacemaker syndrome. Total costs over the 5 years were very similar: £4255 for VVI(R) and £4297 for DDD(R).

The incremental cost-effectiveness ratio (ICER) is estimated in the base case as £477 per QALY. One-way sensitivity analyses were carried out on a range of variables and showed no important effects on the results. These included cost of systems (±10%), proportion of single-chamber rate-responsive devices used (up to 95%), proportion of people with AF treated with anticoagulation, chronicity of AF, pacing diagnosis (95% SSS/AVB), and reimplantation rates for pacemaker syndrome. Where 5% reimplantation is assumed, the ICER becomes £5855 per QALY and if no reimplantation is undertaken, the ICER remains at a level generally considered to represent acceptable value for money (£10,444 per QALY).

Multiway sensitivity analysis was carried out for 100 simulations and a cost-effectiveness acceptability curve generated. This suggests that if decision-makers are willing to pay more than £2500 per QALY the probability that dual-chamber pacing is more cost-effective than single-chamber pacing approaches 100%. In 29% of the simulations dual-chamber dominated single-chamber pacing and in no simulations was the ICER greater than £10,000 per QALY.

The DES approach allows a relatively sophisticated approach to modelling the cohorts of patients with different pacemakers, in particular taking into account the effects of risk factors on the incidence of stroke. The model operates by simulating the experience of a large number of patients (in this case 2000) according to the risks of initial and subsequent events. Time to events, including mortality, is predicted, and tracked in the model. Time in different health states is therefore predicted for each patient and is not constrained by cycle length or the assumption necessary in Markov (state-transition) models that the risk of moving from one state to another is not affected by the states previously occupied. DES may be used in a wide range of decision problems, and may have particular strengths where a large range of treatment options and sequences is possible.

Effectiveness data were taken from CTOPP and MOST and the risk of stroke in AF modelled using data from the Framingham Cohort Study. The number of events predicted by the model is similar to that observed in the RCTs for stroke, but not for complications and AF, which occur less frequently with dual-chamber pacing than was observed in the trials. The impact of complication rates is considered in the sensitivity analysis and found to be insignificant. AF is an important

driver in the model, mainly because of its effect on costs (the incidence of stroke is small). Although the trials were of shorter duration than the Caro model, the difference in the occurrence of AF was around 1.5%, which is about half the difference predicted by the Caro model. The model assumes that different proportions of incident cases of AF will become chronic, based on data from CTOPP. Although the sensitivity analysis shows that equal rates of chronicity between the arms have essentially no effect on results, the assumption of differential rates of AF incidence is not explored in one-way sensitivity analysis. This factor is, however, included in the multiway sensitivity analysis, where AF risk reduction is allowed to vary between 0% and 40% in a triangular distribution around 20%. The multiway sensitivity analysis does not identify a significant impact of uncertainty on the conclusions of the base-case results.

Cost data were taken from routine NHS sources, with the exception of pacemaker hardware prices, which were obtained from manufacturers but are held confidential. The mix of VVI/VVIR and DDD/DDDR pacemakers used in the model is taken from current data on use in the UK. Rate-responsive pacemakers cost more than non-rate-responsive devices and the marginal cost difference is greater for DDD/DDDR than for VVI/VVIR. The ratio of VVIR:VVI is higher (approximately 75%) in the UK than the ratio of DDDR:DDD (around 50%). This means that the costs of the single-chamber pacemaker arm in the model are higher than would be the case if equal proportions of patients received rate-responsive devices in both arms. Since the effectiveness data are not stratified by rate responsiveness, which may have an independent influence on outcome (shown, for example, in the meta-analysis of exercise capacity earlier in this assessment) and the majority of patients in the relevant trials received rate-responsive devices, a bias in cost-effectiveness is introduced. A more appropriate approach would have been to model the mix of rate-responsive/non-rate-responsive devices reported in the trials that informed the model. The cost of pacemaker devices is addressed in one-way sensitivity analysis, but only in the direction of increasing the proportion of VVIR to 95%, which results in single-chamber pacing dominating. That said, the impact is small, and it is probable that the use of similar proportions of rate-responsive devices would not dramatically alter the results of the analysis.

There are several other potential biases in the model, although they are not consistently in the same direction. Costs of stroke include only in-hospital costs and, since the risk of stroke is higher in the single-chamber pacing arm, this biases against dual-chamber pacing, although by a small amount. The costs and consequences of haemorrhagic complications of anticoagulation are not taken into account, and since AF (and therefore anticoagulation) is more common on single-chamber pacing, this biases the model slightly against dual-chamber pacing.

An important issue for consideration is the way in which quality of life differences are modelled, since no difference in mortality is assumed. Utility data are based on patient preferences elicited in MOST using time trade-off, but are not reported in the main trial report (which is cited in the Caro model). It is not possible, therefore, to consider the methods used to obtain these data. Over 4 years in MOST there was a difference of 0.02 QALY between dual- and single-chamber pacing. It is not made clear whether this is a cumulative or an annual difference, but the application of these data in the Caro model results in an overall difference in utility between the two arms of the model over the 5-year time horizon of 0.09, suggesting that an annual difference is applied. The authors acknowledge that the model does not accommodate state-specific utilities (e.g. following stroke). The impact of increasing or decreasing the small difference in utilities is not modelled, but would be considerable on the ICER. Since the difference is very small, it is likely to be subject to considerable measurement error.

Pacemaker syndrome is modelled according to the findings of MOST and 16.8% of people are assumed to have such severe symptoms that cross-over from VVI(R) to DDD(R) is required, offsetting the difference in initial implantation costs between dual- and single-chamber pacemakers. It is debatable whether such a high rate of reimplantation should be accepted, although the sensitivity analysis addresses this issue.

Guidant Medical

The authors were not supplied with an electronic version of this model and so were unable to test varying the assumptions. The structure of the evaluation is sound, although there are some concerns about the choice of inputs.

The evaluation was carried out by the YHEC for Guidant. The degree of independence of the YHEC team is not reported. The YHEC model structure is similar to that developed by PenTAG, and reflects the main options and consequences,

although it is not made clear whether the focus is on single-chamber ventricular or atrial devices. The evaluation was carried out from the perspective of the NHS and reports cost–utility using 2002 costs to a 10-year horizon in a population with an average age of 72 years.

Device costs were obtained from a pacemaker manufacturer (Guidant) and most other costs from NHS reference sources. The cost of dual-chamber pacemaker insertion may have been underestimated as the same procedure costs are assumed for single- and dual-chamber insertion despite the fact that dual-chamber insertion takes longer.

Utilities were obtained from a range of sources. EuroQol 5 Dimensions (EQ-5D) domain scores from a sample of patients after percutaneous coronary intervention (PCI) were used for the state 'well after pacemaker insertion', and disutilities relative to this for heart failure, pacemaker syndrome and stroke were taken from the literature, although the methods for obtaining these and justification for the particular values used are not given.

There are insufficient details of the sources for data, in particular transition probabilities, and some evidence suggesting selective use of data which is likely to favour dual-chamber pacing in the analysis. In particular, the relative probabilities of developing heart failure and stroke are considered to be of limited reliability because of the lack of detail on sources and methods for calculation. In contrast to the concerns about the assumptions made in the base case, parameter uncertainty was handled well. One-way sensitivity analysis was somewhat restricted, parameter ranges being only ±1.0 SD from the central value. Probabilistic analysis was carried out, although the ranges for the distributions used are not reported. Two alternative scenarios to the base case were modelled:

- cost–utility in younger patients (age 50 years) over a 30-year period assuming generator replacement every 10 years and adjustment of baseline risk of death
- use of biventricular pacemakers for the treatment of heart failure.

In the 30-year scenario it is not clear whether probabilities of death, which were set at 50% of those for the base-case cohort, are time dependent. The account of the assumptions for upgrading is not clear.

The authors acknowledge the "severe lack of data" regarding the use of biventricular pacemakers and are conservative in the assumptions made regarding their use (2–7% of patients with heart failure). Even this level of use probably represents a considerable increase on current usage. This figure is based on clinical opinion, but the methods for obtaining the estimate are not reported.

The results of the base-case scenario (10 years) suggest that dual-chamber pacing would yield an additional 0.399 QALYs for an additional cost of £742 per patient, a cost per QALY ratio of £1780. Based only on mortality, the cost per life-year gained is estimated as £3416. The probabilistic analysis showed that 65% of simulations resulted in more QALYs at higher cost in dual-chamber pacing, although the probability of the ICER being below any given threshold for willingness to pay is not reported. There was a 10% chance that dual-chamber pacing would dominate (i.e. more QALYs at less cost) and a 23% chance that single-chamber pacing would dominate.

The 30-year scenario used to evaluate implantation in younger patients showed that dual-chamber pacing dominates (10.73 versus 10.03 QALYs for £8166 versus £9223 per patient). In the scenario used to explore the use of biventricular pacemakers for heart failure, a cost per QALY of £3693 is reported for dual-chamber pacing.

The main concern with this evaluation is the choice of values in the base case, which may be biased in favour of dual-chamber pacing. Despite this, there is clearly considerable uncertainty about the cost-effectiveness of dual-chamber pacing, as indicated by the 25% probability that single-chamber pacing is more effective as well as less costly.

St Jude Medical

The analysis was carried out by Abacus International on behalf of St Jude Medical. The model compares costs and outcomes of dual- versus single-chamber pacemakers in individuals with AVB and SSS and in individuals with SSS only. The evaluation considers costs and outcomes, but not QALYs, for a hypothetical cohort of 280 individuals for the AVB/SSS model and 111 for the SSS model. These numbers are estimated from the incidence of implants of (485 per million) in a hypothetical primary care trust (PCT) with a catchment population of 1 million, excluding 13% of potential recipients who have chronic AF. The model uses a 7.5-year time horizon.

TABLE 37 *Summary of estimates for key events used in the St Jude Medical analysis*

Incidence of	Ventricular in SSS population	Dual in SSS population	Ventricular in SSS and/or AVB population	Dual in SSS and/or AVB population
AF	27.1% (MOST[48])	21.4% (MOST[48])	6.6% (year) (CTOPP[52])	5.3% (year) (CTOPP[52])
Stroke	–	–	18% (Mattioli[46])	9.5% (Mattioli[46])
Heart failure	12.3% (MOST[48])	10.3% (MOST[48])	–	–
Pacemaker syndrome	28–37.6% (MOST,[48] Wharton[47])	0% (MOST,[48] Wharton[47])	26% (PASE[35])	0% (PASE[35])
Mortality	6.8% (Wharton[47])	3.2% (Wharton[47])	–	–

TABLE 38 *Main results of St Jude Medical economic analysis*

Cost of main events	SSS, VVI	SSS, DDD	SSS/AVB, VVI	SSS/AVB, DDD
Implant (including complications)	£4793	£5979	£4793	£5979
Cost of subsequent events (7.5 years)	£2060	£609	£1810	£441
Total cost (7.5 years)	£6852	£6588	£6602	£6420

The report does not specify the type of model developed. It is therefore difficult to assess methodological features. From the electronic copy received, it appears that the model uses simple calculations of the incidence of main events and associates costs with these. The disease pathway over time does not appear to have been modelled. The model does not account for background mortality or the time-dependency of key events (e.g. AF).

The submission includes detailed information on the sources of data for effectiveness and costs. Device costs were obtained from tendering audits provided by the manufacturer. The base year for costs is not stated. Although cost calculations appear reasonable, the estimates for the incidence of main events incorporated in the model appear to be highly selective. Differences in the incidence of main adverse events are included only where there is a significantly higher risk for ventricular pacing, regardless of the available evidence from systematic reviews. *Table 37* shows the range of values identified in the literature review carried out for the analysis and incorporated into the model. Some outcomes are presented, but their incorporation in the model is unclear (e.g. mortality).

Some therapeutic options following key events are not considered. Drug treatment in primary care and reprogramming from dual to ventricular chamber following AF are not considered. Pacemaker syndrome is assumed to result in upgrading in all cases, which is unrealistic. Results for the stroke incidence are taken from Mattioli and colleagues.[46] This study was excluded from the systematic review and results are dramatically different from the meta-analysis reported in this assessment. *Table 38* shows the main results of the St Jude Medical evaluation.

The model estimates a total of 101/280 (36%) events avoided using dual-chamber pacing in individuals with AVB/SSS (72.7 cases of pacemaker syndrome, 3.7 cases of AF and 23.7 strokes). Higher numbers of events avoided are estimated for individuals with SSS (56/128, 44%), mainly for pacemaker syndrome (42 cases).

The submission concludes that dual-chamber pacing is dominant, that is, cost-saving when prevention of all events is considered. When only pacemaker syndrome cases avoided are considered, dual-chamber pacing is dominant in SSS recipients and regarded as cost-effective in AVB/SSS recipients (£423 per pacemaker syndrome case avoided).

One-way sensitivity analyses were conducted on the ICER according to the incidence of pacemaker syndrome. The impact on the ICER was presented for all adverse events avoided and for pacemaker syndrome cases avoided only. For all events avoided, the ICER varies between dominance (assuming a 26% incidence of pacemaker syndrome) and £3641 (6.5% pacemaker syndrome

incidence) in individuals with AVB/SSS. For individuals with SSS only, the ICER varies from dominance (at a particularly high value of 32.8% for pacemaker syndrome incidence) to £3661 (8.2% pacemaker syndrome incidence).

For cases of pacemaker syndrome avoided in AVB/SSS, the ICER varies between £423 (26% incidence) and £5689 (6.5% incidence). In recipients with SSS, the ICER varies between dominance (32.8% incidence) and £4409 (8.2% incidence).

Summary: existing economic analyses

- Three economic evaluations were included in submissions to NICE. These were of varying quality.
- All suggest that dual-chamber pacing is, at best, likely to be cost-saving and produce additional benefits (i.e. dominate single-chamber pacing) and, at worst, to yield additional benefits at a cost that would be considered acceptable to decision-makers. All have some methodological limitations.
- The model produced for St Jude Medical is the lowest in methodological quality, with evidence of selective choice of inputs which biases the model in favour of dual-chamber pacing, and failure to model cost–utility. Dual-chamber pacing is predicted to dominate single-chamber devices in this model.
- The model produced by the YHEC for Guidant Medical is structurally sound and includes probabilistic sensitivity analysis. The analysis is limited by incomplete reporting of methods and a range of potential biases that would favour dual-chamber pacing. Dual-chamber pacing is predicted to yield additional QALYs at a cost of £1780 based on similar costs and a small benefit (0.399 QALYs over 10 years).
- The ABHI model, produced by Caro Research, uses discrete event simulation. The evaluation appears to be of good quality. The main consequences modelled are simpler than in the YHEC model (i.e. heart failure and mortality are not assumed to differ between options). Although there are some potential biases in this model, they do not consistently favour dual-chamber pacing. The ICER predicted is £477 per QALY, based on a small difference in QALYs (0.09) over the 5-year duration of the model and near-identical costs. Although pacemaker syndrome is an important driver for the model results, when assumptions regarding reimplantation are relaxed to the levels shown in the trials of device, ICERs remain at a level generally considered affordable by decision-makers (approximately £5000–10,000 per QALY). This may be because the QALY gain is independent of events in the model.

PenTAG economic evaluation of dual-chamber pacing

Methods

The costs and benefits of dual-chamber pacing compared with single-chamber atrial and ventricular pacing we estimated using a series of Markov models developed in Microsoft Excel®.

The incremental cost-effectiveness of dual-chamber pacemakers compared with single-chamber ventricular and atrial pacemakers for bradycardia was calculated for three hypothetical cohorts of 2000 individuals with AVB or SSS, considering the stream of clinical events, total healthcare costs and total benefits associated with each mode of pacing.

The analysis was undertaken from the perspective of the UK NHS. Outcomes were expressed in QALYs. Benefits and costs were discounted at 1.5% and 6%, respectively. Costs are in UK pounds (2003) and estimates from earlier years were inflated using the Consumer Price Index. Time horizons of 5 and 10 years are considered.

The structural features of the model are described in the following two subsections. The section on Model assumptions describes assumptions regarding each of the key states in the model, namely, clinical treatment transition probabilities, costs and utilities, and how they differ between the arms of the model.

The analysis of uncertainty is then described; this includes one-way sensitivity analyses on the most important parameters and probabilistic sensitivity analysis. The type and frequency of events occurring in the cohorts are tabulated alongside associated costs and QALYs.

Model structure and overview

The model is based on cohorts of 2000 individuals.

Two separate models were created according to the underlying cause of bradycardia: AVB or SSS. SSS and AVB are modelled separately because outcomes differ by cause. Individuals with AVB are less likely to progress to AF than individuals with SSS. In addition, the development of atrioventricular block in people with SSS on single-chamber atrial pacing may lead to upgrade.

In the AVB model, ventricular pacing was compared with dual pacing only (*Figure 31*). In the SSS model both single-chamber atrial and ventricular pacing are considered (*Figure 32*). Although atrial pacing is recommended for SSS in the BPEG Guidelines,[11] clinical opinion was that ventricular pacing is often carried out for this indication.

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.

In each treatment option a series of states was defined to reflect the main outcomes following pacemaker insertion. These include complications of insertion, remaining well with the pacemaker, pacemaker syndrome (mild or severe); upgrade to dual-chamber pacemaker, AF, heart failure, stroke, generator expiry and death.

The model employs a 1-month cycle beginning with implantation of the pacemaker device. Perioperative complications may occur. Following successful implantation, people may develop pacemaker syndrome in the ventricular arm only. This is assumed to be mild in the majority of cases, but may be sufficiently severe to warrant reimplantation with a dual-chamber device. Patients with SSS may develop AVB and, if an atrial pacemaker is being used, this results in upgrade to a dual-chamber device. Dual-chamber and ventricular pacemakers are not affected by the development of AVB. Where AVB is present, no effect on SSS is assumed. The populations modelled are homogeneous, that is, there is no assumption of a mix of SSS and AVB in the same people.

Patients with any form of pacemaker may develop AF, heart failure or stroke. Where AF occurs with a dual-chamber pacemaker, the pacemaker is reprogrammed to act as a single-chamber ventricular device and subsequent risks of stroke and heart failure are assumed to be as for single-chamber ventricular devices.

Heart failure and stroke may occur with or without AF. Crude assumptions are made about the clinical progression and treatment of heart failure and stroke, including the use and risks of anticoagulants. The authors considered the use of biventricular pacemakers as a treatment option in heart failure and rejected this as current use of this technology is very limited.

The model runs, in the base case, for 5 years. This is longer than the follow-up in most of the randomised trials to date. There was some concern that modelling longer term consequences may lead to difficulty in interpreting the relative cost-effectiveness of dual- and single-chamber pacemakers, particularly since the consequences of stroke and heart failure are modelled using relatively simple assumptions. However, it is also important to consider the entire stream of costs and benefits from the decision point, and therefore a 10-year time horizon was included. Given that the average age at entry to the model is 75 years, this is likely to reflect the clinically realistic lifetime of the technologies in the majority of cases.

Death is a possibility from all states. The risk of death is specific to each state (e.g. mortality from stroke). Where people are 'well' with a pacemaker, death rates are estimated from general population mortality data.

Model assumptions

This section reports on the main assumptions made in relation to each health state. Details of the sources of all input values are given in *Tables 45* and *46* (pp. 88–90).

Progression of individuals across states was modelled based on probabilities obtained from trials included in the systematic review conducted earlier in this assessment. Where possible, a baseline risk was applied to single-chamber pacing and then relative risk estimates from the meta-analyses or single trials reported earlier in the assessment were applied.

Effectiveness data for individuals with SSS were obtained from MOST[48] since it was the largest and most homogeneous study to report on individuals with this underlying indication.

Time spent in health states was weighted for quality of life to calculate QALYs. Utilities for health states were mostly obtained from time trade-off values obtained from patients in the PASE trial[99] or from reports of studies held on the Harvard Catalogue of Preference Scores.[100]

The model assumes that the population receiving pacemaker implantation is 75 years of age. Within each cohort, half receive a dual-chamber device in each treatment comparison. Results are reported

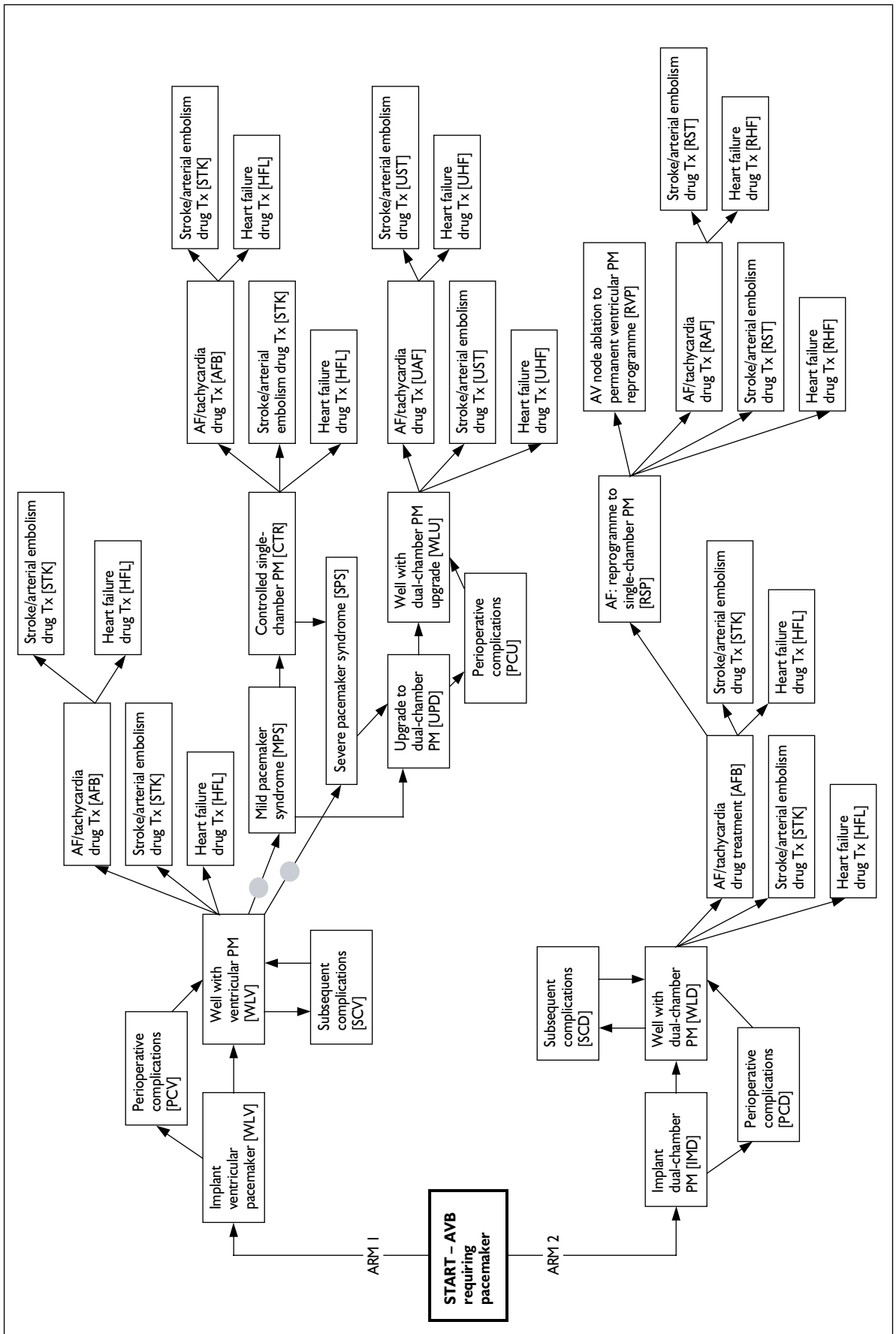


FIGURE 31 *Major pathways for patients with AVB. All states include generator replacement (from year 1) and death from other causes [DTO]. PM, pacemaker; Tx, treatment;* ●*, cycle-dependent probability.*

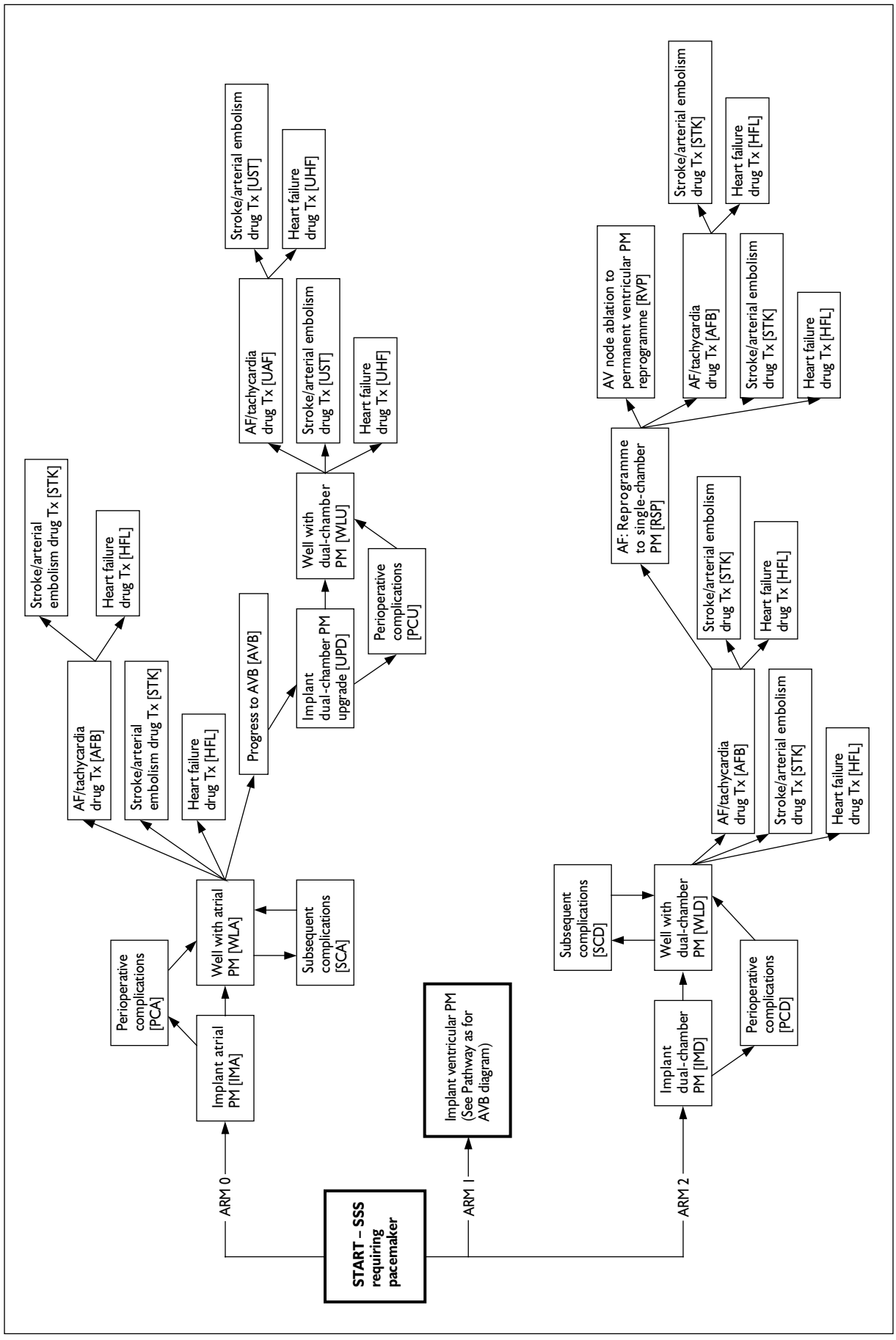


FIGURE 32 *Major pathways for patients with SSS. All states include generator replacement (from year 1) and death from other causes [DTO].*

TABLE 39 *Hardware costs from ten hospitals sampled as part of UKPACE*

Hospital	VVI	VVIR	DDD	DDDR	Atrial lead	Ventricular lead
A	738	1075	1260	1775	–	–
B	685	1233	1590	3211	145	180
C	698	1160	1323	2038	164	148
D	597	1023	1234	1663	161	146
E	853	1185	1279	1753	171	166
F	658	1144	1545	–	206	206
G	–	–	–	–	–	–
H	–	1042	1443	2023	208	208
I	–	1107	1421	2394	171	171
J	605	921	1187	1995	178	148
Mean	690	1099	1365	2107	175	172

separately for the AVB population (dual versus ventricular pacemakers) and the SSS population (dual versus atrial and dual versus ventricular pacemakers). *Tables 45* and *46* (pp. 88–90), summarise the transition probabilities, costs and utility estimates used in the model.

Pacemaker implantation

People enter the model at the time of implantation of the relevant pacemaker. In the first cycle, during which implantation occurs, the utility value reflects quality of life before having a pacemaker implanted (0.76, from PASE[99]). People who have an uncomplicated insertion move to being well with pacemaker state. No difference in utility is assumed for this state by pacemaker type. People who experience complications spend one cycle (1 month) with a utility slightly worse than the initial state (0.75). This decrement (0.01) is also applied to cases where upgrading or replacement is required later in the course of the model, that is, a reduction in utility for 1 month of 0.01 is assumed from the 'well' state.

Hardware costs

Variations in the costs of pacemakers are driven by pacemaker model, functions (such as rate responsiveness) and programmable modes. Additional programming features, which are not considered in this assessment, may increase the price of pacemakers considerably, for example, mode-switching, which allows the pacemaker to switch automatically to ventricular mode if a supraventricular arrhythmia occurs.

The initial hardware costs of dual-chamber pacemakers are higher than those of single-chamber devices owing to the higher level of sophistication of the pulse generator. The addition of rate responsiveness increases the cost of dual- and single-chamber devices, although the additional cost for this feature is greater in dual-chamber devices. In the UK, currently, rate responsiveness is included more frequently in single-chamber ventricular pacemakers than in dual-chamber pacemakers, because fixed rate dual-chamber pacemakers are suitable in individuals with AVB when sinoatrial conduction is intact.

An estimate of average cost, taking into account the current use of VVIR or DDDR pacemakers in the UK, would slightly underestimate the cost difference between the single- and dual-chamber devices in relation to the effectiveness inputs used for the model. Therefore, it was assumed that rate responsiveness would be included in the same proportion of pacemakers as is reported in the clinical trials.

Very limited information was available on the purchase price to NHS trusts of pulse generators and leads and there is likely to be local variation. An economic evaluation was carried out in association with UKPACE. The authors of the unpublished UKPACE trial have agreed that the price of devices may be made public (Dixon S, ScHARR, University of Sheffield, personal communication, draft report of the UKPACE cost-effectiveness analysis, 2004). Resource use was measured retrospectively in a subgroup of participants and valued, to obtain costs in each arm of the trial, using estimates from a survey of ten hospitals. The mean costs of the generator plus the appropriate leads from this study were obtained and are used in the model (*Table 39*).

TABLE 40 *Summary of cost and utility values used in relation to initial implantation*

Event	Incidence rate		Cost		Utility	
	Single	**Dual**	**Single**	**Dual**	**Single**	**Dual**
Implant pacemaker	–	–	£4025 (ventricular and atrial)	£4925	0.76	0.76
Perioperative complications	3.3% both atrial and ventricular	6.8%	£816 (ventricular), £894 (atrial)	£894	0.75	0.75
Subsequent complications	0.1%	0.1%	£816 (ventricular), £894 (atrial)	£894	0.75	0.75
Well with pacemaker	–	–	£40	£40	0.925	0.925

Implantation procedure costs

Procedure costs were estimated from the Resource Cost Initiative (RCI)[101] with some corrections to account for differences in costs between dual- and single-chamber devices.

The RCI database[101] includes costs of pacemaker implants [Health Resource Group (HRG) E08, Pacemaker without AMI or heart failure] for 441 hospital trusts in England and Wales. These are determined using a top–down method. The costs include all relevant components, including intervention and ward costs, hardware, consumables and overheads. This source has two advantages over the cost data collected as part of UKPACE: the data are more representative and include additional HRGs reporting estimates of the cost of implantation as a revision procedure or where complications occur (HRG E09, Pacemaker revision, and HRG D30, Pneumothorax). The RCI is limited in that it does not provide costs by type of pacemaker. Therefore, the average hardware costs reported in UKPACE were subtracted from the relevant HRG costs and the resulting estimate was adjusted to take account of the differences in type of pacemaker.

The absolute cost estimates are higher than those from UKPACE, but the difference between dual- and single-chamber pacemakers is extremely close to that measured in UKPACE (£900 versus £917 in UKPACE). A sensitivity analysis was carried out in which UKPACE costs were used and the costs of a revision, an upgrade or a complicated implantation estimated by applying the ratio of simple:complicated implantation from RCI data to the UKPACE estimates.

The cost of inserting atrial pacemakers was assumed to be equal to that of ventricular pacemakers, including the cost of one atrial lead.

Perioperative complications

The incidence of perioperative complications is based on the data reported in the systematic review (see section 'Adverse effects of implantation', p. 61). The overall complication rate was similar in MOST, PASE and CTOPP. CTOPP reported a higher rate for dual-chamber devices than the other studies (9.0%), but this excess was due to the inclusion of inadequate atrial sensing as a complication. This event was not considered in MOST since its occurrence was a reason for exclusion from the trial. Therefore, the complication rate considered here was calculated from CTOPP excluding the incidence of inadequate atrial sensing (2.2% for dual chamber and 0.3% for ventricular, see section 'Non-fatal complications', p. 61) (*Table 40*).

A small decrement in utility is assumed for complications (0.01), taken from an estimate for the disutility associated with lead-related complications during implantable cardiac defibrillator insertion, derived from clinicians' estimates.[100,102]

The cost of perioperative complications was calculated from NHS Resource Costs.[101] The HRG costs for pacemaker revision (HRG E09) and pneumothorax (HRG D30) were combined according to the proportions of people experiencing different types of complications in CTOPP. Atrial pacing was assumed to have the complication rate of single-chamber ventricular pacing and the unit cost of complications of dual chamber, since it was assumed that the relative occurrence of lead dislodgement is higher in dual- and single-chamber atrial than in single-chamber ventricular pacing.

Complication rates for upgrades were arbitrarily assumed to be double those of primary dual-chamber device insertion.

TABLE 41 *Summary of values used in relation to pacemaker syndrome*

	Incidence rate	Cost	Utility
Total incidence	26% (3 years)	–	–
Mild pacemaker syndrome	21.7% (44% occur in month 1, 33% months 2–6, 23% at constant rate throughout duration of the model)	£40	0.80
Severe pacemaker syndrome	16% of incident cases of pacemaker syndrome	£176	0.62
Upgrade to dual chamber (severe pacemaker syndrome)	100% of all individuals alive	£4925	0.915
Perioperative complications during upgrade	13.6%	£894	0.915

Pacemaker syndrome

Individuals in the ventricular arm may progress to pacemaker syndrome.

There is some direct evidence for a spectrum of severity of pacemaker syndrome[34] and, indirectly, from the difference in incidence rates between the trials of mode (PASE and MOST) and reimplantation rates in the trials of device (CTOPP). The model therefore includes two states for pacemaker syndrome: mild and severe.

Total incidence of pacemaker syndrome is taken from MOST (26%) as this was the largest study that measured incidence using an explicit definition. Upgrade is not assumed in all cases of pacemaker syndrome. Instead, the same proportion of cases that were severe enough to lead to reimplantation in CTOPP was modelled, that is, 4.3% of the total cohort, or 16.5% of cases of pacemaker syndrome (*Table 41*).

The incidence of pacemaker syndrome is clearly time dependent.[35,48,52] Rates of occurrence were similar in MOST and PASE, with the latter providing more details. In PASE, 44% of cases of pacemaker syndrome were reported in the first month, 77% occurred within 6 months and 23% during the remainder of the study. The model uses the rates reported in PASE.

In the base case, people with mild pacemaker syndrome remain in that state unless they develop stroke, AF, heart failure, or die.

Severe pacemaker syndrome leads to upgrade to dual-chamber pacing with the implantation of an atrial lead and generator replacement. All people with severe pacemaker syndrome are assumed to receive an upgrade within 3 months.

The utility for pacemaker syndrome was calculated from data reported in PASE[99] that mild pacemaker syndrome was equivalent to NYHA classes I and II and severe pacemaker syndrome to NYHA classes III and IV. Corresponding utility weights obtained using the time trade-off method in PASE were 0.80 and 0.62, respectively. The utility decrement (0.01) assumed at initial implantation is applied in cases when an upgrade to a dual-chamber device occurs.

The cost accruing to severe pacemaker syndrome, excluding device upgrade, is assumed to be the same as the cost of reprogramming a dual-chamber pacemaker, that is, the cost of cardiological consultation, pacing check and ECG.

The cost of upgrading from a single- to a dual-chamber device is assumed to be the same as the cost of primary implantation of a dual-chamber pacemaker. Although the procedure may take longer because of the need to remove the old generator, this additional resource consumption is, to some extent, compensated by the fact that only one new lead will be introduced.

For mild pacemaker syndrome, costs are assumed to be the same as for routine follow-up. This may underestimate the cost of a more intensive follow-up (i.e. an extra clinician visit) as symptoms occur.

The influence of the utility of pacemaker syndrome, mild and severe, and waiting time for upgrade in severe cases is explored in sensitivity analyses.

Progression to AVB

Individuals with SSS who receive atrial chamber pacemakers are at risk of progression to AVB. This

TABLE 42 *Summary of values used in relation to progression to AVB*

	Incidence rate	Cost	Utility
Total incidence	1.9% per annum	£176	0.76
Upgrade for AVB	100%	£4925	0.915

TABLE 43 Incidence, cost and utility for AF according to diagnosis and pacing mode

	Incidence rate		Cost	Utility
Diagnosis/treatment group	**Dual**	**Single**	**Both**	**Both**
SSS on ventricular pacemaker	Cumulative incidence (36 months): 30% First 6 months: 12%; following periods (30 months): 18% (MOST)	Cumulative incidence (36 months): 39% First 6 months: 12%; following periods (30 months): 27% (MOST)	£41	0.87
SSS on atrial pacemaker	As for SSS on ventricular (MOST)	RR = 0.42 of rate for dual chamber in SSS[91]	£41	0.87
AVB	*[CiC removed – data from the UKPACE study]*	*[CiC removed – data from the UKPACE study]*	£41	0.87

requires upgrade to a dual-chamber device. There is limited evidence on the rate of progression, but Nielsen and colleagues[91] report an annual rate of 1.9%. This is therefore used in the model. Where progression occurs, an upgrade to a dual-chamber device is assumed in 100% of cases after spending 1 month (cycle) with preimplantation utility (0.76). This assumes that AVB is of sufficient severity to result in symptoms in all cases. Costs for the cycle in which AVB develops are assumed to be the same as for severe pacemaker syndrome (i.e. cardiology consultation and ECG). Costs of an upgrade are assumed to be equal to the cost of a dual chamber (*Table 42*).

The utility decrement (0.01) associated with the implantation cycle is applied. Costs of upgrade are as described in the section on pacemaker syndrome (p. 84).

Atrial fibrillation

Assumptions regarding the incidence of AF according to type of pacing are shown in *Table 43*. There is conflicting evidence from trials on the patterns of incidence. MOST included people with SSS and showed a significant effect for dual chamber pacing on AF. CTOPP, which included roughly equal proportions of people with SSS and AVB, also demonstrated a significant effect on AF but with a delay in the effect. *[CiC removed – comparison of data from the CTOPP and UKPACE trials.]* AF rates were modelled from UKPACE for the AVB population because of the homogeneous trial population. Values for AF in SSS were taken from MOST and for atrial pacing from Nielsen and colleagues.[91] The variation in AF rates with time was modelled based on the appropriate trials and the effect of assuming a range of relative risks was explored in sensitivity analysis. The impact of assuming a constant relative risk of AF was also explored.

The probability of AF in the comparison of atrial and dual pacing was handled in the following way. Nielsen and colleagues[91] showed a significant difference between dual- and single-chamber pacing for the incidence of AF in favour of atrial pacing (7.4% versus 20%). In the SSS model it was assumed that these findings apply to the atrial arm only. Rates for AF in the dual-chamber arm are taken from MOST and the relative risk of AF for single atrial versus dual-chamber devices (see section 'Mortality, stroke, atrial fibrillation and heart failure', p. 68) derived from Nielsen and colleagues[91] was applied to obtain the probabilities of AF with atrial pacing. The dual-chamber population in MOST experienced a higher rate of AF than the corresponding population in Nielsen. The difference between dual- and single-chamber atrial pacing, which favours the latter in the limited clinical evidence base, is therefore increased slightly further.

Sixty-seven per cent of episodes of AF are assumed to become chronic.[14] Cases that occur on dual-chamber pacing are addressed by reprogramming, which attracts the cost of an additional specialist visit and ECG. A utility decrement of 0.01 is applied to the cycle in which reprogramming occurs. Pacemaker syndrome is assumed not to occur in the presence of AF as atrial contraction is not present. AV node ablation is not used in this model.

Estimates for antithrombotic and anticoagulant treatment in AF are taken from a cross-sectional community study of over 7000 people carried out in 1998.[103] Thirty-six per cent of all (transient and chronic) cases are treated with aspirin, and 29% of chronic cases are treated with warfarin to maintain a target international normalised ratio (INR) of 2.5. Digoxin treatment is assumed in 54% of chronic cases, based on the AFFIRM trial.[104–106] It is important to note that only resource-use data were taken from this trial and estimates for clinical effectiveness were not included. Based on AFFIRM, β-blocker and calcium-channel blocker use in people with AF was estimated as 59% and 26%, respectively.

All people with chronic AF are assumed to have eight GP visits per year. Those on warfarin have INR tests monthly, two specialist outpatient visits per year and eight anticoagulant clinic visits, based on a recent community study carried out in Scotland by Stewart and colleagues.[107] Based on the same study, people with paroxysmal AF have two blood tests per year and eight GP visits.

Utility estimates for living with AF were derived from a study[108] reporting clinician estimates for the difference between AVB and AF, reported in the Harvard Catalogue of Preference Scores,[100] of 0.05. This decrement is therefore applied to the 'well' states in the model, giving a utility for AF of 0.875.

AF is well established as a risk factor for stroke. Progression is modelled using estimates published in a review by Chugh and colleagues in 2001.[14] An annual rate of 3.2% is assumed.

Progression to heart failure is assumed to occur in 3.3% of cases per annum, based on a review by Wang and colleagues using data from the Framingham Heart Study.[109]

Heart failure

Patients may develop heart failure from the AF and well states. Risk of heart failure from AF is taken from Wang and colleagues (3.3% per annum).[109] Development of heart failure from the well state is modelled using the meta-analysis reported earlier in this assessment (annual rates of 2.6% in single chamber and 2.5% in dual chamber). For the atrial arm in SSS, the relative risk from the trial by Nielsen and colleagues[91] (see section 'Mortality, stroke, atrial fibrillation and heart failure', p. 68) has been applied to atrial pacing (RR = 1.07).

Utility values for heart failure are taken from data collected using time trade-off in the PASE study (0.64). Costs of heart failure are estimated as £152 per month, based on assumptions regarding hospital admission and drug use. The use of biventricular pacemakers was considered but not included in the model.

Mortality from heart failure is estimated as 21% per annum, based on a very large cohort study of people hospitalised for heart failure in Scotland.[110] This is consistent with the incidence data for heart failure collected in the main pacemaker trials, which measured hospital admissions *[comment on the CiC UKPACE trial removed]*.

Stroke

Stroke occurs in the model following AF and from the well state. The progression from AF was reported earlier. Progression from the well state is modelled using the estimates of stroke incidence from the meta-analysis of trials reported earlier in the assessment. The difference in stroke rates in trials is in the region of 0.5% (note that the weighted average trial duration was just over 3 years). For the atrial arm in SSS the relative risk calculated from the trial by Nielsen and colleagues[91] (see section 'Mortality, stroke, atrial fibrillation and heart failure', p. 68) has been applied to atrial pacing (RR = 0.62).

Community cost of stroke was derived from a UK study of resource use in people with stroke living in the community, in lone or shared accommodation.[111] Data relevant to the NHS perspective were taken from this study and valued using 2003 unit cost reference data for community care.[112] Costs of hospital care were taken from NHS Reference Costs[101] for 2002, actualised to 2003.[113] Total cost for stroke is estimated as £9792 per annum (£816 per cycle).

Mortality from stroke is assumed to be 33% per annum. This value was derived from death rates observed in a community-based cohort of individuals with first ever stroke in the year 2000 in Sweden.[114]

Utility for stroke was estimated as 0.39. This is the median value reported in a systematic review of utility estimates after stroke.[115,116] This included 67 studies using a range of preference elicitation methods, carried out in patients, members of the general public and clinicians.

Reimplantation at the end of generator life

The National Pacemaker Database[23] contains information on the life expectancy of different types of pacemaker up to 10 years. This was used to predict the risk of generator expiry during the course of the model. Generator expiry data from the national database in year 1 includes a higher proportion of cases of upgrade due to pacemaker syndrome. The need for generator replacement therefore begins in year 2 and increases from 0.7% and 0.6% respectively per year for dual and single pacemakers to 25.5% and 18% in year 10. Atrial and ventricular replacement rates are assumed to be equal.

Mortality

Perioperative mortality is taken from PASE and has a probability of 2.5 per 1000. Mortality is assumed to be equal across the different arms of the model from all states, with the exception of upgrading from single to dual chamber, in which the mortality from complications is assumed to double.

Background risk of death is calculated using all-cause mortality statistics for 2002,[117] taking the weighted average for age groups 75 years and older. This is applied in the model as a constant rate and with equal rate for the dual- and single-chamber arms.

Once an individual has developed AF, heart failure or stroke, progression to death from these specific causes is dependent on death rates from specific causes. An adjustment is made to prevent double counting of cardiovascular mortality, which is predicted within the model: mortality from stroke, heart failure, conduction disease and heart block were subtracted from all-cause mortality. Mortality predicted by the model from stroke and heart failure is termed cardiovascular deaths.

Cost and utility of deaths are assumed to be zero.

Analysis of uncertainty

Several approaches have been used to address uncertainty. The consequences of developing AF, stroke and heart failure are necessarily modelled simplistically: the use of reasonably short (5 year) and longer term (10 year) horizons addresses uncertainty from longer term modelling. Second, one-way sensitivity analyses are used to investigate the influence of variation in single parameters on model outputs.

Third, a probabilistic Monte Carlo simulation has been developed to explore the impact on cost-effectiveness of parameter uncertainty in the underlying model inputs. This is applied only to the base case (5-year model). In this stochastic approach, the Markov model is run for 1000 trials with key input values randomly drawn from probability density functions for each trial. In these simulated trials, values were sampled for utilities, costs and transition probabilities using the following distributions (see also *Table 47*).

- Utility values: sampled from a β-distribution since these utilities are bounded in the [0,1] interval (i.e. assuming positive values). α and β parameters for the distribution were derived using standard formulae from the observed means and standard deviations.
- Cost values: sampled from log-normal distributions (to represent the essentially skewed nature of cost data). Parameter values for mean were derived from aggregated cost data. Standard deviation was estimated from aggregated cost data.
- Transition probabilities: sampled from β-distributions since these probabilities are

TABLE 44 *Summary of mortality estimates used in the PenTAG model*

	Mortality rates	
Event	**Dual**	**Single**
Mortality from all other causes	8.7% per annum	8.7% per annum
Perioperative mortality	0.25% per cycle (PASE[35])	0.25% per cycle (PASE[35])
Mortality after subsequent complications	0.5% per cycle (assumption)	0.5% per cycle (assumption)
Perioperative mortality, upgrade	0.5% (assumption) per cycle	0.5% (assumption) per cycle
Mortality from heart failure	20.8% per annum[110]	20.8% per annum[110]
Mortality from stroke	33% per annum[114]	33% per annum[114]

TABLE 45 *Summary of transition probabilities used in the PenTAG model*

	Annual rate of main events in the model (or cycle rate)	Single chamber	Description (source)
(a) Single-chamber pacing: transitions between states			
Implant pacemaker	Incidence of perioperative complications (atrial and ventricular)	3.3%	Applies to single cycle only (CTOPP[52])
	Incidence of perioperative deaths	0.25%	Applies to single cycle only (PASE[29])
	Subsequent complications	Complications 0.1% Perioperative mortality 0.5% of complications	Applies to single cycle only (assumptions). Perioperative death was assumed to be twice perioperative death rate at first implant
Progression to pacemaker syndrome		Total rate modelled: 26% (of which 16% severe, 84% mild)	Total cumulative rate for 3 years (MOST[48] and CTOPP[52])
	Progression to mild pacemaker syndrome	7.2% (first cycle), 5.4% (cumulative, cycles 2–6), 3.8% (cumulative to end of period modelled)	(MOST[48] and CTOPP[52])
	Progression from well to severe pacemaker syndrome	4.2% (first cycle), 3.2% (cumulative, cycles 2–6), 2.2% (cumulative to end of period modelled)	(MOST[48] and CTOPP[52])
	Upgrade to dual-chamber pacing from severe pacemaker syndrome	100% of alive individuals	(CTOPP[52])
	Perioperative complications during dual-chamber upgrade	13.6%	Double perioperative complications as first implant (assumption). Cycle rate from CTOPP[52]
Progression to AF	Progression to AF (ventricular pacing), individuals with SSS	Cumulative rate for 36 months 39% First 6 months 12%, following periods (30 months) 27%	(MOST[48])
	Progression to AF (ventricular pacing), individuals with AVB	*CiC removed [UKPACE]*	*CiC removed [UKPACE]*
	Progression to AF (Atrial pacing)	RR = 0.42 of progression to AF in the dual-chamber arm (SSS only)	Annual rate (Nielsen[91])
Progression to AVB	Progress to AVB (Atrial pacing)	1.9%	Annual rate (Nielsen[91])
	Upgrade to dual-chamber after AVB in SSS on atrial pacemaker	100% of alive individuals	(Assumption)
Progression to stroke	Progression to stroke (without AF)	Single-chamber ventricular 1.25% Single-chamber atrial RR = 0.62 of progression to AF in the dual-chamber arm (SSS only)	Annual rate (this review) (Nielsen[91])
	Progression to stroke (after AF)	3.2%	Annual rate (Chugh[14])

continued

TABLE 45 *Summary of transition probabilities used in the PenTAG model (cont'd)*

	Annual rate of main events in the model (or cycle rate)	Single chamber	Description (source)
Progression to heart failure	Progression to heart failure (without AF, ventricular and atrial pacing)	2.6% Single-chamber atrial RR = 1.07 of progression to AF in the dual-chamber arm (SSS only)	Annual rate (this review) (Nielsen[91])
	Progression to heart failure (after AF)	3.3%	Annual rate (Wang[109])
Long-term outcomes	Death from stroke	33%	Annual rate (Appelros[114])
	Death from heart failure	20.8%	Annual rate (MacIntyre[110])
(b) Dual-chamber pacing: transitions between states			
Implant pacemaker	Incidence of perioperative complications	6.6%	Applies to single cycle only (CTOPP[52])
	Incidence of perioperative deaths	0.25%	Applies to single cycle only (PASE[29])
	Subsequent complications	Complication 0.1% Mortality 0.5% of complications	Perioperative death was assumed to be equal to perioperative deaths of first implant doubled (assumption). Applies to single cycle only
Progression to AF	Progression to AF, individuals with SSS	Cumulative rate for 36 months 30% First 6 months 12%, following periods (30 months) 18%	(MOST[48])
	Progression to AF, individuals with AVB	*CiC removed [UKPACE]*	*CiC removed [UKPACE]*
	Reprogramming to single chamber	100%	(Assumption)
Progression to stroke	Progression to stroke (without AF)	1.07%	Annual rate (this review)
	Progression to stroke (after AF)	3.2%	Annual rate (Chugh[14])
Progression to heart failure	Progression to heart failure (without AF)	2.5%	Annual rate (this review)
	Progression to heart failure (after AF)	3.3%	Annual rate (Wang[109])
Long-term outcomes	Death from stroke	33%	Annual rate (Appelros[114])
	Death from heart failure	20.8%	Annual rate (MacIntyre[110])

bounded in the [0,1] interval. α and β parameters were derived using standard formulae from mean and standard deviation measures. Mean values were based on clinical outcome data. Standard deviation was derived from authors' assumptions based on an assessment of the likely variability in outcome.

The influence of pacemaker syndrome in single ventricular pacing is explored in more detail in the analyses of uncertainty. This factor has been repeatedly cited as influential on the clinical decision to implant dual- or single-chamber pacemakers. Early iterations of the model demonstrated the particular importance of pacemaker syndrome and this phenomenon remains the subject of much clinical debate.

The results of the probabilistic analysis are presented graphically on the incremental cost-effectiveness plane and as cost-effectiveness

TABLE 46 *Summary of cost and utility values used in the PenTAG model*

	Cost (per cycle)		Utility	
Health state	**Dual**	**Single**	**Dual**	**Single**
Implant pacemaker	£4925	£4025 (ventricular and atrial)	0.76 (PASE[99])	0.76 (PASE[99])
Perioperative complications	£894	£816	0.75 (assumption, 1% less than uncomplicated pacemakers, based on PASE[99])	0.75 (assumption, 1% less than uncomplicated pacemakers, based on PASE[99])
Subsequent complications	£894	£816	0.75 (assumption, 1% less than uncomplicated pacemakers, based on PASE[99])	0.75 (assumption, 1% less than uncomplicated pacemakers, based on PASE[99])
Well with pacemaker	£40	£40	0.925 (PASE[99])	0.925 (PASE[99])
Mild pacemaker syndrome	–	£40	0.80 (PASE[99]) Individuals with a history of heart failure class I or II	0.80 (PASE[99]) Individuals with a history of heart failure class I or II
Severe pacemaker syndrome	–	£176	0.62 (PASE[99]) Individuals with a history of heart failure class III or IV	0.62 (PASE[99]) Individuals with a history of heart failure class III or IV
AVB before upgrade to dual chamber	–	£176	0.76 (as at baseline)	0.76 (as at baseline)
Upgrade to dual chamber	–	£4925	–	0.915 (PASE[99])
Perioperative complications during upgrade	–	£894	–	0.915 (PASE[99])
AF	£41	£41	0.875 (assumed a decrement of 0.05 from well, based on utility from Harvard database, difference between heart block and AF)	0.875 (assumed a decrement of 0.05 from well, based on utility from Harvard database, difference between heart block and AF)
Reprogramming to single chamber after AF with dual chamber	£176	–	0.875 (assumed equal to AF)	0.875 (assumed equal to AF)
Heart failure	£152	£152	0.64 (PASE[99])	0.64 (PASE[99])
Stroke	£820	£820	0.39 (Tengs[116])	0.39 (Tengs[116])

acceptability curves (CEACs), in which the probability of an option being the most cost-effective is estimated across a range of values that decision-makers may be willing to pay for an additional QALY.

Results of PenTAG economic evaluation

Deterministic analysis

The deterministic analysis is based on a single value for each of the parameters in the model, as detailed in the description of the base case.

The results demonstrate small incremental benefits from dual-chamber pacing over single-ventricular pacing. The difference in acquisition costs of dual-chamber pacemakers is defrayed by a greater accumulation of costs in the single ventricular chamber arm of the model over time (*Tables 48* and *49*).

Over a 10-year time horizon, the cost-effectiveness of dual-chamber pacing improves. A combination of factors operates as time since implantation increases. Pacemaker syndrome in the ventricular arm is important throughout the course of the models comparing dual and single ventricular

TABLE 47 *Summary of approach to probabilistic sensitivity analysis*

Data parameter	Simulation distribution	Source of central estimate	Value and source of distribution variance	Rationale
Utility values	Beta	Derived from PASE[99]	Assumed to be a quarter of central estimate	Constrained within [0,1] interval
Cost values	Log-normal	Derived from RCI data	Variance derived from RCI data	Provides an acceptable fit to skewed cost data
Transition probabilities	Beta	Calculated from trial outcome data. Rates converted to probabilities using the formula $P = 1 - e^{-rt}$, where P = probability of event and r = rate during period (t)	Assumed to be a quarter of central estimate	Constrained within [0,1] interval

TABLE 48 *Base-case analysis: dual- versus single-chamber ventricular pacemakers in AVB over 5 or 10 years*

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)
5-year time horizon					
Single-chamber ventricular pacemaker	£6,689	3.35			
Dual-chamber pacemaker	£7,387	3.41	£698	0.082	£8,458
10-year time horizon					
Single-chamber ventricular pacemaker	£8,226	4.98			
Dual-chamber pacemaker	£9,013	5.13	£787	0.14	£5,483

devices. Effects on costs are most pronounced in the 5-year models since reimplantation follows quickly on the development of severe pacemaker syndrome and happens shortly after implantation. However, as time since implantation increases, the consequences of developing AF, heart failure and stroke accumulate more rapidly in the ventricular arm. In contrast, the background mortality rate means that people leave the model and so a smaller number of people are available to experience worse outcomes in the ventricular arm. Finally, generator replacement rates increase towards the 10-year horizon with higher costs (due to the higher unit cost of the generator and slightly higher rate of generator failure) in the dual-chamber arm.

In the AVB population, dual-chamber pacing appears only slightly less cost-effective than in the SSS population. However, cost-effectiveness tends to become similar in the long term to that of the SSS group.

Table 50 shows the base-case results for single-chamber atrial pacemakers compared with dual-chamber pacemakers.

Atrial pacing dominates dual-chamber pacing, that is, it costs more and produces fewer benefits. This is a consequence of the favourable relative risk for AF. This has a direct effect, mainly on benefits, and an indirect effect on the incidence of stroke. Over the course of the model, of the 1000 people in the dual-chamber cohort, 300 cases develop AF (compared with 150 in the atrial arm). An excess of 20 strokes is also predicted.

The magnitude of the advantage is such that a significant proportion of people progress to stroke in 5 years. At 10 years this effect is more marked despite losses from the model due to background mortality.

In this comparison, the rates of upgrade to dual-chamber pacing are much lower than in the

TABLE 49 *Base-case analysis: dual- versus single-chamber ventricular pacemakers in SSS over 5 or 10 years*

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)
5-year time horizon					
Single-chamber ventricular pacemaker	£6785	3.29			
Dual-chamber pacemaker	£7513	3.37	£728	0.076	£9552
10-year time horizon					
Single-chamber ventricular pacemaker	£8473	4.88			
Dual-chamber pacemaker	£9274	5.01	£801	0.14	£5732

TABLE 50 *Base-case analysis: dual- versus single-chamber atrial pacemakers in SSS over 5 or 10 years*

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)
5-year time horizon					
Single-chamber atrial pacemaker	£6572	3.41			
Dual-chamber pacemaker	£7513	3.37	£941	–0.044	Single atrial dominates
10-year time horizon					
Single-chamber atrial pacemaker	£8219	5.13			
Dual-chamber pacemaker	£9274	5.01	£1054	–0.12	Single atrial dominates

comparison with single ventricular pacing: the risk of AVB is 1.9% per year compared with a 26% incidence of pacemaker syndrome. Furthermore, pacemaker syndrome occurs in the early stages of the model and its impact continues for the rest of the duration, while AVB occurs at a constant rate.

One-way sensitivity analyses

Table 51 shows the effects of varying the main inputs to the model on the ICER at 5 years, across the three comparisons.

The sensitivity analyses show the following.

Cost of implant

The cost of implantation is a key driver in the cost-effectiveness of dual chamber compared with single-chamber ventricular. A decrease of 50% in implantation cost reduces the ICER to approximately £3000 for AVB and £3600 for SSS. An increase of 50% increases the ICER to approximately £14,000 (AVB) and £15,000 (SSS). Values for the cost of implantation were also calculated based on assumption of the likely list prices of devices. These prices were incorporated in the cost of implant following a method similar to that used for the costs of the base case (see section 'Implantation procedure costs', p. 83). The average costs based on list prices were, for dual chamber, £6500 (range £5200–8400) and for single-chamber ventricular £5000 (range £4600–£5300). Using the central average, the ICER doubles with respect to the base case (corresponding to a difference in the implantation cost between dual and single ventricular of approximately £1500). When the difference in the cost between dual-chamber and single-chamber ventricular devices rises to £3000 the ICER increases to approximately £34,000 (AVB) and £37,000 (SSS). When the difference in cost is reduced to approximately £500, the ICER falls to below £5000.

Upgrading from ventricular to dual-chamber pacing

When 100% of individuals with mild pacemaker syndrome receive an upgrade, dual chamber becomes dominant since the additional cost of the initial implant is completely offset by 26% of the ventricular cohort being upgraded. Since most pacemaker syndrome cases occur near the beginning of the analysis, losses through mortality and discounting have no significant effect on this relationship.

TABLE 51 *One-way sensitivity analyses (5-year time horizon)*

Parameters	Values tested	ICER (£/QALY)		
		Dual chamber vs single-chamber ventricular (AVB)	**Dual chamber vs single-chamber ventricular (SSS)**	**Dual chamber vs single-chamber atrial (SSS)[a]**
	Base case	£8,458	£9,552	–£21,917
Implant cost	Costs as reported in UKPACE	£9,381	£10,525	–£25,091
	Difference between modes:			
	increased by 50%	£13,956	£15,504	–£32,365
	decreased by 50%	£2,960	£3,600	–£11,468
List hardware prices:	Cost of implantation including average hardware list price	£15,896	£17,616	–£35,447
	Cost of implantation including minimum hardware list price	£4,427	£5,192	–£14,052
	Cost of implantation including maximum hardware list price	£34,019	£37,246	–£69,310
Perioperative complications	RR in dual-chamber pacing:			
	increased by 100%	£9,242	£10,369	–£22,796
	decreased by 50%	£8,073	£9,150	–£21,467
	Cost increased by 100%	£9,563	£10,686	–£22,473
	Utility decrement increased to 0.2	£8,643	£9,780	–£21,375
Pacemaker syndrome	Risk of occurrence:			
	increased to 40%	£5,815	£6,875	NA
	decreased to 10%	£9,418	£10,481	NA
	Utility of mild state:			
	increased to 0.9	£22,882	£20,870	NA
	decreased to 0.7	£5,188	£6,194	NA
	Utility of severe state:			
	increased to 0.8	£8,509	£9,613	NA
	decreased to 0.4	£8,397	£9,480	NA
	Upgrade frequency for mild pacemaker syndrome:			
	increased to 100% of cases	Dual chamber is dominant (–£2918)	Dual chamber is dominant (–£445)	NA
	increased to 5% of cases	£8,307	£9,365	NA
AF	Risk of occurrence assumed not time dependent	£13,380	£14,262	–£16,984
Heart failure	RR follows confidence intervals of meta-analysis:			
	= 0.75	£8,030	£9,053	–£15,418
	= 1.08	£8,602	£9,720	–£26,893
	Utility difference between heart failure and well state:			
	increased by 50%	£8,305	£9,410	–£21,623
	decreased by 50%	£8,660	£9,738	–£22,300
	Risk of death from heart failure:			
	increased by 100%	£8,582	£9,682	–£22,391
	decreased by 50%	£8,386	£9,474	–£21,614

continued

TABLE 51 *One-way sensitivity analyses (5-year time horizon) (cont'd)*

Parameters	Values tested	ICER (£/QALY)		
		Dual chamber vs single-chamber ventricular (AVB)	**Dual chamber vs single-chamber ventricular (SSS)**	**Dual chamber vs single-chamber atrial (SSS)[a]**
	Cost of heart failure:			
	increased by 50%	£8,555	£9,633	–£21,843
	decreased by 50%	£8,361	£9,472	–£21,990
Stroke	RR follows confidence intervals of meta-analysis:			
	= 0.62	£8,195	£9,196	–£21,270
	= 1.04	£8,487	£9,591	–£22,182
	Utility:			
	increased to 0.6	£8,880	£10,049	–£24,978
	decreased to 0.2	£8,109	£9,144	–£19,729
	Risk of death from stroke:			
	increased by 100%	£8,945	£10,002	–£17,982
	decreased by 50%	£8,107	£9,235	–£25,085
	Cost of stroke:			
	increased by 20%	£8,610	£9,731	–£22,962
	decreased by 20%	£8,101	£9,133	–£19,677
Background mortality	Double current rates	£11,031	£12,439	–£28,903
Generator replacement	Risk assumed to be equal between pacing types	£7,989	£9,047	–£21,022
Progression to AVB in SSS (atrial pacing only)	Risk of progression:			
	doubled	£8,458	£9,552	–£17,176
	halved	£8,458	£9,552	–£24,145
Discount rate	3.5% for benefits and costs	£8,787	£9,947	–£23,472

[a] All negative values indicate dominance of single-chamber atrial pacing over dual chamber.
NA, not applicable.

The threshold for pacemaker upgrading for mild pacemaker syndrome is at 97% for SSS and 91% for AVB of the incident cases, that is, at this point the cost per QALY is equal to 0. Assuming an incidence of 26%, as in MOST, this means an upgrade rate for the cohort receiving a ventricular pacemaker of around 25% for SSS and 23% for AVB. For people with SSS, this is much higher than the 4.3% upgrade rate reported among people with ventricular pacemakers in CTOPP.

The model is highly sensitive to the value of utility for mild pacemaker syndrome. As this value becomes close to the utility of the well state, the ICER increases to around £23,000. This is due to the accrual of disutility while individuals stay in mild pacemaker syndrome, which improves the ICER in favour of dual chamber.

The risk of occurrence and utility of severe pacemaker syndrome are much less influential in the analysis than the impact on costs from upgrading to dual chamber and the impact of time spent in the mild pacemaker state, which is explored in more detail later in this section.

Incidence of AF

The incidence of AF is an important driver of cost-effectiveness. A simplifying assumption, that a non-significant summary hazard of AF is shown throughout the life of the cohort, increases the ICER for dual-chamber pacing. The results of the meta-analysis suggest that dual-chamber pacing may protect against AF, although the contrasting results of MOST, PASE (SSS patients), CTOPP (mixed) and Nielsen (atrial pacing superior to dual chamber) remain to be explained. If one applies

the summary odds ratio from the meta-analysis in the section 'atrial fibrillation' (p. 39) (0.8) to the cycle probability of developing AF there is a moderate impact on the ICER, which becomes less favourable to dual chamber (approximately between £13,000 and £14,000 per QALY). *[CiC information on the UKPACE study has been removed.]*

The costs and utility associated with AF are less important as sources of uncertainty than the relative incidence of this outcome.

Heart failure and stroke
Although the risks of developing heart failure or stroke are significant from AF, the number of people predicted to develop these outcomes is reasonably small in the base case. The analysis is not very sensitive to assumptions about incidence of heart failure within the confidence limits suggested by the meta-analysis reported earlier in the assessment. A similar pattern is shown for stroke. In stroke, the high cost and low utility of the state may suggest that changes to these parameters have a greater effect than in heart failure. However, reducing the difference in utility between the well state and stroke does not have a marked effect on the ICER.

Background mortality
This has a moderate impact on the ICER. When the background risk of death is doubled, the ICER increases by around 30%. This is because, with a higher rate of death from all states, more people are removed from the model and so the differential effects of dual-chamber pacing are attenuated. Under base-case assumptions, after 5 and 10 years around 60% and 30% of the cohorts remain alive, respectively.

Progression to AVB in SSS
In the SSS model, progression to AVB in people with SSS results in upgrade. The base case assumed an annual upgrade rate for this reason of 1.9%. Doubling this did not have an important impact on either the mixed model or the SSS cohort.

Discount rate
Altering the discount rate to the values that will be used in future assessments for NICE (3.5% for benefits and costs) did not have a major impact on the results.

Single atrial pacing dominates dual pacing under all assumptions, reflecting the relative benefits reported by Nielsen and colleagues for AF and, consequently, stroke and death. The threshold values (at which the ICER for dual versus single atrial = £0 per QALY) are shown in *Table 52*.

TABLE 52 *Threshold values in the comparison of dual versus single atrial pacing*

Parameter	Threshold value
AF	RR = 1.772
Stroke	RR = 1.48
Development of AVB	9.5% per year

The ICER for atrial pacing remains below £10,000 per QALY even when the risk of developing AVB approaches 20%.

It should be noted that the threshold analyses remain one way, that is, all other parameters are held constant.

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis, based on 1000 simulations, for dual-chamber compared with single-chamber pacing ventricular in the AVB population over 5 years are shown in *Figures 33* and *34*.

The probabilistic analysis demonstrates a high degree of uncertainty in the decision model, as would be expected with benefits and costs so close over the period modelled.

The results for the SSS population are similar (*Figures 35–38*).

Mild pacemaker syndrome: impact of duration and severity

A key driver of the models of dual versus single ventricular pacing is the incidence, duration and disutility of pacemaker syndrome. In the base case, it is assumed that severe pacemaker syndrome results in an early upgrade from single- to dual-chamber pacing. This acts mainly as a driver for the comparison of costs and offsets the increased acquisition costs of dual over ventricular pacemakers.

The mild pacemaker syndrome state is very important as a determinant of overall benefits in the model. In the base case it has been assumed that pacemaker syndrome that is insufficiently severe to warrant a further implant procedure becomes chronic. People in this state have a utility (0.80) that is 0.125 lower than the state for 'well with pacemaker'. Although further events (AF, stroke, heart failure and death) operate on this

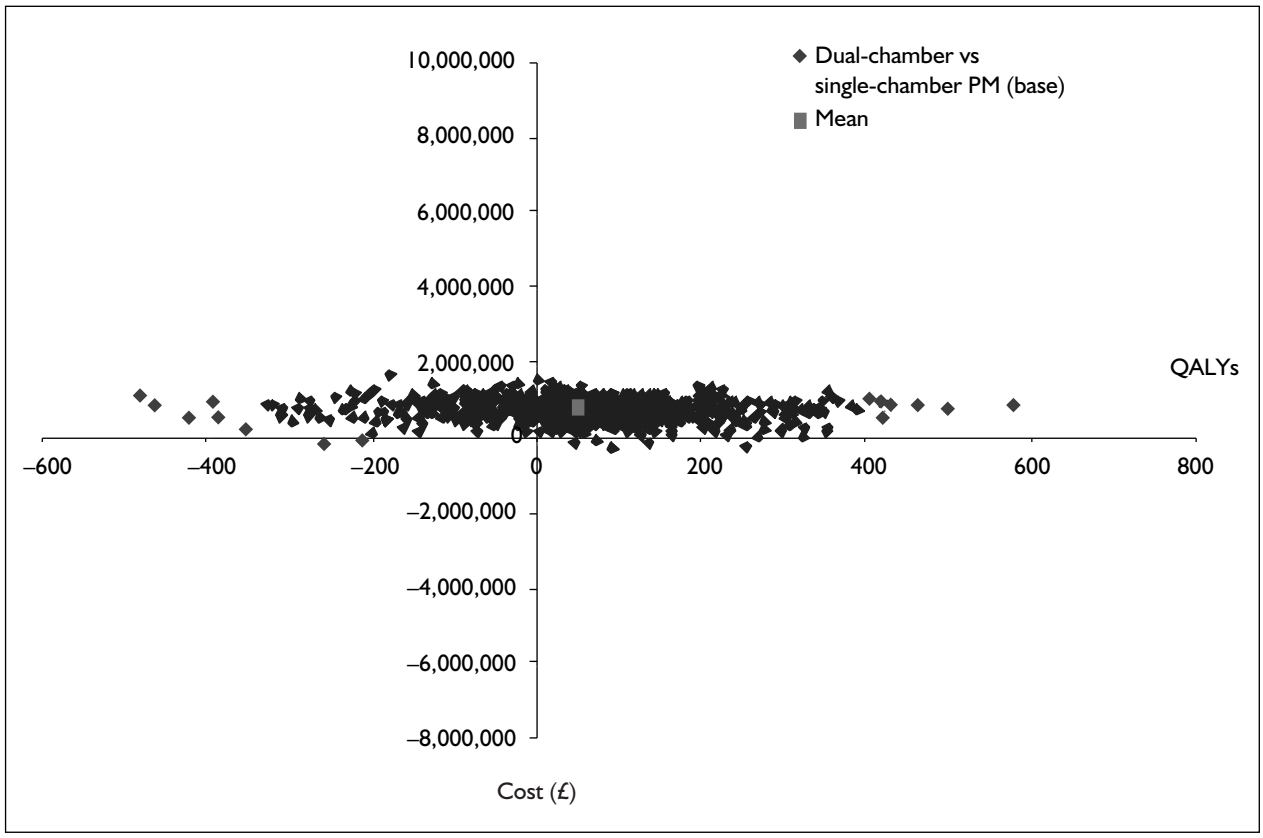


FIGURE 33 *ICER: dual- versus single-chamber ventricular pacemakers in AVB (5-year model)*

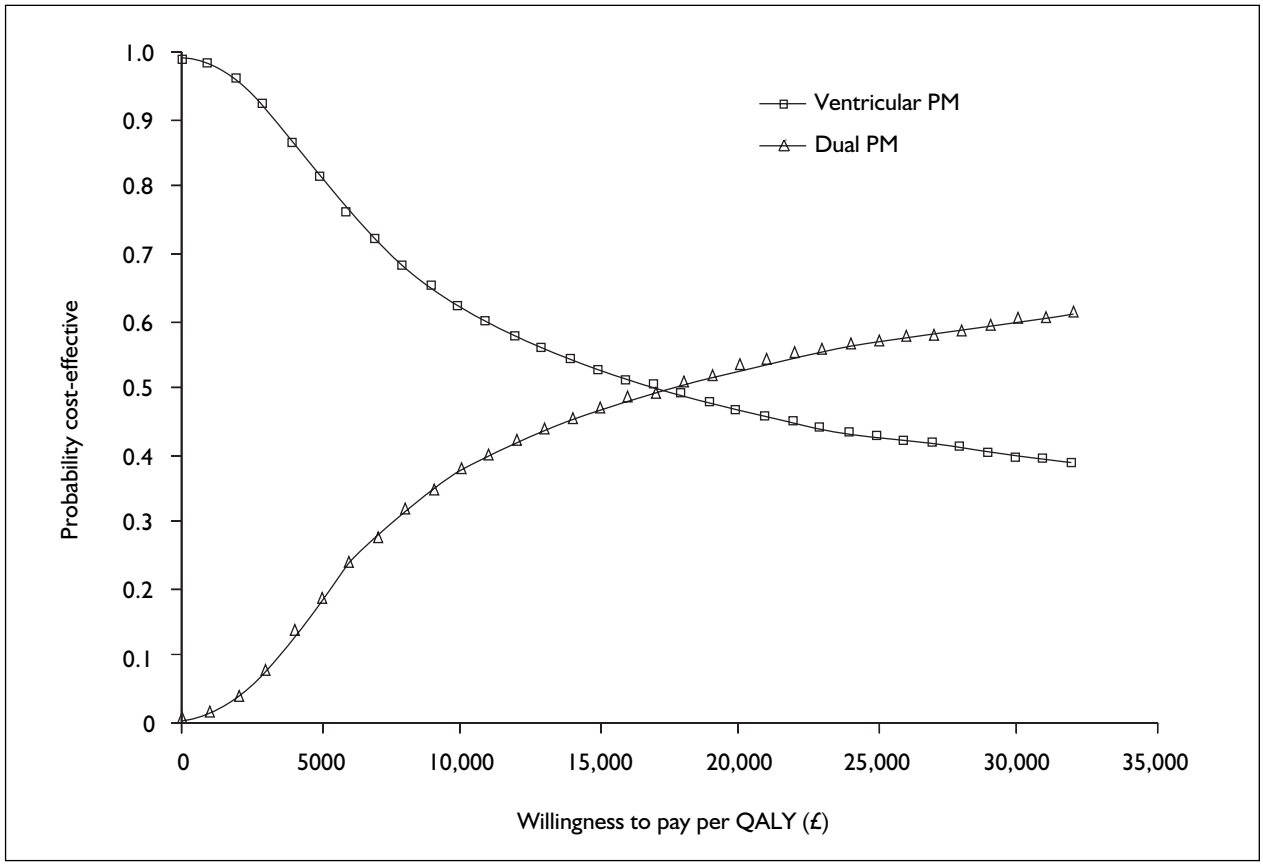


FIGURE 34 *CEAC: dual- versus single-chamber ventricular pacemakers in AVB (5-year model)*

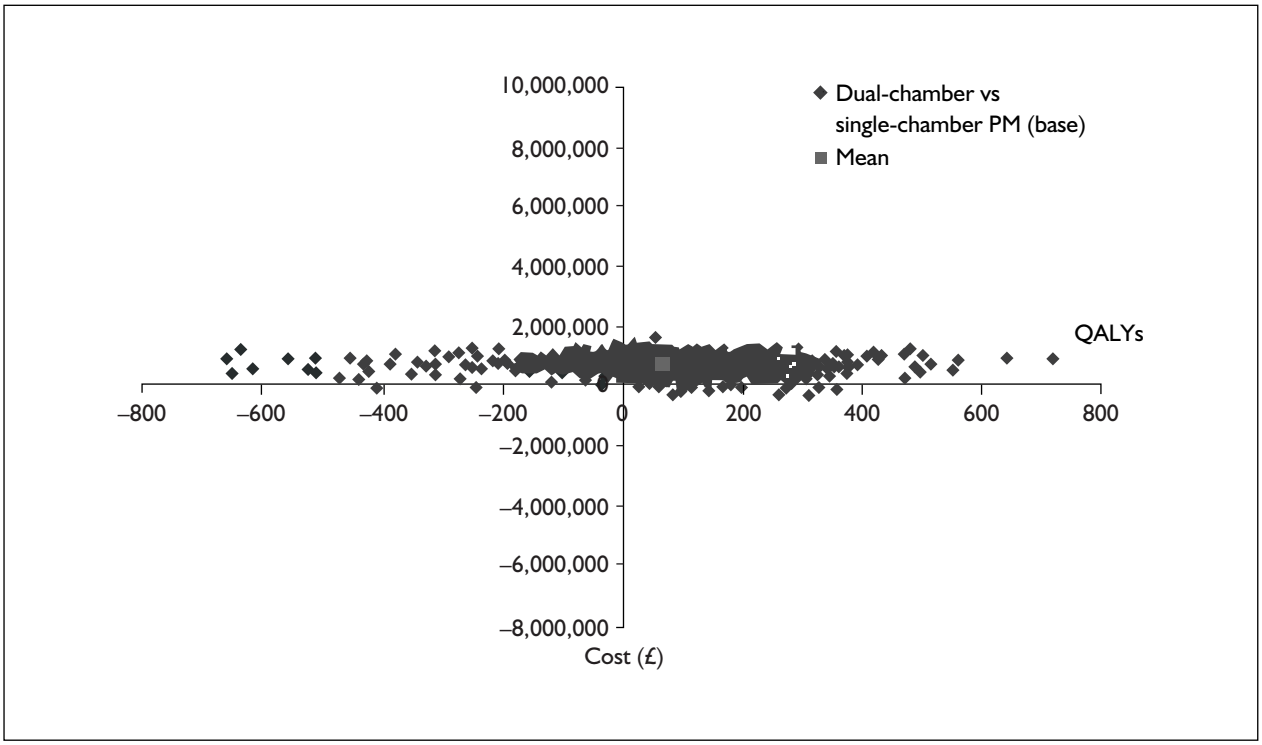


FIGURE 35 *ICER: dual- versus single-chamber ventricular pacemakers in the SSS population (5-year model)*

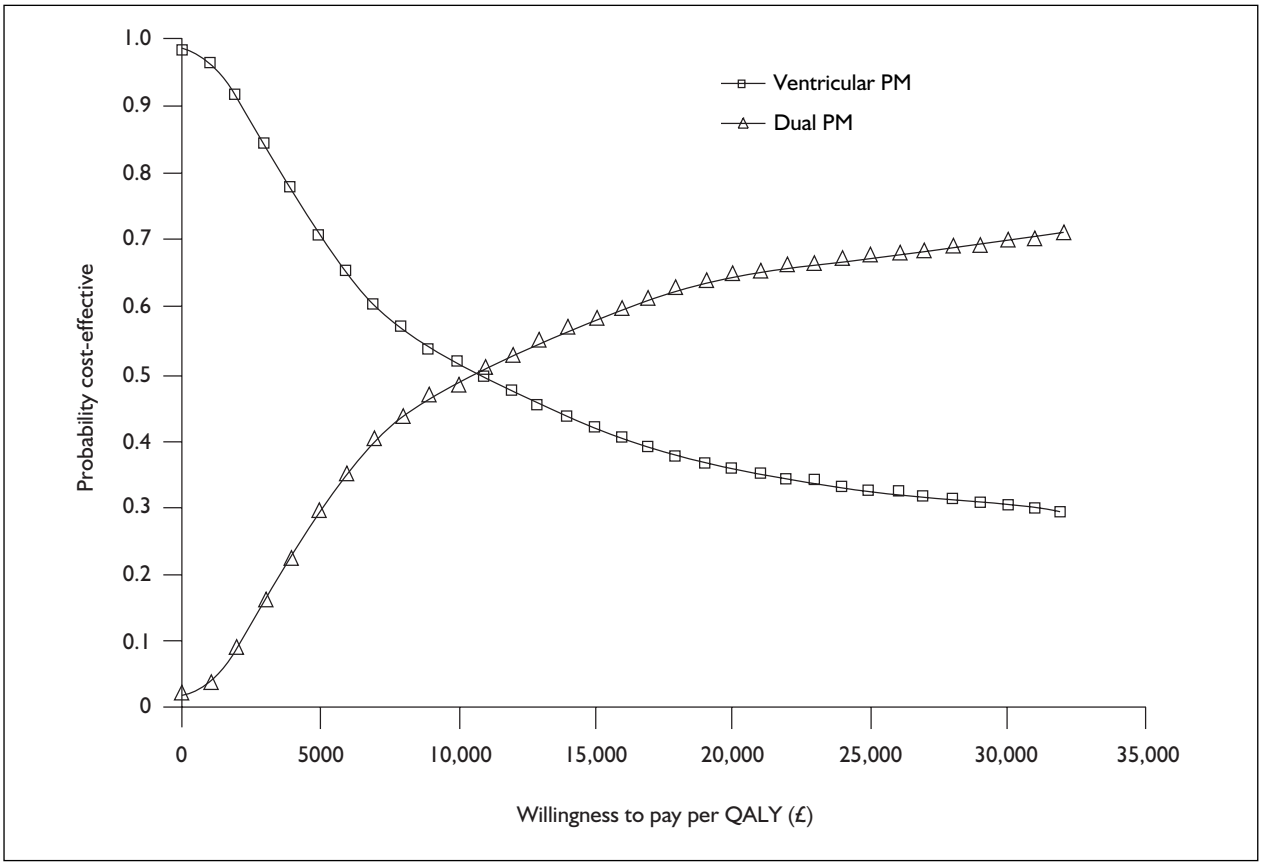


FIGURE 36 *CEAC: dual- versus single-chamber ventricular pacemakers in the SSS population (5-year model)*

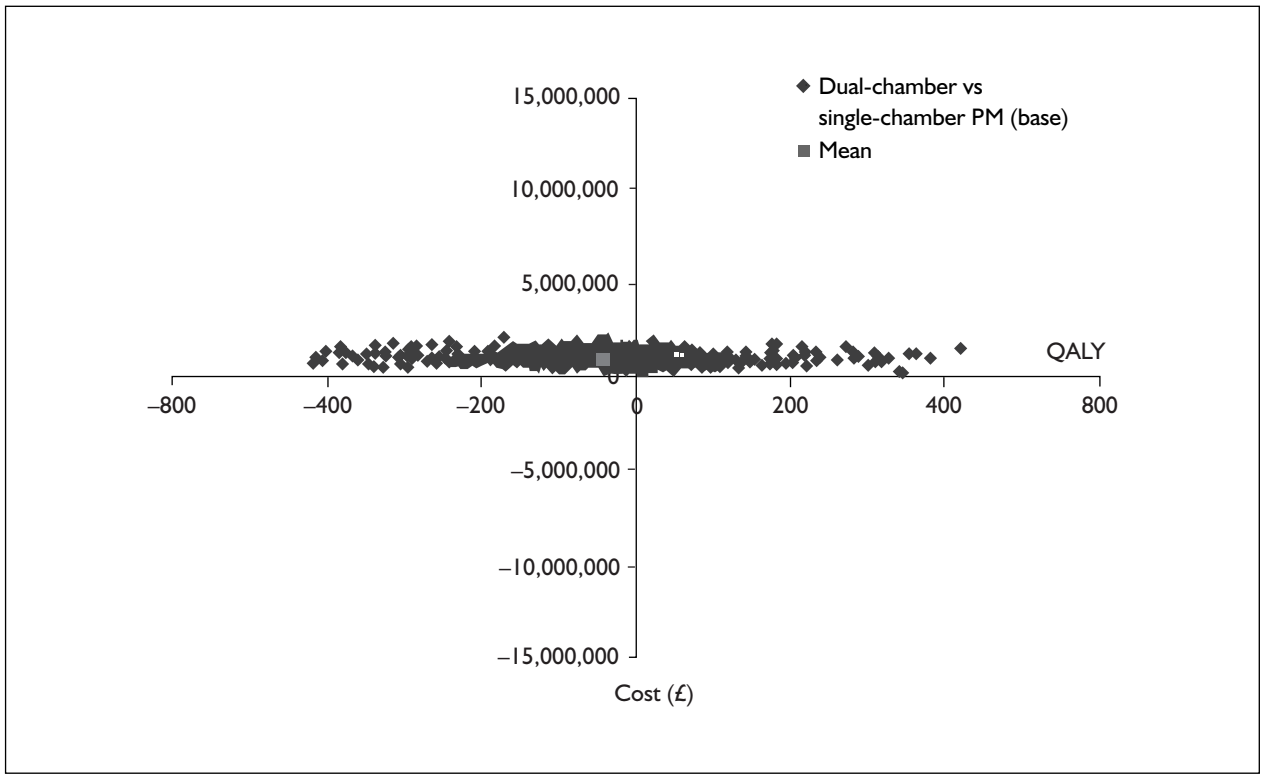


FIGURE 37 *ICER: dual- versus single-chamber atrial pacemakers in the SSS population (5-year model)*

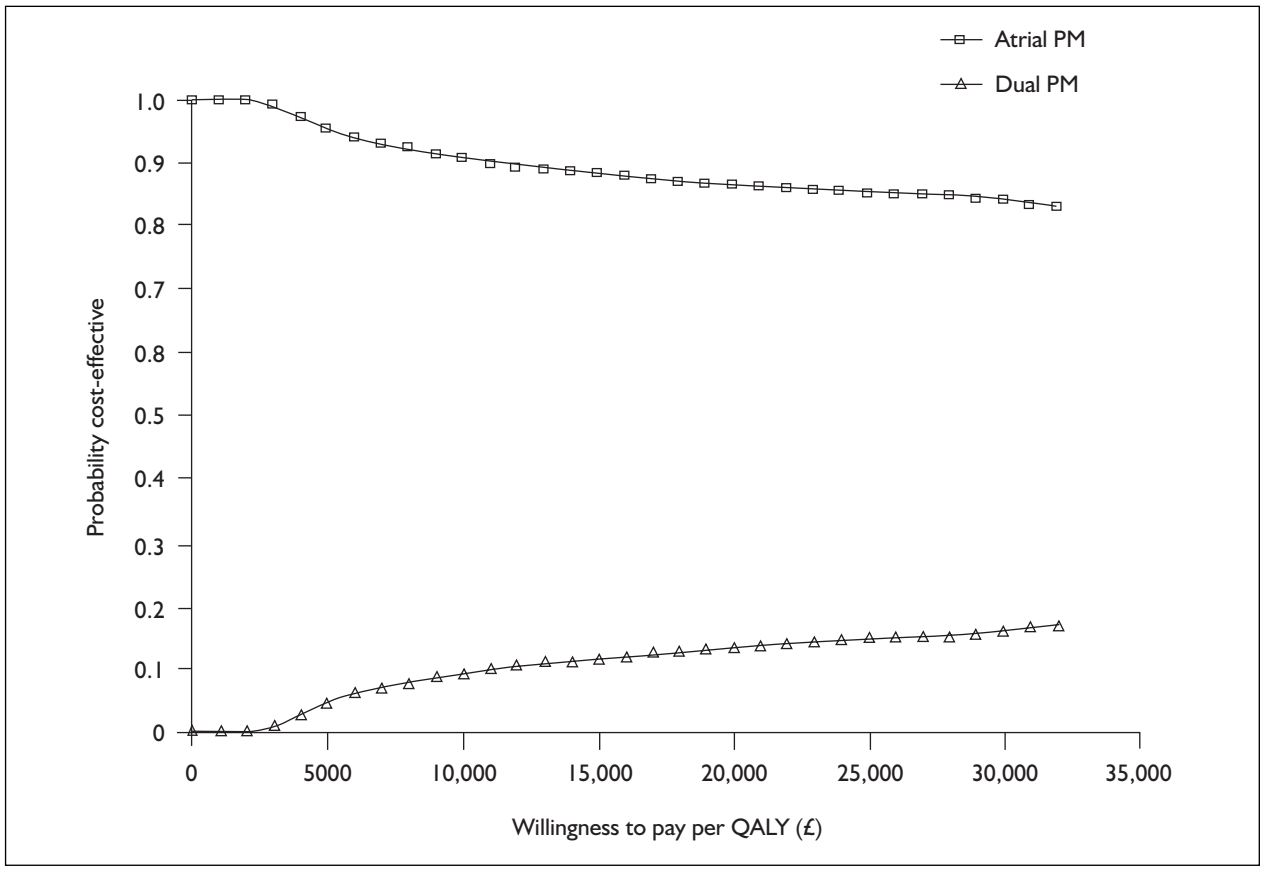


FIGURE 38 *CEAC: dual- vs single-chamber atrial pacemakers in the SSS population (5-year model)*

group, a considerable length of time is spent in this state. This accounts for much of the difference in quality-adjusted time between the arms of the model. This assumption may be seen as reflecting social preferences in avoiding the disutility of mild pacemaker syndrome.

In practice, however, people may recover from pacemaker syndrome or may adjust to the impaired quality of life. Some evidence for accommodation of symptoms may be inferred from the limited difference in longer term quality of life scores in the clinical trials of dual-chamber pacing. Given this, it seems reasonable to explore the possibility that mild pacemaker syndrome resolves to a state with utility similar to 'well with pacemaker syndrome' which may reflect the patient's perspective on utility.

In this scenario, it is assumed that 50% of people with mild pacemaker syndrome resolve to a 'controlled' state with a utility of 0.925, that is, 98% of cases resolve within 6–7 months. All other assumptions remain as in the base case.

The deterministic results are shown in *Tables 53* and *54*.

A probabilistic sensitivity analysis was carried out in which the only difference between this scenario and the base case was the probability of resolution of mild pacemaker syndrome. The CEACs for the SSS model are shown in *Figure 39*.

Comparison of economic evaluations

There are differences between the results of the four economic evaluations undertaken for the NICE appraisal of dual-chamber pacemakers.

Table 55 summarises the types of model, comparisons, populations and main results of the different analyses.

In general, the sponsor submissions suggest that dual-chamber pacing is likely to be better value for money than the PenTAG models. *Table 56* reports the main input values used in each of the models and demonstrates some of the reasons for the variation in conclusions.

TABLE 53 *Cost–utility of dual- versus single-chamber ventricular pacing in SSS assuming resolution/accommodation of mild pacemaker syndrome*

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)
5-year time horizon					
Single ventricular pacemaker	6,780	3.34			
Dual-chamber pacemaker	7,514	3.37	733	0.026	27,755
10-year time horizon					
Single ventricular pacemaker	8,469	4.94			
Dual-chamber pacemaker	9,274	5.01	805	0.073	11,090

TABLE 54 *Cost–utility of dual- versus single-chamber ventricular pacing in AVB assuming resolution/accommodation of mild pacemaker syndrome*

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)
5-year time horizon					
Single ventricular pacemaker	6,684	3.39			
Dual-chamber pacemaker	7,387	3.41	702	0.020	35,727
5-year time horizon					
Single ventricular pacemaker	8,222	5.09			
Dual-chamber pacemaker	9,013	5.13	791	0.044	17,878

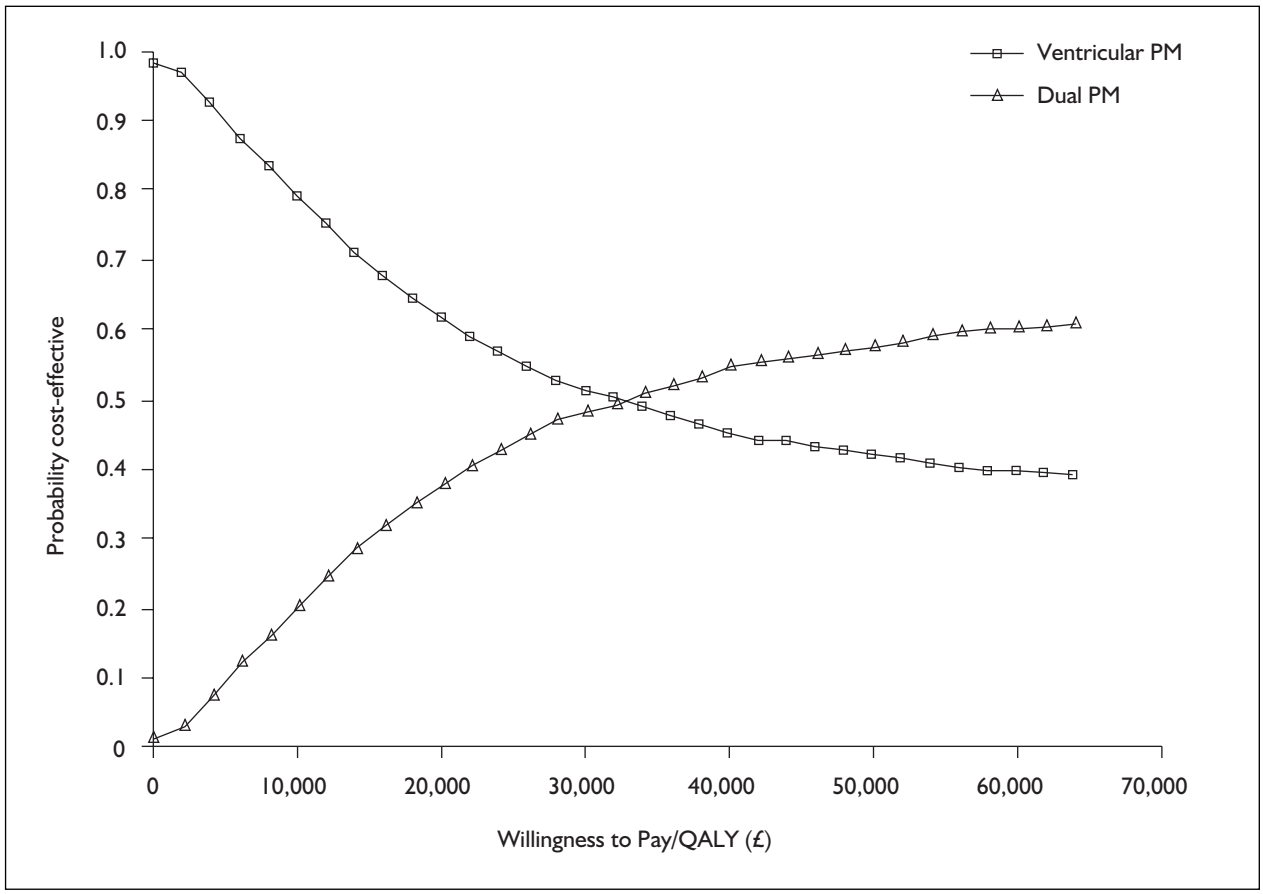


FIGURE 39 *CEAC: for dual versus ventricular chamber pacemakers in SSS assuming resolution of mild pacemaker syndrome*

The main difference between the PenTAG and Guidant (YHEC) models is in the predicted benefits from dual-chamber versus single ventricular pacing. The Guidant model predicts nearly three times more QALYs at 10 years. This appears to be driven by the assumption in the Guidant model of a mortality advantage for dual-chamber pacing and greater benefits in heart failure and stroke. Costs are similar between the models.

The comparison between the outputs of the St Jude model and other evaluations is difficult as this evaluation reports on costs per event prevented and does not consider differences in quality or quantity of life associated with events. Significant advantages for dual pacing are assumed in terms of mortality, heart failure and stroke.

The predicted benefit of dual chamber pacing in the ABHI model is very similar to that of the PenTAG models for single ventricular pacing. The difference here is in costs, which in the ABHI (Caro) model appear to be driven by a higher assumed incidence of pacemaker syndrome, which results in upgrade to dual-chamber pacing. A similar finding is predicted in the PenTAG model if high proportions of people with mild pacemaker syndrome receive a dual-chamber device. Dual-chamber pacing dominates single ventricular pacing in the PenTAG evaluation when the proportion of upgrades approaches 25% of the cohort (i.e. 100% of the incident cases assuming incidence as in the PASE study).

Summary: cost-effectiveness of dual-chamber versus single-chamber pacing

- Published economic analyses were reviewed in 2001 and no further informative evaluations have been published since.
- Three evaluations carried out on behalf of sponsors of dual-chamber pacing were reviewed. One is of poor quality. The other two (Guidant and ABHI) are of reasonable quality in terms of structure.
- The sponsor models suggest that benefits accrue in dual-chamber pacing at relatively low cost and, in many cases, will be accompanied by cost saving. The differences between the

TABLE 55 *Overview of economic models submitted to NICE for appraisal of dual-chamber pacing*

Model	Type	Comparisons	Populations	Duration	Costs	Benefits	Cost-effectiveness
ABHI (Caro)	DES	Dual chamber vs single ventricular chamber (rate responsive)	95% SSS/AVB	5 years	VVI(R) £4,255 DDD(R) £4,297 Incremental: £42	Incremental: 0.09 QALYs	£477 per QALY
Guidant Medical (YHEC)	Markov	Dual chamber vs single ventricular (assumed)	Not clear	10 years (up to 30 years)	Incremental: 10 years £742, 30 years –£1,057	Incremental: 10 years, 0.399 QALYs, 30 years 0.70 QALYs	£1,780 per QALY Dual dominates
St Jude (Abacus)	Unclear	Dual chamber (DDD) vs single ventricular (VVI) Costs of events avoided are compared with costs of implant	72% AVB, 28% SSS Based on PCT population	7.5 years	SSS/AVB VVI = £6,602, DDD = £6,420 Incremental: £438	Events avoided: Pacemaker syndrome: 72.7, stroke 23.7, AF 3.7	Dual dominates
PenTAG	Markov	Dual vs single ventricular (mix of rate responsive and non-rate responsive)	SSS or AVB	5 or 10 years	SSS at 5 years: VVI(R) £6,785, DDD(R) £7,513 Incremental: £728	0.076 at 5 years, 0.14 at 10 years	£9,552 per QALY
					AVB at 5 years: VVI(R) £6,689, DDD(R) £7,387 Incremental: £698	0.082 at 5 years 0.14 at 10 years	£8,458 per QALY
		Dual vs. single atrial (mix of rate responsive and non-rate responsive)	SSS	5 or 10 years	SSS at 5 years: AAI(R) £6,572, DDD(R) £7,513 Incremental: £941	Incremental (dual vs single): –0.044	Single atrial dominates

PenTAG and sponsor models are accounted for by choice of inputs. The apparently large differences in cost-effectiveness reflect the small incremental benefits and costs associated with dual-chamber pacing, making the ICER subject to considerable variation for small changes, particularly in predicted benefits.

- The present modelling is more conservative and suggests that, over 5 years, dual-chamber pacing is likely to give additional QALYs, compared with single ventricular pacing, at a cost of around £8500 in AVB and £9500 in SSS. This estimate is subject to considerable uncertainty, although stochastic analysis shows that dual-chamber pacing is likely to be considered cost-effective at levels of willingness to pay generally considered acceptable by NHS decision-makers.
- The PenTAG model predicts that dual-chamber pacing will become more cost-effective as a longer time horizon is taken. At 10 years, the cost-effectiveness is estimated to be around £5500 per QALY in both AVB and SSS.
- These estimates are particularly sensitive to assumptions regarding the incidence, duration and severity of pacemaker syndrome, which drives both costs and benefits. Incremental benefits and costs are small. Where conservative assumptions are made regarding the persistence of mild pacemaker syndrome, the incremental cost-effectiveness of dual-chamber pacing is in the region of

TABLE 56 *Model inputs: comparison of PenTAG model to economic models submitted to NICE*

Annual rate of main events in the model (or cycle rate)		PenTAG		CARO		YHEC		St Jude	
		Single chamber	**Dual chamber**	**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**
Implant pacemaker	Incidence of perioperative complications	3.3%	6.6%	2.1% (month 1)	4.8% (month 1)			Taken into account but not specified	Taken into account but not specified
	Incidence of perioperative deaths	0.25%	0.25%						
	Subsequent complications	Complications 0.1% Perioperative mortality 0.5% of complications	Complications 0.1% Mortality 0.5% of complications	0.5% (month 2) 1.5% (annual, from month 3)	0.5% (month 2) 1.5% (annual, from month 3)			Taken into account but not specified	Taken into account but not specified
Progression to pacemaker syndrome		Total: 26% (16% severe, 84% mild)		Symptoms 38%, of which 47% severe	Symptoms 31%	15.5% p.a.	–	32.8% (total, SSS) 26% (total AVB)	–
	Progression to mild pacemaker syndrome	7.2% (first cycle), 5.4% (cumulative, cycles 2–6), 3.8% (cumulative until end of model)							
	Progression from well to severe pacemaker syndrome	4.2% (first cycle), 3.2% (cumulative, cycles 2–6), 2.2% (cumulative until end of model)							
	Upgrade to dual-chamber pacing from severe pacemaker syndrome	100% of alive individuals		69% cross-over within 3 months, 73% within 6 months				100%	
	Perioperative complications during dual-chamber upgrade	13.6%							

continued

TABLE 56 *Model inputs: comparison of PenTAG model to economic models submitted to NICE (cont'd)*

		PenTAG		CARO		YHEC		St Jude	
Annual rate of main events in the model (or cycle rate)		**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**
Progression to AF	Ventricular pacing, individuals with SSS	Cumulative rate for 36 months 39% First 6 months 12%, following periods (30 months) 27%	Cumulative rate for 36 months 30% First 6 months 12%, following periods (30 months) 18%	8.85% (annual risk) Risk of becoming chronic 58.2%	11.02% (annual risk) Risk of becoming chronic 52.8%	13.5% (64% transient, 36% chronic)	13.6% (64% transient, 36% chronic)	27.1% (total)	21.4% (total)
	Ventricular pacing, individuals with AVB	*CiC removed [derived from UKPACE]*	*CiC removed [derived from UKPACE]*	3.63 (annual risk) Risk of becoming chronic 58.2%	2.91% (annual risk) Risk of becoming chronic 52.8%	13.5% (64% transient, 36% chronic)	13.6% (64% transient, 36% chronic)	6.6% (total)	5.3% (total)
	Atrial pacing	RR, atrial vs dual 0.42		–	–	–	–	–	–
	Reprogramming to single-chamber	–	100%						
Progression to AVB	Atrial pacing (SSS)	1.9%							
	Upgrade to dual-chamber after AVB block in SSS	100% of alive individuals							
Progression to stroke	Progression to stroke (without AF)	1.25%	1.07%	0%	0%	3.9%, Subsequent stroke 12%	2.2%, Subsequent stroke 12%	18% (AVB only)	9.5% (AVB only)
	Progression to stroke (after AF)	3.2%	3.2%	Framingham equation, calculated directly from patients' characteristics	Framingham equation, calculated directly from patients' characteristics	–	–	–	–
Progression to heart failure	Progression to heart failure (without AF, ventricular and atrial pacing)	2.6%	2.5%	–	–	4.5%	3%	12.3% (SSS only)	10.3% (SSS only)

continued

TABLE 56 *Model inputs: comparison of PenTAG model to economic models submitted to NICE (cont'd)*

Annual rate of main events in the model (or cycle rate)		PenTAG		CARO		YHEC		St Jude	
		Single chamber	**Dual chamber**	**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**	**Single chamber**	**Dual chamber**
	Progression to heart failure (after AF)	3.3%	3.3%	–	–	–	–	–	–
Long-term outcomes	Death from stroke	33%	33%	–	–	28.3%	28.3%	–	–
	Death from heart failure	20.8%	20.8%	–	–	–	–	–	–
	Total deaths	Other-cause mortality 8.7%	Other-cause mortality 8.7%	Time to death obtained by solving the equation $S = -0.0049t + 0.9924$	Time to death obtained by solving the equation $S = -0.004t + 0.9924$	Cardiac death 6.1% Other death 2.2%	Cardiac death 5.3% Other death 2.4%	6.8% (SSS)	3.2% (SSS)

£27,000–35,000 per QALY over 5 years and £11,000–18,000 over 10 years.
- The cost of implant is a more predictable determinant of cost-effectiveness.
- Compared with atrial pacing, dual-chamber devices appear to be less effective and more costly in SSS under all the assumptions modelled. This reflects the influence of a single small trial on the analysis, in which a large protective effect on AF was shown. The apparent benefits of atrial pacing are not offset by upgrades to dual-chamber pacing owing to the development of AVB until the risk of this event approaches 10% per year.

Chapter 6

Implications for other parties

There are implications for family and carers. Cardiac pacing results in a considerable increase in quality of life for patients and it is likely that this reduces carer burden and has a positive effect on other family members. The additional benefit that may accrue from dual-chamber pacing is small. It is difficult to predict what this effect may be on family and carers and it will vary depending on what form the benefit takes. Prevention of AF will result in slightly less clinical contact and this may have implications for travel and support. Much more significant would be the effects of preventing stroke, which results in a major burden for carers. However, the number of strokes prevented through dual-chamber pacing is small. The case is similar for heart failure.

Chapter 7

Factors relevant to the NHS

In this section the potential impact on the NHS budget is considered using four scenarios. In each case, the costs are for hardware only, obtained from *Table 39* (p. 82), adding the cost of the pacemaker generator to the cost of one or two leads as appropriate.

Scenario 1 illustrates the financial impact of using dual-chamber pacemakers in all potentially eligible new cases for implantation, that is, the maximum diffusion of dual-chamber devices based on current incidence. Because it is likely that a proportion of people will be found to have AF at implantation, a maximum of 90% of the presenting population is assumed to be eligible.

Scenarios 2 and 3 illustrate the impact of increasing implantation rates from the current levels (429 per million population) to 600 per million population, approximately the median implantation rate in other European countries. Scenario 2 assumes that the current mix of pacemaker types would be maintained with such an increase. Scenario 3 assumes that the increase will be achieved through the use of dual-chamber pacing in 90% of new cases, allowing for AF as in Scenario 1. Results are shown in *Table 57*.

The additional expenditure for increasing the current rate of dual-chamber pacemakers to 90% of the total would approach £10 million. This would be the maximum increase in hardware expenditure assuming that all individuals receive a dual-chamber pacemaker at first implant, when appropriate. This also assumes the average costs of implantation detailed earlier in this assessment. Considerable variation and uncertainty exist around these estimates. Costs to the NHS may be greater because of additional capital and staff resource use associated with longer implant time and increased rate of complications. However, these elements would be offset by a reduction in the need for more time-consuming and risky upgrade procedures.

Around £17 million would be required to increase the UK implantation rate to 600 per million population. To increase the use of dual-chamber

TABLE 57 *Current and projected total hardware expenditure*

Pacemaker type	Total current number of implants (n = 25,397)	%	Unit cost of hardware £	Present cost of hardware (estimated) £	Projected cost (£)		
					Scenario 1: 90% of new implants are dual chamber	Scenario 2: Increased population rate from current rates to 600 implants per million (current pacemaker mix)	Scenario 3: Increased population rate from current rates to 600/m (90% new implants with dual chamber)
VVI	4165	16.4	862	3,590,323	6,776,631	5,024,219	9,483,067
VVIR	6095	24.0	1,271	7,747,101	14,236,745	10,841,122	19,922,587
DDD	7441	29.3	1,712	12,739,542	12,739,542	17,827,433	17,827,433
DDDR	7416	29.2	2,454	18,198,677	18,198,677	25,466,827	25,466,827
AAI	127	0.5	865	109,842	206,643	153,711	289,171
AAIR	152	0.6	1,274	194,135	355,964	271,668	498,129
Average cost of pacemaker (actual mix)			1,677	42,579,620	52,514,202	59,584,978	73,487,213
Increased expenditure (compared with current estimated expenditure)					9,934,583	£17,005,358	£30,907,593

TABLE 58 *Current and projected total hardware expenditure, sensitivity analysis*

Incidence of AF in recipient population (%)	Projected cost (£)	
	Scenario 1: All new implants are dual chamber	Scenario 3: Increased population rate from current rates to 600 per million (all dual chamber)
0	11,038,425	32,452,286
5	10,486,504	31,679,940
15	9,382,661	30,135,247
20	8,830,740	29,362,901
25	8,278,819	28,590,554

pacemakers in all potentially eligible cases would require about £31 million.

The proportion of individuals affected by AF is an assumption. This has been tested in a sensitivity analysis (*Table 58*) by varying the incidence of AF in the recipient population between 0% and 25%. The total additional cost of implanting dual-chamber pacemakers in all new incident cases varies between +£8.3 million (25% of new recipients have AF) and £11 million (no new recipients have AF). Assuming that the diffusion of pacemakers increases to 600 per million population, the total additional cost varies from £28.6 million to £32.5 million (*Table 58*).

Chapter 8
Discussion

Clinical effectiveness of dual-chamber versus single-chamber ventricular pacing

Dual-chamber pacing has been used in the majority of people with AVB and sick SSS since the mid-1990s. In 2003, 70% of people who were paced for complete heart block received a dual-chamber device and 74% of those paced for bradycardia in sick SSS received such a device. Only 3.5% of people paced for SSS received an atrial pacemaker. Although atrial pacing is included in this assessment of dual- and single-chamber devices, clinical practice suggests the comparison of ventricular and dual-chamber pacing to be of greater policy importance.

Dual-chamber pacing is age dependent, with older people less likely to have received such a device since 1990. Unfortunately, data are not available on time trends in the age distribution of dual-chamber pacing, and it is possible that the proportion of older people receiving this type of device has increased as use of dual-chamber devices has become much more widespread. The cross-over point, at which the use of single-chamber ventricular pacemakers was more common than dual-chamber devices, is 75–79 years of age. This is likely to relate to the prevalence of AF and perceived value of dual-chamber over single-chamber pacing in relation to the potential for gains in quality of life for individual patients.

The evidence base for the clinical effectiveness of dual-chamber pacing versus single-chamber ventricular pacing is mixed. Early trials were predominantly small, short-duration cross-over studies that were appropriate to the stage of development of the technology. Cross-over trials have the advantage of higher power for a given number of participants. The ability to switch pacemaker mode easily and the absence of concerns about washout period, which are a challenge in cross-over trials of pharmaceuticals, made this design appropriate for the initial phases of technology assessment. The short duration and relatively small size of the cross-over trials brought limitations in the outcomes that could feasibly be measured. Functional measures and symptoms were predominant, although global and multidimensional measures of quality of life were included. The findings were promising and supported the initiation of much longer term studies. The four-parallel group RCTs reviewed in this assessment included a total of 7006 people. These were much larger and longer than cross-over studies and consequently were able to include more clinically and policy relevant outcomes (e.g. mortality, AF, stroke and quality of life).

An important distinction between the large trials is that two each were trials of mode (PASE and MOST) and trials of device (CTOPP and UKPACE). This has implications, in particular, for the findings regarding the incidence of reprogramming or reimplantation from single to dual chamber, which are discussed further below.

The quality of the parallel-group trials included in the systematic review was considered poor by the authors of a previous HTA and systematic review.[43] This judgement was based on the presence of two major threats to validity based on critical appraisal using the Jadad score. The present authors do not agree that the quality of CTOPP, PASE and MOST should be categorised as 'poor', although there are some potential threats to validity. They were large, appropriately randomised trials in which good follow-up was achieved for a clinically relevant time and, for most outcomes, measurement of effect was undertaken without knowledge of allocation. There are some causes for concern, particularly the baseline imbalance apparent in the MOST study, in which there were slightly higher proportions of people with diabetes, previous ventricular arrhythmias and heart failure in the dual-chamber arm. Although these were taken into account in the analysis, unknown confounding may remain. The size of any identifiable bias cannot be estimated, but its direction is likely to be against dual-chamber pacing, as the factors concerned are independently associated with increased risks of death or stroke. UKPACE has only recently been completed. The findings are currently unpublished and have not been peer reviewed or subject to extensive scientific scrutiny. The present

reviewers were fortunate to obtain the preliminary results, although they might be viewed with some caution at this early stage in dissemination. *[CiC removed – discussion of the quality of the UKPACE study.]*

Although information is limited, the RCTs of dual-chamber pacing appear to have reasonable external validity, in that they were not so highly selective that the findings should be considered uninformative for routine practice. CTOPP included about one-third of people who attended the participating centres for first pacemaker implantation, about half the number who were eligible. The exclusion criteria suggest that the trial populations may have had less severe disease than might be encountered in routine practice, such as pre-existing CVD. *[CiC removed – comment on the eligibility criteria for the UKPACE trial.]*

There were important differences between trials, particularly in history of AF. CTOPP was more stringent on this factor than MOST and PASE.

No difference in mortality associated with device type was shown in any trials. The meta-analysis showed the odds ratio for death to be close to 1.0 (0.97) and although the confidence intervals cannot rule out an increase or decrease in the odds of death of approaching 10%, it seems unlikely that there is a statistically and clinically significant impact on mortality from dual-chamber pacing. Around 50,000 people would be needed in a trial to show whether the 1% benefits shown in MOST were due to chance.

AF occurred less frequently on dual-chamber pacing in the two large trials (MOST and CTOPP). The largest difference was found in MOST and this was clearly significant. Because the number of events was highest in MOST (owing to the large proportion with a baseline history of atrial events) this trial gives most weight to the meta-analysis which shows an overall odds ratio of 0.76 (95% CI 0.65 to 0.90) in favour of dual-chamber pacing. In CTOPP, a smaller number of people developed AF, reflecting the more stringent inclusion criteria in this trial. Nevertheless, the point estimate was similar to MOST. The crude odds ratio and relative risk were not significant in CTOPP, but survival analysis showed a significant effect. CTOPP further demonstrates that the impact on AF is time dependent, with the benefit being greater with longer follow-up. Whether a similar effect is shown in MOST or PASE is not known. *[CiC removed – comparison of AF rates in CTOPP and UKPACE.]*

In CTOPP, around one-third of participants had sinoatrial disease and this factor was a significant predictor of AF in a further analysis of the trial data. Other possible reasons for the contrasting results include differences in history of AF.

[CiC removed – comment on the effect of the UKPACE trial on the meta-analysis.]

Trials have consistently shown small but statistically insignificant effects on stroke in favour of dual or physiological pacing. The meta-analysis gives a pooled odds ratio of 0.81. It is reasonable to speculate that if there is a positive effect on AF, this will translate into an impact on stroke given the established relationship between the conditions. This effect may be more marked outside the context of an RCT, where patients may not be so closely monitored and treated to reduce the risk of stroke in AF.

Although the relative measures of effect in MOST and CTOPP favoured dual-chamber pacing (pooled OR 0.83, 95% CI 0.66 to 1.05) and appear clinically important, the absolute risk of events was small in CTOPP (around 3%). In contrast, the survival analysis on heart failure in MOST, when adjusted for baseline differences, was statistically significant. In view of the potential for unknown confounding and the absence of confirmatory findings from other large parallel studies, this finding should be viewed with caution, although the difference (12.3% versus 10.3%) in hospitalisations could be clinically important. *[CiC removed – comment on the incidence of heart failure in the UKPACE trial.]*

Evidence for the impact of dual-chamber pacing on symptoms is mixed and mostly comes from the cross-over trials. The impact on effort tolerance is confounded by rate responsiveness. Although breathlessness, chest pain and dizziness appear to be improved with dual-chamber pacing in cross-over studies, no significant effect on functional class (i.e. SAS) has been shown and effects on quality of life (where present) are small, suggesting that individual symptom effects may not amount to a clinically significant impact. However, the high rates of pacemaker syndrome reported in MOST and PASE, leading to reprogramming, suggest that some important symptomatic differences exist.

Although a standard definition of pacemaker syndrome was used in MOST and PASE, the diagnostic uncertainty that exists around the syndrome has already been noted. Unfortunately,

pacemaker syndrome was not reported in CTOPP and so it is not possible to compare the incidence and severity of the syndrome in trials of device rather than mode.

There is a striking difference in rates of transfer from single to dual chamber between the trials of mode (18% in PASE and 26% in MOST) and the trials of device (4% in CTOPP *[UKPACE figure removed, – CiC]*). It seems highly likely that this is due to procedural differences. In trials of mode, reprogramming can be carried out non-invasively, but in trials of device a new lead and generator must be inserted. It is probable, therefore, that the results of MOST and PASE indicate the upper limits for the incidence of clinically important pacemaker syndrome; that is, the threshold for diagnosis is low because treatment is easy to perform. However, the contrast between the results for the incidence of pacemaker syndrome and the quality of life results using generic measures suggest that the impact of pacemaker syndrome may be smaller than suggested by the incidence data alone.

The threshold for diagnosing pacemaker syndrome in CTOPP was probably higher than in the trials of pacing mode because the diagnosis would lead to another invasive procedure rather than simply reprogramming. As such, the rates of reimplantation in trials of device, assuming that all cases were carried out for pacemaker syndrome, estimate the incidence of severe pacemaker syndrome in individuals for whom reimplantation was feasible and desirable. These probably underestimate the incidence of pacemaker syndrome, although the equivocal results for quality of life further suggest that the impact of pacemaker syndrome, on average, is less severe than suggested by early cross-over trials and trials of mode.

The results for quality of life are interesting. Using a range of single global measures of quality of life, cross-over trials showed a consistent direction of effect in favour of dual-chamber pacing. In some cases this effect was marked, although it is not possible to pool the results for these studies to summarise the effect size. In contrast, the results on quality of life from the methodologically superior parallel group trials are more equivocal.

Using the SF-36, only MOST reported a significant difference between groups, which was shown for seven of the ten domains. There are some concerns about the way in which quality of life data were measured in MOST; this may not have been carried out in the same way in people who were reprogrammed as in other trial participants, and the data were not strictly analysed on an ITT basis. In CTOPP, results for quality of life depended on the instrument used. In CTOPP a significant difference was shown in one dimension of the SF-6D (general health at month 6) and on the physical domains and total score for the QLAP, a disease-specific measure. Three possible interpretations of these findings are that:

- There are no clinically important differences in quality of life between pacing modes when measured over a long period; any differences are very small or observed purely by chance.
- Clinically important differences exist, but are accommodated by the patient over time. This may be true, since the measures of quality of life are necessarily subjective. The quality of life measurement in MOST showed an improvement after reprogramming. However, in contrast, the meta-analysis of cross-over studies on functional ability did not show a difference between groups, which might be expected if accommodation of significant symptoms had occurred.
- Generic measures of quality of life are too insensitive to identify clinically important differences. A problem with this argument is the somewhat contradictory findings of CTOPP. The SF-36 is more sensitive to change than the SF-6D and yet, in CTOPP, differences were shown on the SF-6D but not the SF-36. However, the disease-specific QLAP, which might be expected to be more sensitive in this context, did show a difference.

The authors' conclusion is that small effects on quality of life probably do exist between pacing modes. However, they are difficult to quantify mainly because they are small and may be accommodated by the patient over time, and are therefore considerably affected by measurement method.

Adverse events occur more frequently during dual-chamber lead insertion and, excluding cases of inadequate atrial capture (which is treatment failure rather than an adverse event), were reported with similar frequency in the large parallel device trial (CTOPP). The risk of perioperative complications in dual-chamber pacing is around twice that for ventricular pacing and this difference relates mainly to the placement of the atrial lead. More serious complications, such as pneumothorax, haemorrhage and

infection, occurred approximately equally between pacing types.

This review of clinical effectiveness has several strengths and potential limitations. Since the systematic review published by Dretzke and colleagues in 2002,[43] the evidence base for dual-chamber pacing has increased considerably with the publication of MOST and the completion of UKPACE. The assessment therefore includes the most up-to-date evidence available on the effectiveness of dual-chamber pacing. The evidence has been addressed from an independent standpoint, without vested interests (either professional or pecuniary), with the support of an expert advisory group which includes a mix of clinical and academic perspectives on dual-chamber pacing.

Among the potential limitations of this review are the potential for having missed relevant studies. The authors consider this to be extremely unlikely, as the search strategies were comprehensive and carried out in a wide range of sources, including contact with manufacturers of pacemakers and review of their submissions to NICE. Although the main sources searched were electronic, the Cochrane Heart Group's registry of studies has been informed by handsearching of journals. The range of sources searched was considerably greater than has been shown to be necessary to obtain the majority of relevant studies in HTAs.[118] The searches on electronic databases were restricted to English language studies and this may have resulted in studies being missed. However, it is unlikely that influential studies would have been omitted as the most important studies are the large parallel-group trials which are well known. It seems unlikely that additional studies of particular importance would have been published in this field without the knowledge of the clinical advisors and the manufacturers of pacing devices.

The selection of studies including symptomatic individuals only, diagnosed according to objective evidence, was constrained by limited information provided in the trials. The key criterion used in the trials was that individuals were eligible for permanent therapeutic pacing based on clinical judgement and practice of the investigators. These individuals were also deemed eligible for inclusion in the trials. There may be variations in clinical practice, particularly between the UK and the USA, where pacing may be deemed necessary in some individuals with non-symptomatic bradycardia. However, the strict application of this criterion would have eroded the available base of evidence, resulting from the exclusion of three of the largest trials and of most cross-over trials. Therefore, the pragmatic definition of eligibility used by the original investigators had to be accepted.

No scoring system was adopted to judge the quality of studies included in the review and some might consider this a weakness. However, available scoring systems are not well validated and may be used in a mechanistic and insensitive fashion, being a poor substitute for careful consideration of the direction and potential influence of possible biases identified by qualitative appraisal within an explicit framework. None of the included studies was so poor as to be excluded completely, although all have some limitations, and these have been considered. It should be noted that the report of UKPACE is currently unpublished and, while it has not been peer reviewed, sufficient methodological details were given to appraise quality.

The key differences between this assessment and the systematic review by Dretzke and colleagues[43] arise from the inclusion of MOST and UKPACE in the current review. This review excluded a small parallel study by Mattioli and colleagues[46] (n = 210), which was included in the previous review. This study did not meet the inclusion criteria for separate reporting of results for the population of interest. In the context of the much larger studies that have been included, omission of this study would be unlikely to have affected the results even if disaggregated results could have been obtained. An individual patient meta-analysis would be required to include this study appropriately in any further review.

Dretzke and colleagues found no statistically significant differences between single- and dual-chamber pacing on the main outcomes reported, but noted a trend towards dual pacing being more effective. The results of MOST for AF have since confirmed this trend. On stroke, the Mattioli trial[46] showed a positive effect, but did not weight the meta-analysis by Dretzke and colleagues to the extent that the pooled estimate was significant. The inclusion of the much larger MOST and UKPACE studies confirms the finding of no significant impact on this outcome over the duration of the trials. Dretzke and colleagues report their findings on heart failure as a "trend towards dual chamber pacing but not significant". The inclusion of a further trial in the meta-analysis does not result in a significant finding for this outcome and the fact that there may not be a trend in favour of dual-chamber pacing. *[CiC removed – comment on the UKPACE trial.]*

Overall, the findings indicate that the early studies suggesting potentially large benefits from dual-chamber pacing are likely to have overestimated benefits. MOST shows a range of benefits from dual-chamber pacing, including effects on quality of life and AF. However, the impact of design, as a trial of mode, makes it difficult to consider what the implications are for practice when compared to the trial of device, CTOPP, which suggest considerably less benefit from dual-chamber pacing *[CiC removed – comment on the UKPACE trial.]* It may be that the benefits of dual-chamber pacing in preserving atrioventricular synchrony are offset by the loss of ventricular synchrony.

Clinical effectiveness of dual-chamber versus single-chamber atrial pacing

CTOPP included people with SSS and AVB and allowed for optional atrial testing at implantation, leading to implantation of an atrial pacemaker where appropriate. However, this group was a very small minority and is included in the overall results for CTOPP. Only three RCTs were found that specifically addressed the effectiveness of atrial versus dual-chamber pacing: one small parallel device trial and two very small cross-over mode trials. No effects were shown on mortality or individual symptoms. Small effects were shown on exercise capacity in the cross-over trials favouring atrial pacing, although these may not be clinically significant and no differences were shown between groups using a functional measure of effort tolerance (SAS).

The most striking finding was an effect on AF, incidence being higher (20%) on dual than on atrial (7.4%) pacing in the parallel group study by Nielsen and colleagues.[91] The groups are reported to have been similar at baseline. However, there were some potentially important differences which, although not statistically significant in direct testing, may be a source for confounding. There were higher proportions of the following groups in either or both of the dual-chamber arms: brady–tachy syndrome at baseline, NYHA class I, and warfarin or aspirin treatment. Brady–tachy syndrome was recognised as a confounder for AF and the analysis adjusted accordingly. The reasons for people taking antithrombotic therapy are not given. Chronic AF was an exclusion criterion for the trial, but details of past history of episodes of AF are not reported and may be a further source of confounding. Measurement bias may also be a possibility in this trial as recording of AF may be better with a dual-chamber device. Finally, the time to development of AF is not reported by Nielsen and colleagues, making it difficult to tell whether the time-dependent effects shown in CTOPP are evident in atrial pacing. *[CiC removed – comment on the UKPACE trial.]*

It is difficult to explain the findings of increased AF in this trial, although there may be some corresponding evidence from CTOPP. In CTOPP, a subgroup analysis suggested that the effect of dual-chamber pacing on risk of cardiovascular death may be lower in people with sinoatrial disease than where this is not present. The authors of CTOPP go on to speculate that atrial pacing may confer greater benefit than physiological pacing (by which they mean dual-chamber pacing, as the majority of people in the physiological pacing arm received dual-chamber devices) because synchrony between ventricular contractions is preserved. Furthermore, the Nielsen trial stopped far short of its recruitment target when a much larger study (DANPACE), for which it was a pilot, started. DANPACE should complete in 2007 and will provide more definitive evidence on the effectiveness of dual versus atrial pacing.

An important factor in the comparison of atrial versus dual-chamber pacing is the development of AVB, leading to reprogramming. Nielsen and colleagues report the annual incidence of high-grade AVB to be 1.9%.[91] Higher rates were reported in one of the shorter duration cross-over trials, but not the other, demonstrating uncertainty on this issue.

Overall, there is therefore some evidence for benefit from dual-chamber compared with single-chamber ventricular pacing, although the development of the evidence base suggests that the benefit, if present, is modest. The findings for dual versus atrial pacing are less robust and suggest that, in the presence of intact AV conduction, dual-chamber pacing may be less effective. The apparent benefits of dual-chamber pacing in AVB can be summarised as avoidance of pacemaker syndrome by maintaining AV synchrony and, although the precise mechanism is not well understood, protecting against the development of AF. The mechanisms underlying the contrary findings in dual versus atrial pacing are poorly understood, but may relate to the maintenance of left–right ventricular synchrony in atrial pacing, which is lost in artificial ventricular pacing.

If one accepts the potential superiority of atrial pacing, the possibility remains that the benefits of a policy of adopting atrial pacing as the initial treatment in SSS will be eroded by the need to upgrade to a dual-chamber device if AVB develops. This was explored further in the economic analysis.

Cost-effectiveness of dual-chamber versus single-chamber pacing

The published economic literature is not informative and is not discussed further.

The models submitted to NICE as part of the national appraisal of dual-chamber pacing are of variable quality. The Guidant (YHEC) and ABHI (Caro) models are of higher quality and include similar events as the PenTAG model. However, a much lower ICER is predicted by both models, each falling well within the range considered as representing good value to the NHS (i.e. between dual chamber being dominant and giving an additional QALY at less than £10,000). It is unfortunate that the reviewers did not have access to either model to permit exploration of the impact of changing inputs on the conclusions of these models. The Guidant (YHEC) model may have underestimated the incremental cost-effectiveness of dual-chamber pacing as a result of the choice of inputs. The ABHI (Caro) model has a more conservative structure and, while the choice of inputs may bias the results, these are not consistently in favour of dual-chamber pacing. High rates of upgrade from single- to dual-chamber devices are assumed in this model. The St Jude (Abacus) evaluation is of poorer quality than the others submitted to NICE.

The PenTAG models have a more complex structure than the ABHI (Caro) and St Jude (Abacus) models and are similar, in some respects, to the Guidant (YHEC) Markov model. However, the present analysis included a comparison between dual-chamber and single atrial as well as ventricular pacing in SSS, and estimated cost-effectiveness separately in SSS and AVB populations. In the base case it was assumed that the mix of atrial and ventricular pacing in SSS is as reported in the CTOPP trial, which is higher than current rates of use of this type of device.

The current results are less optimistic than the sponsor models of dual-chamber pacing for the comparison with ventricular pacing, the base-case estimates being £8500 and £9500 per QALY over 5 years in the AVB and SSS populations, respectively. This is in the region that NHS decision-makers generally consider as representing acceptable value for money. There is, however, considerable uncertainty around this estimate, although it is not sensitive to variation in all parameters. A key issue is the size of the benefit from dual-chamber pacing. As this is small (around 0.08 QALY, or about 4 weeks of quality-adjusted life-time), the resulting cost-effectiveness ratio is sensitive to large relative, but small absolute, changes in benefits.

In common with the ABHI (Caro) model, this study highlighted the importance of pacemaker syndrome as a determinant of cost-effectiveness, upgrade rates from ventricular to dual-chamber pacing being an important factor in the short term, principally exerting an effect on costs. The analysis assumed similar overall upgrade rates to those seen in CTOPP (a trial of device), but that the incidence of pacemaker syndrome is as reported in MOST. Both of these estimates have problems. The threshold for diagnosing pacemaker syndrome in MOST may have been lower than would be experienced in routine clinical practice. In contrast, the threshold for reprogramming in CTOPP is probably considerably higher than would have been the case in a trial of device owing to the need for an invasive procedure. It was assumed that no cases of pacemaker syndrome occur in dual-chamber pacing. Therefore, a policy of implanting all cases with dual-chamber pacemakers may prevent all cases of pacemaker syndrome, including cases who would have moderate symptoms but would not be considered for reimplantation. However, in MOST, 6.3% of the recipients who were reprogrammed from ventricular pacemakers to dual later reverted to the original mode.

Differential costs are also extremely important and the data on hardware and implantation costs are variable. The authors believe that the estimates of implantation cost are as accurate as are currently available, being based on a survey of NHS hospitals using patient-level data on resource use. Nevertheless, the sample was small and the costing methods used to place a value on resource use may be variable. An alternative set of hardware prices based on assumptions of the range of list prices demonstrated a significant effect on the estimated cost-effectiveness. A wide range of additional features is available for pacing devices and the study has not considered the impact on costs of including these, which increase hardware costs. A combination of increased acquisition costs and conservative assumptions regarding the

importance of pacemaker syndrome is likely to make the estimate of the cost-effectiveness of dual-chamber pacing much less favourable.

The utility associated with pacemaker syndrome has been crudely estimated, based on data collected in patients in the PASE trial and corresponding to NYHA classes. This is a broad classification and the precision of these utility estimates may be limited. Pacemaker syndrome is only possible as an outcome on ventricular pacing and leads to a decrement in utility and a small increase in costs. This might be seen as a potential bias in the structure of the model, particularly since a small percentage of people in the dual-chamber arm in MOST had their device reprogrammed to single-chamber pacing.

An important reason for the difference in the cost–utility estimates between the PenTAG and sponsor models is the assumptions made regarding risk of stroke, mortality and heart failure. None of the trials included in the review showed a significant effect on these outcomes. The PenTAG model is therefore, the authors believe, more appropriately conservative than the sponsor models in this regard. The importance of these outcomes to cost-effectiveness, in the view of the authors, confirms their cautious approach in modelling the longer term.

Although the cost-effectiveness of dual-chamber pacing becomes more attractive as the time horizon increases, several competing risks must be considered. Background mortality rate is important and may be considered low in this model, being based on routine mortality statistics. Higher background mortality increases the ICER. Alternatively, a longer term horizon allows more complete modelling of the stream of consequences, particularly from AF, which might reasonably be expected to result in increased mortality through stroke and heart failure. However, this highlights the relatively crude modelling of longer term outcomes undertaken to date. For example, the risks consequent on AF could not be stratified by age, gender, history of diabetes, stroke or TIA and left ventricular function. It is difficult to predict whether more sophisticated modelling would be worthwhile given the estimates of cost-effectiveness produced, although it may guide the identification of particular subgroups in whom dual-chamber pacing may be more or less value for money.

In addition to these uncertainties, other potentially important limitations in the PenTAG model should be considered.

Rate responsiveness has not been considered explicitly. The importance of rate responsiveness to the effectiveness of pacing devices is currently uncertain, although there is some evidence that the impact of dual-chamber pacemakers on exercise capacity in cross-over trials may be confounded by rate responsiveness. The possible impact of pacemaker dependency was not considered. Sweeney and colleagues have presented some evidence that the risk of AF may vary with the proportion of time in which the pacemaker is active.[56] They suggest that risk increases with pacing frequency, up to 80–85% of the time, and that risk is higher in VVIR mode than DDDR. The impact on the ICER of not including chronotropic incompetence and pacemaker dependency is difficult to predict and could be in either direction.

The model does not include a refined description of the additional diagnostic cost necessary to diagnose pacemaker syndrome, although in most centres this diagnosis is likely to be made predominantly on clinical and straightforward electrophysiological assessment.

The utility estimates used come from a range of different sources and, notably, are not derived from preference-based measurement in a sample of the general population. This may introduce bias in either direction to the model. In general, although by no means invariably, state-specific utility values obtained from patients are higher than those from the general public, reflecting adaptation to the condition. However, it is the difference in utility between states that drives the cost–utility analysis and this may remain the same, be higher or be lower depending on the source of values and method of elicitation used. Further work would be required to investigate this further, although, in general, utility values appear to be less important than transition probabilities in determining cost–utility. The most important exception to this is the value for pacemaker syndrome, in particular mild pacemaker syndrome. In the base-case analysis it was assumed that pacemaker syndrome is persistent, which may be at odds with the findings for quality of life reported in clinical trials. It is not possible, on the basis of the available information, to resolve the uncertainty around how pacemaker syndrome should be taken into account in the decision-analytic model.

However, only under circumstances where pacemaker syndrome is considered unlikely to have any impact on quality of life does the

estimate of cost-effectiveness show a high probability of exceeding levels generally considered by decision-makers as acceptable. The reasons for this are that effects of AF remain in favour of dual pacing and that upgrades are still likely to occur, offsetting the initial cost difference.

Atrial pacing is likely to be more cost-effective than dual pacing in people with SSS. However, this finding may be viewed with some caution as it is informed by only one small trial which showed a dramatic effect on AF and limited progression to AVB. Both of these features make it highly likely that atrial pacing will be favoured in the economic analysis. In the review of clinical effectiveness a range of potential problems was noted with the Nielsen study, which underpins the analysis, and it was noted that the DANPACE trial, for which Nielsen and colleagues' study was a pilot, is still underway. This, and the low current uptake rates of atrial pacing in the UK, suggest that the case for clinical effectiveness of atrial pacing is not established.

This analysis of the current diffusion and impact of further adoption of dual-chamber pacing in the NHS is necessarily crude, but highlights the fact that current levels of use are high.

Chapter 9

Recommendations for further research

Several important studies are already underway. In particular, DANPACE will provide much improved estimates of the effectiveness of dual-chamber pacing compared with single-chamber atrial pacing.

The trial populations in MOST, PASE, CTOPP and UKPACE are different in a number of potentially important respects and this has hampered the authors' ability to explore and take account of statistical and clinical heterogeneity in the meta-analyses carried out for this assessment. An individual patient meta-analysis of the completed trials of dual-chamber pacing is being carried out by an international collaboration of researchers and results may be available in the near future. This will be particularly important for generating and, to some extent, testing hypotheses regarding the effectiveness of dual-chamber pacing in specified groups (e.g. chronotropic incompetence, left ventricular failure and pacemaker dependency). Given that the use of dual-chamber pacing is less frequent in older pacemaker recipients, an important further analysis of existing data should address effectiveness and cost-effectiveness in this population.

The economic evaluation of UKPACE, in which data collection is complete and preliminary analyses are underway, will provide the first UK-based empirical estimate of the cost-effectiveness of dual-chamber pacing. Benefits were measured using the EQ-5D and SF-6D, for which UK community tariffs are available. Results are expected in the near future. It would assist future modelling studies if the results of UKPACE could include summary data on utility by health state.

Further research into the classification, diagnosis and utility associated with pacemaker syndrome is needed.

There is a striking lack of evidence for the use of different types of pacemaker in children. The organisational challenges of establishing trials in a small population are considerable.

Chapter 10
Conclusions

Dual-chamber pacing results in small but potentially important benefits in populations with SSS and/or AVB compared with ventricular pacemakers. There is no evidence of superiority in terms of mortality in the medium term (up to 5 years), which increases the importance of intermediate outcomes such as AF and of impacts on quality of life through, for example, pacemaker syndrome.

AF results compared with ventricular pacing are somewhat conflicting. However, there is evidence from pooling all available trials of a reduction in the odds of this outcome of around 20%. This is likely to result, in the longer term, in reduced rates of stroke and heart failure, although this has not been shown empirically in the trials to date.

As well as the potential avoidance of a small number of important CVD consequences, pacemaker syndrome is a crucial factor in determining cost-effectiveness. However, difficulties in standardising diagnosis and measurement of severity make it difficult to quantify precisely its impact.

The cost-effectiveness of dual-chamber pacing compared with ventricular pacing is also sensitive to the difference in costs between dual- and single-chamber devices, although upgrades, for pacemaker syndrome or other reasons, defray the initial difference in acquisition cost over time. For this reason, and because of the development of longer term outcomes from medium-term differences in AF, dual-chamber pacing is likely to be more cost-effective as a longer time horizon for the technology is considered.

At 5 years, dual-chamber pacing in SSS and AVB is likely to yield additional QALYs at a cost of less than £10,000, although there is some uncertainty around this estimate, particularly with regard to pacemaker syndrome. More conservative assumptions suggest that the cost-effectiveness ratio may be around £30,000 per QALY.

The evidence base comparing dual-chamber with single atrial pacing is much smaller and less robust. A single, small, parallel, pilot RCT is available and informs the cost-effectiveness analysis. This suggests that atrial pacing is likely to be cost-effective compared with dual-chamber pacing.

Dual-chamber pacing is in common usage in the UK, although recipients are more likely to be younger within the eligible populations. Insufficient evidence is currently available to inform policy on specific groups who may benefit most from pacing with dual-chamber devices, although overall the assessment is that the technology is likely to yield benefits at a level that is generally considered acceptable value for money compared with ventricular devices.

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Contribution of authors

Emanuela Castelnuovo (Research Fellow in health technology assessment) wrote the protocol, critically appraised studies, led the economic analysis and drafted the report. Ken Stein (Senior Lecturer in public health) contributed to the protocol and development of the economic model, critically appraised studies and drafted the report. Ruth Garside (Research Fellow in health technology assessment) commented on the protocol, critically appraised studies and commented on the draft report. Martin Pitt (Research Fellow in decision analysis) developed the economic model and commented on the draft report. Liz Payne (Information Scientist) commented on the draft protocol, carried out all literature searches and commented on the draft report.

About PenTAG

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multidisciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which health technology assessment is a strong and recurring theme.

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Appendix 1

Members of the advisory group

The authors are very grateful to the members of the clinical expert advisory group, who provided advice during the development of the assessment and commented on the draft report. However, any errors remaining are the responsibility of the authors.

Dr Richard Charles (Consultant Cardiologist, The Liverpool Cardiothoracic Centre, UK)

Dr John Dean (Consultant Cardiologist, Royal Devon and Exeter Hospital, Exeter, UK)

Dr Neil Sulke (Consultant Cardiologist, Eastbourne, UK)

Dr William Toff (Senior Lecturer in Cardiology, University of Leicester, UK)

Appendix 2

Search strategy

Searches started 4 November 2003, update started 10 May 2004.

Cochrane Library – CDSR

2003, Issue 4 (searched 13 November 2003)

#1.ddd 143
#10.(physiological* and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 118
#11.((av or atrioventricular) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 271
#2.dddr 57
#3.ddi 136
#4.ddir 6
#5.vdd 34
#6.vddr 1
#7.vdi 4
#8.vdir 1
#9.((dual or double) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 416
#12.((av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 54
#13.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) 787
#14.(pacing or pacemaker* or (pace next maker*) or paced or pacer*) 1395
#15.(#1 or #3 or #6 or #7) 271
#16.(#14 and #15) 124
#17.(#2 or #4 or #5 or #8 or #9 or #10 or #11 or #12 or #16) 642

42 complete reviews and 9 protocols retrieved; 0 relevant references and 1 protocol downloaded.

Upgrade
Cochrane Library – CDSR

2004, Issue 2 (searched 10 May 2004)

Same strategy run as November search. Limited to 2003–2004.

21 complete reviews and 4 protocols; 1 relevant reference and 1 protocol downloaded.

Cochrane Library – CENTRAL

2003, Issue 4 (searched 13 November 2003)

#1.ddd 143
#10.(physiological* and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 118
#11.((av or atrioventricular) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 271
#12.((av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 54
#13.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) 787
#14.(pacing or pacemaker* or (pace next maker*) or paced or pacer*) 1395
#15.(#1 or #3 or #6 or #7) 271
#16.(#14 and #15) 124
#17.(#2 or #4 or #5 or #8 or #9 or #10 or #11 or #12 or #16) 642
#2.dddr 57
#3.ddi 136
#4.ddir 6
#5.vdd 34
#6.vddr 1
#7.vdi 4
#8.vdir 1
#9.((dual or double) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 416

569 references retrieved; 569 references downloaded (297 after deduplication).

Upgrade
Cochrane Library – CENTRAL

2004, Issue 2 (searched 10 May 2004)

Same strategy run as November search. Limited to 2003–2004.

30 references; 25 references downloaded.

Cochrane Heart Group – Specialised Register

No additional references found.

MEDLINE (OVID)

1966–2003, October week 5 (searched 12 November 2003)

1 ddd.ti,ab. (2174)
2 dddr.ti,ab. (233)

3 ddi.ti,ab. (846)
4 ddir.ti,ab. (23)
5 vdd.ti,ab. (329)
6 vddr.ti,ab. (37)
7 vdi.ti,ab. (68)
8 vdir.ti,ab. (1)
9 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1373)
10 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (362)
11 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (140)
12 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (250)
13 Pacemaker, Artificial/ (16180)
14 Cardiac Pacing, Artificial/ (12278)
15 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (33005)
16 13 or 14 or 15 (41306)
17 1 or 3 or 6 or 7 (3089)
18 16 and 17 (1012)
19 2 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 18 (2761)
20 limit 19 to human (2605)
21 limit 20 to english language (2129)
RCTs:
22 randomized controlled trial.pt. (184388)
23 controlled clinical trial.pt. (65285)
24 Randomized Controlled Trials/ (31418)
25 Random Allocation/ (49965)
26 Double-Blind Method/ (76989)
27 single-blind method/ (7727)
28 22 or 23 or 24 or 25 or 26 or 27 (312525)
29 clinical trial.pt. (373560)
30 exp Clinical Trials/ (152583)
31 (clin$ adj2 trial$).ti,ab. (77941)
32 ((singl$ or doubl$ or tripl$ or trebl$) adj2 (blind$ or mask$)).ti,ab. (74025)
33 placebo$.ti,ab. (82499)
34 random$.ti,ab. (275581)
35 cross over.ti,ab. (10732)
36 crossover.ti,ab. (20868)
37 crossover studies/ (13550)
38 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (625152)
39 Comparative Study/ (1080263)
40 Follow-Up Studies/ (276271)
41 Prospective Studies/ (168637)
42 (controls or controlled or prospective$ or volunteer$).ti,ab. (690209)
43 39 or 40 or 41 or 42 (1893105)
44 28 or 38 or 43 (2235671)
45 21 and 44 (925)

925 references (English and human) retrieved; 900 references downloaded (after deduplication).

Upgrade
MEDLINE (OVID)
1996–2004, April week 4 (searched 10 May 2004)

79 references (English and human); 79 references downloaded.

EMBASE (OVID)
1980–2003, week 45 (searched 12 November 2003)

1 ddd.ti,ab. (2056)
2 dddr.ti,ab. (237)
3 ddi.ti,ab. (796)
4 ddir.ti,ab. (23)
5 vdd.ti,ab. (344)
6 vddr.ti,ab. (42)
7 vdi.ti,ab. (192)
8 vdir.ti,ab. (2)
9 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1310)
10 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (303)
11 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (112)
12 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (208)
13 artificial heart pacemaker/ (6294)
14 heart pacing/ (4840)
15 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (24673)
16 13 or 14 or 15 (26796)
17 1 or 3 or 6 or 7 (3049)
18 16 and 17 (941)
19 2 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 18 (2592)
20 limit 19 to human (2352)
21 limit 20 to english language (1921)
RCTs:
22 Randomized Controlled Trial/ (79774)
23 randomization/ (8060)
24 Double Blind Procedure/ (49843)
25 Single Blind Procedure/ (4462)
26 22 or 23 or 24 or 25 (106870)
27 Clinical Trial/ (279517)
28 Controlled Study/ (1652786)
29 (clin$ adj2 trial$).ti,ab. (70233)
30 ((singl$ or doubl$ or tripl$ or trebl$) adj2 (blind$ or mask$)).ti,ab. (68979)
31 placebo$.ti,ab. (76859)
32 random$.ti,ab. (237460)

33 cross over.ti,ab. (9598)
34 crossover.ti,ab. (19062)
35 Crossover Procedure/ (14312)
36 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (1933886)
37 comparative study/ (46576)
38 Follow Up/ (120347)
39 Prospective Study/ (33605)
40 (controls or controlled or prospective$ or volunteer$).ti,ab. (610336)
41 37 or 38 or 39 or 40 (750299)
42 26 or 36 or 41 (2295082)
43 21 and 42 (783)

783 references (English and human) retrieved; (295 after deduplication).

Upgrade
EMBASE (OVID)

1996–2004, week 19 (searched 10 May 2004)

108 references (English and human); 108 references downloaded.

Medline In-process and other non-indexed citations (OVID)
(Used to be called PreMEDLINE)

12 November 2003 (searched 13 November 2003)

1 ddd.ti,ab. (53)
2 dddr.ti,ab. (10)
3 ddi.ti,ab. (17)
4 ddir.ti,ab. (0)
5 vdd.ti,ab. (12)
6 vddr.ti,ab. (0)
7 vdi.ti,ab. (4)
8 vdir.ti,ab. (0)
9 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (46)
10 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (11)
11 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1)
12 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (0)
13 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (694)
14 1 or 3 or 6 or 7 (74)
15 13 and 14 (18)
16 2 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 15 (76)
17 limit 16 to english language (69)

RCTs:
18 randomized controlled trial.pt. (23)
19 controlled clinical trial.pt. (0)
20 clinical trial.pt. (329)
21 (clin$ adj2 trial$).ti,ab. (3234)
22 ((singl$ or doubl$ or tripl$ or trebl$) adj2 (blind$ or mask$)).ti,ab. (1454)
23 placebo$.ti,ab. (1989)
24 random$.ti,ab. (11819)
25 cross over.ti,ab. (210)
26 crossover.ti,ab. (1186)
27 (controls or controlled or prospective$ or volunteer$).ti,ab. (21044)
28 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (32848)
29 17 and 28 (22)

22 references retrieved; 22 references downloaded (after deduplication).

Upgrade
MEDLINE In-process and other non-indexed citations (OVID) (used to be called PreMEDLINE)

7 May 2004 (searched 10 May 2004)

17 references; 17 references downloaded.

PubMed
(Not searched; searched PreMEDLINE instead; see above)

ISI – Web of Knowledge – Science Citation Index
1981–2003 (searched 19 November 2003)

#1 TS=(((dual or double) same (pacing or pacemaker* or (pace same maker*) or paced or pacer*)))
#2 TS=(physiological* same (pacing or pacemaker* or (pace same maker*) or paced or pacer*))
#3 TS=((av or atrioventricular) same (pacing or pacemaker* or (pace same maker*) or paced or pacer*))
#4 TS=((av or atrioventricular) same (synchron* or sequential) same (pacing or pacemaker* or (pace same maker*) or paced or pacer*))
#5 TS=(pacing or pacemaker* or (pace same maker*) or paced or pacer*)
#6 TS=(ddd or ddi or vddr or vdi)
#7 #5 and #6
#8 TS=(dddr or ddir or vdd or vdir)
#9 #1 or #2 or #3 or #4 or #7 or #8

3666 references (English) retrieved; 789 references selected and downloaded (533 after deduplication).

Upgrade
ISI – Web of Knowledge – Science Citation Index

2003–2004 (searched 13 May 2004)

52 references (English); 52 references downloaded.

Web of Science Proceedings
1990–2003 (searched 20 November 2003)

#1 TS=(((dual or double) same (pacing or pacemaker* or (pace same maker*) or paced or pacer*)))
#2 TS=(physiological* same (pacing or pacemaker* or (pace same maker*) or paced or pacer*))
#3 TS=((av or atrioventricular) same (pacing or pacemaker* or (pace same maker*) or paced or pacer*))
#4 TS=((av or atrioventricular) same (synchron* or sequential) same (pacing or pacemaker* or (pace same maker*) or paced or pacer*))
#5 TS=(pacing or pacemaker* or (pace same maker*) or paced or pacer*)
#6 TS=(ddd or ddi or vddr or vdi)
#7 #5 and #6
#8 TS=(dddr or ddir or vdd or vdir)
#9 #1 or #2 or #3 or #4 or #7 or #8

703 references (English) retrieved; 83 references selected and downloaded (45 after deduplication).

Upgrade
Web of Science Proceedings

1990–2003 (searched 13 May 2004)

23 references (English); 3 references selected and downloaded.

BIOSIS
1985–2003 (searched 24 November 2003)

((((((al: ((av n3 pacing) or (av n3 pacemaker) or (av n3 paced) or (av n3 pacer*))) or (al: ((atrioventricular n3 pacing) or (atrioventricular n3 pacemaker*) or (atrioventricular n3 paced) or (atrioventricular n3 pacer*)))) or (al: ((double n3 pacing) or (double n3 pacemaker*) or (double n3 paced) or (double n3 pacer*)))) or (al: ((physiological* n pacing) or (physiological* n pacemaker*) or (physiological* n paced) or (physiological* n pacer*)))) or (al: ((physiological* n pacing) or (physiological* n pacemaker*) or (physiological* n paced) or (physiological* n pacer*)))) or (al: ((dual n3 pacing) or (dual n3 paced) or (dual n3 pacemaker*)))) limited to English and Meetings*

493 references retrieved; 295 references selected and downloaded (245 after deduplication).

DARE (Cochrane Library)
Issue 4, 2003 (searched 13 November 2003)

#1.ddd 143
#2.dddr 57
#3.ddi 136
#4.Ddir 6
#5.vdd 34
#6.vddr 1
#7.Vdi 4
#10.(physiological* and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 118
#11.((av or atrioventricular) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 271
#12.((av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 54
#13.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) 787
#14.(pacing or pacemaker* or (pace next maker*) or paced or pacer*) 1395
#15.(#1 or #3 or #6 or #7) 271
#16.(#14 and #15) 124
#17.(#2 or #4 or #5 or #8 or #9 or #10 or #11 or #12 or #16) 642
#8.Vdir 1
#9.((dual or double) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 416

5 references retrieved; 1 reference selected.

Upgrade
DARE (Cochrane Library)

Issue 2, 2004 (searched 10 May 2004)

Same strategy run as November search. Limited to 2003–2004.

3 references; 1 reference selected.

DARE (CRD databases)
(Searched 13 November 2003)

Repeated above strategy. Same results, but reference chosen is importable into Ref Man from CRD version.

1 reference imported.

Upgrade
DARE (CRD databases)

(Searched 13 November 2003)

Same strategy run as November search. Limited to 2003–2004.

1 reference.

HTA database (Cochrane Library)

Issue 4, 2003 (searched 13 November 2003)

#1.ddd 143
#10.(physiological* and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 118
#11.((av or atrioventricular) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 271
#12.((av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 54
#13.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) 787
#2.dddr 57
#3.ddi 136
#4.ddir 6
#5.Vdd 34
#6.vddr 1
#7.vdi 4
#8.vdir 1
#9.((dual or double) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 416
#14.(pacing or pacemaker* or (pace next maker*) or paced or pacer*) 1395
#15.(#1 or #3 or #6 or #7) 271
#16.(#14 and #15) 124
#17.(#2 or #4 or #5 or #8 or #9 or #10 or #11 or #12 or #16) 642

2 references retrieved; 1 reference selected.

Upgrade
HTA database (Cochrane Library)

Issue 2, 2004 (searched 10 May 2004)

1 references; 1 reference selected.

HTA database (CRD databases)

(Searched 13 November 2003)

Repeated above strategy; results are importable into Ref Man from CRD version

3 references downloaded.

NRR

Issue 3, 2003 (searched 20 November 2003)

#1 ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir
#2 (pacing or pacemaker* or (pace same maker*) or paced or pacer*)
#3 #1 and #2
#4 (dual or double) and (pacing or pacemaker* or paced or pacer*)
#5 physiological* and (pacing or pacemaker* or paced or pacer*)
#6 (av or atrioventricular) and (pacing or pacemaker* or paced or pacer*)
#7 (av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or paced or pacer*)
#8 #3 or #4 or #5 or #6 or #7

90 references retrieved; nrr1.txt, 1 reference downloaded; nrr2.txt, 1 reference; nrr3.txt, 32 references; nrr4.txt, 11 references; nrr5.txt, 1 reference; nrr6.txt, 1 reference; nrr7.txt, 1 reference.

NRR

Issue 4, 2003 (searched 20 November 2003)

#1 ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir
#2 (pacing or pacemaker* or (pace same maker*) or paced or pacer*)
#3 #1 and #2
#4 (dual or double) and (pacing or pacemaker* or paced or pacer*)
#5 physiological* and (pacing or pacemaker* or paced or pacer*)
#6 (av or atrioventricular) and (pacing or pacemaker* or paced or pacer*)
#7 (av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or paced or pacer*)
#8 #3 or #4 or #5 or #6 or #7

1 extra reference retrieved; NRR Issue 4.txt, 1 reference downloaded.

Upgrade
NRR

Issue 2, 2004 (searched 13 May 2004)

4 references.

Biomed Central

(Searched 27 November 2003)

(av pacing) OR (av pacemaker*) OR (av paced) OR (av pacer*) OR (atrioventricular pacing) OR (atrioventricular pacemaker*) OR (atrioventricular

paced) OR (atrioventricular pacer*) OR (double pacing) OR (double pacemaker*) OR (double paced) OR (double pacer*) OR (physiological* pacing) OR (physiological* pacemaker*) OR (physiological* paced) OR (physiological* pacer*) OR (physiological* pacing) OR (physiological* pacemaker*) OR (physiological* paced) OR (physiological* pacer*) (dual pacing) OR (dual paced) OR (dual pacemaker*)

329 references retrieved; 3 references selected (0 after deduplication).

Current Controlled Trials (International Standard RCT Number Register)

http://controlled-trials.com/ (searched 20 November 2003)

ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir[a]
(dual or double) and (pacing or pacemaker* or paced or pacer*)[b]
physiological* and (pacing or pacemaker* or paced or pacer*)[c]
(av or atrioventricular) and (pacing or pacemaker* or paced or pacer*)[d]
(av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or paced or pacer*)[e]

[a]1 reference retrieved (0 selected); [b]1 reference retrieved (0 selected); [c]0 reference retrieved (0 selected); [d]2 references retrieved (2 selected); [e]0 reference retrieved (0 selected).

Current Controlled Trials (metaRegister of Controlled Trials) – all registers except NRR searched

http://controlled-trials.com/ (searched 20 November 2003)

ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir[a]
(dual or double) and (pacing or pacemaker* or paced or pacer*)[b]
physiological* and (pacing or pacemaker* or paced or pacer*)[c]
(av or atrioventricular) and (pacing or pacemaker* or paced or pacer*)[d]
(av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or paced or pacer*)[e]

[a]109 references retrieved (3 selected); [b]19 references retrieved (2 extra selected); [c]1 reference retrieved (1 extra selected); [d]10 references retrieved (1 extra selected); [e]0 references retrieved (0 selected).

Clinical Trials.gov

http://clinicaltrials.gov/ (searched 27 November 2003)

ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir[a]
(dual) AND (pacemaker* or pacing or paced or pacer*)[b]
(double) AND (pacemaker* or pacing or paced or pacer*)[c]
(physiological*) AND (pacing or pacemaker* or paced or pacer*)[d]
(atrioventricular) AND (pacing or pacemaker* or paced or pacer*)[e]
(av) AND (pacing or pacemaker* or paced or pacer*)[f]

[a]0 references retrieved (0 selected); [b]2 references retrieved (2 selected); [c]1 reference retrieved (0 selected); [d]1 reference retrieved (0 selected); [e]1 reference retrieved (0 selected); [f]1 reference retrieved (0 selected).

FDA

http://www.fda.gov

Economics searches

Cochrane Library – CDSR

2003, Issue 4

General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

Cochrane Library – CENTRAL

2003, Issue 4

General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

Medline (OVID)

1996–2003, November, week 2 (searched 20 November 2003)

1 exp "Costs and Cost Analysis"/ (109788)
2 ECONOMICS/ (26004)
3 exp ECONOMICS, HOSPITAL/ (12664)
4 exp ECONOMICS, MEDICAL/ (9939)
5 exp ECONOMICS, NURSING/ (3613)
6 exp ECONOMICS, PHARMACEUTICAL/ (1296)

7 exp "Fees and Charges"/ (21639)
8 exp BUDGETS/ (8260)
9 budget$.ti,ab. (8462)
10 cost$.ti. (41983)
11 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (33170)
12 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (16177)
13 (price$ or pricing$).ti,ab. (10346)
14 (financial or finance or finances or financed).ti,ab. (21706)
15 (fee or fees).ti,ab. (6566)
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (225650)
17 letter.pt. (520048)
18 editorial.pt. (160334)
19 comment.pt. (260423)
20 17 or 18 or 19 (709416)
21 16 not 20 (209709)
22 ddd.ti,ab. (2175)
23 dddr.ti,ab. (233)
24 ddi.ti,ab. (846)
25 ddir.ti,ab. (23)
26 vdd.ti,ab. (329)
27 vddr.ti,ab. (37)
28 vdi.ti,ab. (68)
29 vdir.ti,ab. (1)
30 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1373)
31 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (362)
32 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (140)
33 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (250)
34 Pacemaker, Artificial/ (16192)
35 Cardiac Pacing, Artificial/ (12289)
36 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (33052)
37 34 or 35 or 36 (41356)
38 22 or 24 or 27 or 28 (3090)
39 37 and 38 (1013)
40 23 or 25 or 26 or 29 or 30 or 31 or 32 or 33 or 39 (2762)
41 limit 40 to human (2606)
42 limit 41 to english language (2129)
43 21 and 42 (29)
44 *Pacemaker, Artificial/ec [Economics] (73)
45 *Cardiac Pacing, Artificial/ec [Economics] (21)
46 44 or 45 (81)
47 limit 46 to english language (74)
48 47 not 20 (58)
49 43 or 48 (80)

80 references retrieved; 80 references downloaded (57 after deduplication).

EMBASE (OVID)

1980–2003, week 47 (searched 25 November 2003)

1 ddd.ti,ab. (2045)
2 dddr.ti,ab. (233)
3 ddi.ti,ab. (796)
4 ddir.ti,ab. (24)
5 vdd.ti,ab. (340)
6 vddr.ti,ab. (42)
7 vdi.ti,ab. (191)
8 vdir.ti,ab. (2)
9 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1305)
10 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (298)
11 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (112)
12 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (206)
13 artificial heart pacemaker/ (6257)
14 heart pacing/ (4800)
15 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (24657)
16 13 or 14 or 15 (26775)
17 1 or 3 or 6 or 7 (3037)
18 16 and 17 (932)
19 2 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 18 (2569)
20 limit 19 to human (2335)
21 limit 20 to english language (1897)
22 budget$.ti,ab. (6038)
23 cost$.ti. (26277)
24 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (30453)
25 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (10120)
26 (price$ or pricing$).ti,ab. (7335)
27 (financial or finance or finances of financed).ti,ab. (14268)
28 (fee or fees).ti,ab. (3651)
29 cost/ (15959)
30 cost benefit analysis/ (16840)
31 cost effectiveness analysis/ (31337)
32 cost minimization analysis/ (591)
33 cost of illness/ (1722)
34 cost utility analysis/ (928)
35 drug cost/ (19231)
36 health care cost/ (34072)
37 health economics/ (6165)
38 economic evaluation/ (1666)

39 economics/ (4265)
40 pharmacoeconomics/ (759)
41 budget/ (4860)
42 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 (150628)
43 letter.pt. (254187)
44 editorial.pt. (115767)
45 43 or 44 (369954)
46 42 not 45 (135501)
47 21 and 46 (42)

42 references (English) retrieved; 42 references downloaded (11 after deduplication).

PubMed (PreMEDLINE searched instead)

PreMEDLINE (OVID)

(Now known as MEDLINE In-process and other non-indexed citations)

24 Nov 2003 (searched 25 November 2003)

1 ddd.ti,ab. (55)
2 dddr.ti,ab. (10)
3 ddi.ti,ab. (20)
4 ddir.ti,ab. (0)
5 vdd.ti,ab. (12)
6 vddr.ti,ab. (0)
7 vdi.ti,ab. (4)
8 vdir.ti,ab. (0)
9 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (48)
10 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (11)
11 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (2)
12 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1)
13 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (723)
14 1 or 3 or 6 or 7 (79)
15 13 and 14 (17)
16 2 or 5 or 9 or 11 or 12 or 15 (70)
17 budget$.ti,ab. (302)
18 cost$.ti. (1069)
19 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (1255)
20 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (437)
21 (price$ or pricing$).ti,ab. (650)
22 (financial or finance or finances or financed).ti,ab. (646)
23 (fee or fees).ti,ab. (117)
24 letter.pt. (6623)
25 editorial.pt. (4073)
26 comment.pt. (5634)
27 24 or 25 or 26 (13254)
28 17 or 18 or 19 or 20 or 21 or 22 or 23 (3908)
29 28 not 27 (3783)
30 16 and 29 (0)

0 references retrieved; 0 references selected.

ISI – Web of Knowledge – Science Citation Index

1981–2003

General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

Web of Science Proceedings

General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

DARE

General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

NHS EED (Cochrane Library)

Issue 4, 2003 (searched 13 November 2003)

#1.ddd 143
#10.(physiological* and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 118
#11.((av or atrioventricular) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 271
#12.((av or atrioventricular) and (synchron* or sequential) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 54
#13.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) 787
#14.(pacing or pacemaker* or (pace next maker*) or paced or pacer*) 1395
#15.(#1 or #3 or #6 or #7) 271
#2.dddr 57
#3.ddi 136
#4.ddir 6
#5.vdd 34
#6.vddr 1
#7.vdi 4
#8.vdir 1
#9.((dual or double) and (pacing or pacemaker* or (pace next maker*) or paced or pacer*)) 416
#16.(#14 and #15) 124

#17.(#2 or #4 or #5 or #8 or #9 or #10 or #11 or #12 or #16) 642

12 references retrieved; 6 references selected.

NHS EED (CRD databases)
(Searched 17 November 2003)

Repeated above strategy; results are importable into RefMan from CRD version.

16 references retrieved; 6 references selected.

HTA database
General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

Quality of life searches

Medline (OVID)
1966–2003, November week 2 (searched 27 November 2003)

1 value of life/ (7154)
2 quality adjusted life year/ (1860)
3 quality adjusted life.ti,ab. (1244)
4 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (964)
5 disability adjusted life.ti,ab. (189)
6 daly$.ti,ab. (258)
7 health status indicators/ (7883)
8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (3222)
9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (574)
10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (334)
11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (21)
12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (238)
13 (euroqol or euro qol or eq5d or dq 5d).ti,ab. (362)
14 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (907)
15 (hye or hyes).ti,ab. (47)
16 health$ year$ equivalent$.ti,ab. (32)
17 health utilit$.ab. (213)
18 (hui or hui1 or hui2 or hui3).ti,ab. (251)
19 quality of wellbeing.ti,ab. (2)
20 quality of well being.ti,ab. (454)
21 qwb.ti,ab. (88)
22 willingness to pay.ti,ab. (471)
23 standard gamble$.ti,ab. (294)
24 time trade off.ti,ab. (245)
25 tto.ti,ab. (151)
26 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (22895)
27 letter.pt. (520048)
28 editorial.pt. (160334)
29 comment.pt. (260423)
30 27 or 28 or 29 (709416)
31 26 not 30 (21729)
32 ddd.ti,ab. (2175)
33 dddr.ti,ab. (233)
34 ddi.ti,ab. (846)
35 ddir.ti,ab. (23)
36 vdd.ti,ab. (329)
37 vddr.ti,ab. (37)
38 vdi.ti,ab. (68)
39 vdir.ti,ab. (1)
40 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1373)
41 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (362)
42 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (140)
43 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (250)
44 Pacemaker, Artificial/ (16192)
45 Cardiac Pacing, Artificial/ (12289)
46 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (33052)
47 44 or 45 or 46 (41356)
48 32 or 34 or 37 or 38 (3090)
49 47 and 48 (1013)
50 33 or 35 or 36 or 39 or 40 or 41 or 42 or 43 or 49 (2762)
51 limit 50 to human (2606)
52 limit 51 to english language (2129)
53 31 and 52 (9)
54 from 53 keep 1-9 (9)

9 references retrieved; 9 references downloaded (1 after deduplication).

PreMEDLINE (OVID)
(Now known as MEDLINE In-process and other non-indexed citations) 26 November (searched 27 November 2003)

1 quality adjusted life.ti,ab. (50)
2 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (42)
3 disability adjusted life.ti,ab. (12)
4 daly$.ti,ab. (19)
5 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (235)
6 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (36)
7 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (35)
8 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (0)
9 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (4)
10 (euroqol or euro qol or eq5d or dq 5d).ti,ab. (17)
11 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (73)
12 (hye or hyes).ti,ab. (1)
13 health$ year$ equivalent$.ti,ab. (0)
14 health utilit$.ab. (12)
15 (hui or hui1 or hui2 or hui3).ti,ab. (21)
16 quality of wellbeing.ti,ab. (0)
17 quality of well being.ti,ab. (17)
18 qwb.ti,ab. (1)
19 willingness to pay.ti,ab. (27)
20 standard gamble$.ti,ab. (10)
21 time trade off.ti,ab. (8)
22 tto.ti,ab. (8)
23 letter.pt. (6778)
24 editorial.pt. (4180)
25 comment.pt. (5814)
26 23 or 24 or 25 (13590)
27 1 or 2 or 3 or 4 or 5 or 6 or 7 or 9 or 10 or 11 or 12 or 14 or 15 or 17 or 18 or 19 or 20 or 21 or 22 (508)
28 27 not 26 (503)
29 ddd.ti,ab. (55)
30 dddr.ti,ab. (10)
31 ddi.ti,ab. (20)
32 ddir.ti,ab. (0)
33 vdd.ti,ab. (12)
34 vddr.ti,ab. (0)
35 vdi.ti,ab. (4)
36 vdir.ti,ab. (0)
37 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (48)
38 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (11)
39 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (2)
40 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1)
41 29 or 30 or 31 or 33 or 35 or 37 or 38 or 39 or 40 (140)
42 28 and 41 (1)

1 reference retrieved; 0 selected (not relevant).

EMBASE (OVID)

1980–2003, week 47 (searched 27 November 2003)

1 quality adjusted life year/ (1300)
2 quality adjusted life.ti,ab. (1099)
3 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (798)
4 disability adjusted life.ti,ab. (160)
5 daly$.ti,ab. (196)
6 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (3014)
7 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (654)
8 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (299)
9 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (21)
10 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (154)
11 (euroqol or euro qol or eq5d or dq 5d).ti,ab. (343)
12 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (878)
13 (hye or hyes).ti,ab. (24)
14 health$ year$ equivalent$.ti,ab. (21)
15 health utilit$.ab. (195)
16 (hui or hui1 or hui2 or hui3).ti,ab. (178)
17 quality of wellbeing.ti,ab. (5)
18 quality of well being.ti,ab. (396)
19 qwb.ti,ab. (77)
20 willingness to pay.ti,ab. (453)
21 standard gamble$.ti,ab. (256)
22 time trade off.ti,ab. (231)
23 tto.ti,ab. (164)
24 health status indicator$.ti,ab. (108)
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (8289)

26 letter.pt. (254187)
27 editorial.pt. (115767)
28 26 or 27 (369954)
29 25 not 28 (8127)
30 ddd.ti,ab. (2045)
31 dddr.ti,ab. (233)
32 ddi.ti,ab. (796)
33 ddir.ti,ab. (24)
34 vdd.ti,ab. (340)
35 vddr.ti,ab. (42)
36 vdi.ti,ab. (191)
37 vdir.ti,ab. (2)
38 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (1305)
39 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (298)
40 ((av or atrioventricular) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (112)
41 ((av or atrioventricular) adj (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (206)
42 artificial heart pacemaker/ (6257)
43 heart pacing/ (4800)
44 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab. (24657)
45 42 or 43 or 44 (26775)
46 30 or 32 or 35 or 36 (3037)
47 45 and 46 (932)
48 31 or 33 or 34 or 37 or 38 or 39 or 40 or 41 or 47 (2569)
49 limit 48 to human (2335)
50 limit 49 to english language (1897)
51 29 and 50 (6)
52 from 51 keep 1-6 (6)

6 references retrieved; 6 references downloaded (0 after deduplication).

PubMed
(Searched PreMEDLINE instead)

Science Citation Index
1996–2003

General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

DARE (CRD databases)
General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

NHS EED (CRD databases)
General search without filter carried out as part of economic searches, so no separate economics search needed.

HTA database (CRD databases)
General search without filter carried out as part of clinical effectiveness searches, so no separate economics search needed.

Appendix 3

Inclusion and exclusion

Total number of papers identified = 2333

Total number of hits from literature search = 2330 MEDLINE (900), EMBASE (269), Cochrane Database (295), MEDLINE, Economics (55), PreMEDLINE, NHS HEED, DARE (14), SCI (496), WOSP (44), BIOSIS (247), EMBASE, Economics (9), MEDLINE, QoL (1)

Additional studies from researchers (2) and bibliographies (1)

Update searches (May 2004) = 129 additional studies

Total number of papers identified after updated search = 2462

Studies included based on abstract = 372

Excluded: studies not containing a comparison of dual vs single chamber = 2090

Studies excluded = 324

Studies included = 46

Reasons for exclusion (more than one reason is possible)
Non-randomised studies of two comparison groups (154)
All studies without methodological requisites of usual (observational, follow-up, non-comparative, retrospective) (14)
Narrative, editorial, expert opinions, non-systematic reviews (31)
Preclinical studies (blood haemodynamics, blood pressure, blood compounds, etc.) (112)
Studies that do not report relevant outcomes, or for non-relevant underlying disease (10)
Studies with less than 48 hours' follow-up (17)
Other (non-English language, abstracts, trial details reported elsewhere) (20)

Randomised controlled comparisons (ventricular vs dual, 4 trials) (13 studies)
Cross-over randomised comparisons (ventricular vs dual, 28 trials) (28)
Randomised controlled comparisons (atrial vs dual, 1 trial) (1)
Cross-over randomised comparisons (atrial vs dual, 2 trials) (1 additional paper and 1 paper from the above comparison of dual vs ventricular)[a]
Economic analyses (4)
Systematic review (1)

[a] One study included a comparison of both dual versus atrial and dual versus ventricular; here it is only accounted for once, in the category atrial versus dual.

Appendix 4

Excluded studies

TABLE 59 *Excluded studies*

Study	Reason for exclusion (more than one is possible)
1. Aggarwal RK, Charles RG. Dual chamber pacemaker implantation has a higher early complication rate than single chamber pacing [comment]. *Pacing Clin Electrophysiol* 1995;**18**:t.	Non-comparative study
2. Aggarwal RK, Connelly DT, Ray SG, Ball J, Charles RG. Early complications of permanent pacemaker implantation: no difference between dual and single chamber systems. *British Heart Journal* 1995;**73**:571–5.	Non-randomised study of two comparison groups
3. Ahern T, Nydegger C, McCormick DJ, Maquilan M, Schuster M, Kutalek SP. Incidence and timing of activity parameter changes in activity responsive pacing systems. *Pacing Clinical Electrophysiol* 1992;**15**:762–70.	Non-randomised study of two comparison groups
4. Alpert MA, Curtis JJ, Sanfelippo JF, Flaker GC, Walls JT, Mukerji V, *et al*. Comparative survival after permanent ventricular and dual chamber pacing for patients with chronic high degree atrioventricular block with and without preexistent congestive heart failure. *J Am Coll Cardiol* 1986;**7**:925–32.	Non-randomised study of two comparison groups
5. Alpert MA, Curtis JJ, Sanfelippo JF, Flaker GC, Walls JT, Mukerji V, *et al*. Comparative survival following permanent ventricular and dual-chamber pacing for patients with chronic symptomatic sinus node dysfunction with and without congestive heart failure. *Am Heart J* 1987;**113**:958–65.	Non-randomised study of two comparison groups
6. Bahl VK, Sethi KK, Khalilullah M. Comparison of physical work capacity with physiological and ventricular pacing. *Indian Heart J* 1986;**38**:33–7.	Non-relevant outcomes
7. Barrington WW, Windle JR, Easley AA Jr, Rundlett R, Eisenger G. Clinical comparison of acute single to dual chamber pacing in chronotropically incompetent patients with left ventricular dysfunction. *Pacing Clin Electrophysiol* 1995;**18**:t–40.	Study with less than 48 hours' follow-up
8. Batey RL, Sweesy MW, Scala G, Forney RC. Comparison of low rate dual chamber pacing to activity responsive rate variable ventricular pacing. *Pacing Clin Electrophysiol* 1990;**13**:646–52.	Non-randomised study of two comparison groups
9. Benditt DG, Wilbert L, Hansen R, Alagona P, Greenawald K, Ghali MG, *et al*. Late follow-up of dual-chamber rate-adaptive pacing. *Am J Cardiol* 1993;**71**:714–19.	Non-randomised study of two comparison groups
10. Bernasconi M, Maestri R, Marzegalli M, Pinna GD, Guenzati G, Fiorista F. Time trends in the intracardiac potential recorded by pacemaker telemetry: comparison between steroid-eluting small area electrodes. *Pacing Clin Electrophysiol* 1999;**22**:1164–72.	Preclinical study
11. Boon NA, Frew AJ, Johnston JA, Cobbe SM. A comparison of symptoms and intra-arterial ambulatory blood pressure during long term dual chamber atrioventricular synchronous (DDD) and ventricular demand (VVI) pacing. *Br Heart J* 1987;**58**:34–9.	Study with less than 48 hours' follow-up
12. Brunner-La Rocca HP, Rickli H, Weilenmann D, Duru F, Candinas R. Importance of ventricular rate after mode switching during low intensity exercise as assessed by clinical symptoms and ventilatory gas exchange. *Pacing Clin Electrophysiol* 2000;**23**:32–9.	Preclinical study
13. Byrd CL, Schwartz SJ, Gonzales M, Byrd CB, Ciraldo RJ, Sivina M, *et al*. DDD pacemakers maximize hemodynamic benefits and minimize complications for most patients. *Pacing Clin Electrophysiol* 1988;**11**:t-6.	Non-comparative study
14. Cabello JB, Bordes P, Mauri M, Valle M, Quiles JA. Acute and chronic changes in atrial natriuretic factor induced by ventricular pacing: a self controlled clinical trial. *Pacing Clin Electrophysiol* 1996;**19**:815–21.	Preclinical study
15. Channon KM, Hargreaves MR, Gardner M, Ormerod OJ. Noninvasive beat-to-beat arterial blood pressure measurement during VVI and DDD pacing: relationship to symptomatic benefit from DDD pacing. *Pacing Clin Electrophysiol* 1997;**20**:t-33.	Preclinical study

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
16. Chauhan A, Grace AA, Newell SA, Stone DL, Shapiro LM, Schofield PM, *et al*. Early complications after dual chamber versus single chamber pacemaker implantation [comment]. *Pacing Clin Electrophysiol* 1994;**17**:t-5.	Non-comparative study
17. Connolly SJ, Kerr C, Gent M, Yusuf S. Dual-chamber versus ventricular pacing. Critical appraisal of current data [comment] [review]. *Circulation* 1996;**94**:578–83.	Narrative, editorial or non-systematic review
18. De Sisti A, Leclercq JF, Stiubei M, Fiorello P, Halimi F, Attuel P. P wave duration and morphology predict atrial fibrillation recurrence in patients with sinus node dysfunction and atrial-based pacemaker. *Pacing Clin Electrophysiol* 2002;**25**:1546–54.	Non-randomised study of two comparison groups
19. Donovan KD, Dobb GJ, Lee KY. Hemodynamic benefit of maintaining atrioventricular synchrony during cardiac pacing in critically ill patients. *Crit Care Med* 1991;**19**:320–6.	Preclinical study
20. Douard H, Blaquiere-Roche C, Tourtoulou V, Bordier P, Broustet JP. Effect of atrioventricular synchronous pacing on cardiac output determined by CO_2 rebreathing at constant submaximal exercise. *Am J Cardiol* 1995;**76**:189–91.	Preclinical study
21. Dreifus LS, Zinberg A, Hurzeler P, Puziak AD, Pennock R, Feldman M, *et al*. Transtelephonic monitoring of 25,919 implanted pacemakers. *Pacing Clin Electrophysiol* 1986;**9**:371–8.	Non-comparative study
22. Ebagosti A, Gueunoun M, Saadjian A, Dolla E, Gabriel M, Levy S, *et al*. Long-term follow-up of patients treated with VVI pacing and sequential pacing with special reference to VA retrograde conduction. *Pacing Clin Electrophysiol* 1988;**11**:t-34.	Non-randomised study of two comparison groups
23. Ellenbogen KA, Stambler BS, Orav EJ, Sgarbossa EB, Tullo NG, Love CA, *et al*. Clinical characteristics of patients intolerant to VVIR pacing. *Am J Cardiol* 2000; **86**:59–63.	Non-relevant outcomes
24. Erdogan O, Altun A, Ozbay G. Acute short-term effect of VVI pacing mode on P wave dispersion in patients with dual chamber pacemakers. *Int J Cardiol* 2002;**83**:93–6.	Non-randomised study of two comparison groups and preclinical outcomes
25. Ertas F, Gulec S, Dincer I, Erol C, Tutar E, Guldal M, *et al*. Left atrial appendage function in patients with different pacing modes. *Int J Cardiol* 2000;**73**:135–41.	Non-randomised study of two comparison groups and preclinical outcomes
26. Esperer HD, Singer H, Riede FT, Blum U, Mahmoud FO, Weniger J. Permanent epicardial and transvenous single- and dual-chamber cardiac pacing in children. *Thorac Cardiovasc Surg* 1993;**41**:21-7.	Non-randomised study of two comparison groups
27. Fananapazir L, Bennett DH, Monks P. Atrial synchronized ventricular pacing: contribution of the chronotropic response to improved exercise performance. *Pacing Clin Electrophysiol* 1983;**6**:t-8.	Non-randomised study of two comparison groups
28. Fananapazir L, Srinivas V, Bennett DH. Comparison of resting hemodynamic indices and exercise performance during atrial synchronized and asynchronous ventricular pacing. *Pacing Clin Electrophysiol* 1983;**6**:t-9.	Preclinical study
29. Folino AF, Buja G, Corso LD, Nava A. Incidence of atrial fibrillation in patients with different mode of pacing. Long-term follow-up. *Pacing Clin Electrophysiol* 1998;**21**:t-3.	Non-randomised study of two comparison groups
30. 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 Clin Electrophysiol* 1988;**11**:t-5.	Non-randomised study of two comparison groups
31. Frielingsdorf J, Dur P, Gerber AE, Vuilliomenet A, Bertel O. Physical work capacity with rate responsive ventricular pacing (VVIR) versus dual chamber pacing (DDD) in patients with normal and diminished left ventricular function. *Int J Cardiol* 1995; **49**:239–48.	Non-randomised study of two comparison groups
32. Fukuoka S, Nakagawa S, Fukunaga T, Yamada H. Effect of long-term atrial-demand ventricular pacing on cardiac sympathetic activity. *Nucl Med Commun* 2000;**21**:291–7.	Non-randomised study of two comparison groups and preclinical outcomes
33. Gallik DM, Guidry GW, Mahmarian JJ, Verani MS, Spencer WH III. Comparison of ventricular function in atrial rate adaptive versus dual chamber rate adaptive pacing during exercise. *Pacing Clin Electrophysiol* 1994;**17**:179–85.	Study with less than 48 hours' follow-up

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
34. Ganz DA, Lamas GA, Orav EJ, Goldman L, Gutierrez PR, Mangione CM. Age-related differences in management of heart disease: a study of cardiac medication use in an older cohort. Pacemaker Selection in the Elderly (PASE) Investigators [comment]. *J Am Geriatr Soc* 1999;**47**:145–50.	Preclinical study
35. Garcia-Bolao I, Alegria E. Implantation of 500 consecutive cardiac pacemakers in the electrophysiology laboratory. *Acta Cardiol* 1999;**54**:339–43.	Non-comparative study
36. Gessner M, Blazek G, Kainz W, Gruska M, Gaul G. Application of pulsed-Doppler tissue imaging in patients with dual chamber pacing: the importance of conduction time and AV delay on regional left ventricular wall dynamics. *Pacing Clin Electrophysiol* 1998;**21**:t-9.	Non-randomised study of two comparison groups
37. Gillette PC, Shannon C, Garson A Jr, Porter CJ, Ott D, Cooley DA, *et al*. Pacemaker treatment of sick sinus syndrome in children. *J Am Coll Cardiol* 1983;**1**:1325–9.	Non-randomised study of two comparison groups
38. Gregoratos G. Permanent pacemakers in older persons [review]. *J Am Geriatr Soc* 1999;**47**:1125–35.	Narrative, editorial or non-systematic review
39. Grimm W, Langenfeld H, Maisch B, Kochsiek K. Symptoms, cardiovascular risk profile and spontaneous ECG in paced patients: a five-year follow-up study. *Pacing Clin Electrophysiol* 1990;**13**:t–90.	Non-randomised study of two comparison groups
40. Hildick-Smith DJ, Walsh JT. Single-chamber versus dual-chamber pacemakers [comment]. *N Engl J Med* 1998;**339**:630–2.	Narrative, editorial or non-systematic review
41. Horenstein MS, Karpawich PP, Tantengco MV. Single versus dual chamber pacing in the young: noninvasive comparative evaluation of cardiac function. *Pacing Clin Electrophysiol* 2003;**26**:1208–11.	Non-randomised study of two comparison groups
42. Ijiri H, Komori S, Kohno I, Sano S, Yin D, Takusagawa M, *et al*. Improvement of exercise tolerance by single lead VDD pacemaker: evaluation using cardiopulmonary exercise test. *Pacing Clin Electrophysiol* 2000;**23**:1336–42.	Study with less than 48 hours' follow-up
43. Iliev II, Yamachika S, Muta K, Hayano M, Ishimatsu T, Nakao K, *et al*. Preserving normal ventricular activation versus atrioventricular delay optimization during pacing: the role of intrinsic atrioventricular conduction and pacing rate. *Pacing Clin Electrophysiol* 2000;**23**:74–83.	Preclinical study
44. Irwin M, Carbol B, Senaratne M, Gulamhusein S. Long-term survival of chosen atrial-based pacing modalities. *Pacing Clin Electrophysiol* 1996;**19**:t-8.	Non-randomised study of two comparison groups
45. Jahangir A, Shen WK, Neubauer SA, Ballard DJ, Hammill SC, Hodge DO, *et al*. Relation between mode of pacing and long-term survival in the very elderly. *J Am Coll Cardiol* 1999;**33**:1208–16.	Non-randomised study of two comparison groups
46. Jordaens L, Robbens E, van Wassenhove E, Clement DL. Incidence of arrhythmias after atrial or dual-chamber pacemaker implantation. *Eur Heart J* 1989;**10**:102–7.	Non-randomised study of two comparison groups
47. Jutzy RV, Florio J, Isaeff DM, Marsa RJ, Bansal RC, Jutzy KR, *et al*. Comparative evaluation of rate modulated dual chamber and VVIR pacing. *Pacing Clin Electrophysiol* 1990;**13**:t-46.	Non-randomised study of two comparison groups
48. Jutzy RV, Feenstra L, Pai R, Florio J, Bansal R, Aybar R, *et al*. Comparison of intrinsic versus paced ventricular function. *Pacing Clin Electrophysiol* 1992;**15**:t-22.	Study with less than 48 hours' follow-up
49. Jutzy RV, Houston-Feenstra L, Levine PA. Comparison of cardiac pacing modes in patients with chronic obstructive pulmonary disease. *Chest* 1994;**105**:83–6.	Non-relevant outcomes
50. Kamalvand K, Tan K, Kotsakis A, Bucknall C, Sulke N. Is mode switching beneficial? A randomized study in patients with paroxysmal atrial tachyarrhythmias. *J Am Coll Cardiol* 1997;**30**:496–504.	Non-randomised study of two comparison groups
51. Kano K, Okada M, Tanahashi Y, Hayashi H, Yokota M, Saito H, *et al*. Left ventricular performance at rest and during exercise in patients with dual-chamber pacemakers. *Intern Med* 1992;**31**:1–5.	Non-randomised study of two comparison groups
52. Karpawich PP, Perry BL, Farooki ZQ, Clapp SK, Jackson WL, Cicalese CA, *et al*. Pacing in children and young adults with nonsurgical atrioventricular block: comparison of single-rate ventricular and dual-chamber modes. *Am Heart J* 1987;**113**:t-21.	Non-randomised study of two comparison groups

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
53. Kolettis TM, Kremastinos DT, Kyriakides ZS, Tsirakos A, Toutouzas PK. Effects of atrial, ventricular, and atrioventricular sequential pacing on coronary flow reserve. *Pacing Clin Electrophysiol* 1995;**18**:t-35.	Non-randomised study of two comparison groups and preclinical outcomes
54. Kolettis TM, Kyriakides ZS, Kremastinos DT. Coronary blood flow velocity during apical versus septal pacing. *Int J Cardiol* 1998;**66**:203–5.	Non-randomised study of two comparison groups
55. Kristensson BE, Karlsson O, Ryden L. Holter-monitored heart rhythm during atrioventricular synchronous and fixed-rate ventricular pacing. *Pacing Clin Electrophysiol* 1986;**9**:511–18.	Non-relevant outcomes
56. Krupienicz A, Karczmarewicz S, Marciniak W, Gnilka A, Kulakowski P, Adamus J. Passive-fixation J-shaped versus straight leads in atrial position: comparison of efficacy and safety. *Pacing Clin Electrophysiol* 2000;**23**:2068–72.	Preclinical study
57. Kruse I, Arnman K, Conradson TB, Ryden L. A comparison of the acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. *Circulation* 1982;**65**:846–55.	Non-randomised study of two comparison groups
58. Kubica J, Stolarczyk L, Krzyminska E, Krasowski R , Raczak G, Lubinski A, *et al*. Left atrial size and wall motion in patients with permanent ventricular and atrial pacing. *Pacing Clin Electrophysiol* 1990;**13**:t-41.	Non-randomised study of two comparison groups and preclinical outcomes
59. Kyriakides ZS, Antoniadis A, Iliodromitis E, Michelakakis N, Kremastinos DT. Short-term effects of right atrial, right ventricular apical, and atrioventricular sequential pacing on myocardial oxygen consumption and cardiac efficiency in patients with coronary artery disease [published erratum appears in *British Heart Journal* 1994; **72**:404]. *British Heart Journal* 1994;**71**:536–40.	Preclinical study
60. Lamas GA, Pashos CL, Normand SL, McNeil B. Permanent pacemaker selection and subsequent survival in elderly Medicare pacemaker recipients. *Circulation* 1995; **91**:1063–9.	Non-comparative study
61. Lascault G, Frank R, Iwa T, Girodo S, Fontaine G, Grosgogeat Y. Comparison of DDD and 'VVI-R like' pacing during moderate exercise: echo-Doppler study. *Eur Heart J* 1992;**13**:914–17.	Non-randomised study of two comparison groups
62. Lau CP, Wong CK, Leung WH, Liu WX. Superior cardiac hemodynamics of atrioventricular synchrony over rate responsive pacing at submaximal exercise: observations in activity sensing DDDR pacemakers. *Pacing Clin Electrophysiol* 1990; **13**:t-7.	Preclinical study
63. Lau CP, Tse HF, Cheng G. Effects of atrioventricular asynchrony on platelet activation: implication of thromboembolism in paced patients [comment]. *Heart* 1997;**78**:358–63.	Preclinical study
64. Leclercq C, Gras D, Le Helloco A, Nicol L, Mabo P, Daubert C. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. *Am Heart J* 1995;**129**:1133–41.	Preclinical study
65. Lee TM, Su SF , Lin YJ, Chen WJ, Chen MF, Liau CS, *et al*. Role of transesophageal echocardiography in the evaluation of patients with clinical pacemaker syndrome. *Am Heart J* 1998;**135**:634–40.	Non-randomised study of two comparison groups and preclinical outcomes
66. Leman RB, Kratz JM. Radionuclide evaluation of dual chamber pacing: comparison between variable AV intervals and ventricular pacing. *Pacing Clin Electrophysiol* 1985; **8**:t-14.	Non-randomised study of two comparison groups and preclinical outcomes
67. Lemke B, Dryander SV, Jager D, Machraoui A, MacCarter D, BarMayer J. Aerobic capacity in rate modulated pacing. *Pacing Clin Electrophysiol* 1992;**15**:t-8.	Preclinical study
68. Linde-Edelstam C, Gullberg B, Norlander R, Pehrsson SK, Rosenqvist M, Ryden L. Longevity in patients with high degree atrioventricular block paced in the atrial synchronous or the fixed rate ventricular inhibited mode published [erratum appears in *Pacing Clin Electrophysiol* 1992;**15**:xii]. *Pacing Clin Electrophysiol* 1992;**15**:304–13.	Non-relevant outcomes
69. Lipkin DP, Buller N, Frenneaux M, Ludgate L, Lowe T, Webb SC, *et al*. Randomised crossover trial of rate responsive Activitrax and conventional fixed rate ventricular pacing. *British Heart Journal* 1987;**58**:613–16.	Non-relevant outcomes

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
70. Lukl J, Heinc P. The effect of heart rate on the working capacity of patients with complete heart block and physiological pacemaker. *Cor et Vasa* 1991;**33**:506–13.	Preclinical study
71. 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 J* 1992;**44**:231–4.	Non-randomised study of two comparison groups
72. Markewitz A, Hemmer W. What's the price to be paid for rate response: AV sequential versus ventricular pacing? *Pacing Clin Electrophysiol* 1991;**14**:t-6.	Non-randomised study of two comparison groups
73. Mattioli AV, Castellani ET, Fusco A, Paolillo C, Mattioli G. Stroke in paced patients with sick sinus syndrome: relevance of atrial mechanical function, pacing mode and clinical characteristics. *Cardiology* 1997;**88**:264–70.	Non-randomised study of two comparison groups
74. Mattioli AV, Vivoli D, Mattioli G. Influence of pacing modalities on the incidence of atrial fibrillation in patients without prior atrial fibrillation. A prospective study. *Eur Heart J* 1998;**19**:282–6.	Non-randomised study of two comparison groups
75. Mattioli AV, Castellani ET, Vivoli D, Sgura FA, Mattioli G. Prevalence of atrial fibrillation and stroke in paced patients without prior atrial fibrillation: a prospective study. *Clin Cardiol* 1998;**21**:117–22.	Non-comparative study
76. Mattioli AV, Tarabini CE, Mattioli G. Stroke in paced patients with sick sinus syndrome: influence of left atrial function and size. *Cardiology* 1999;**91**:150–5.	Non-randomised study of two comparison groups
77. McComb JM, Gribbin GM. Effect of pacing mode on morbidity and mortality: update of clinical pacing trials [review]. *Am J Cardiol* 1999;**83**:211–13D.	Narrative, editorial or non-systematic review
78. McMeekin JD, Lautner D, Hanson S, Gulamhusein SS. Importance of heart rate response during exercise in patients using atrioventricular synchronous and ventricular pacemakers. *Pacing Clin Electrophysiol* 1990;**13**:59–68.	Non-randomised study of two comparison groups
79. Michalik RE, Williams WH, Zorn-Chelton S, Hatcher CR Jr. Experience with a new epimyocardial pacing lead in children. *Pacing Clin Electrophysiol* 1984;**7**:831–8.	Non-randomised study of two comparison groups
80. Mohan JC, Sethi KK, Arora R, Khalilullah M. Comparative evaluation of left ventricular function in sick sinus syndrome on different long-term pacing modes. *Indian Heart J* 1994;**46**:303–6.	Non-randomised study of two comparison groups
81. Moller M, Arnsbo P, Asklund M, Christensen PD, Gadsboll N, Svendsen JH, *et al*. Quality assessment of pacemaker implantations in Denmark. *Europace* 2002;**4**:107–12.	Non-comparative study
82. Montanez A, Hennekens CH, Zebede J, Lamas GA. Pacemaker mode selection: the evidence from randomized trials [review]. *Pacing Clin Electrophysiol* 2003; **26**:1270–82.	Narrative, editorial or non-systematic review
83. Mueller X, Sadeghi H, Kappenberger L. Complications after single versus dual chamber pacemaker implantation. *Pacing Clin Electrophysiol* 1990;**13**:711–14.	Non-randomised study of two comparison groups
84. Nakata A, Hirota S, Tsuji H, Takazakura E. I-123 metaiodobenzylguanidine cardiac scintigraphy in patients with an implanted permanent pacemaker. *Jpn Heart J* 1995; **36**:583–91.	Non-randomised study of two comparison groups and preclinical outcomes
85. Nielsen JC, Bottcher M, Nielsen TT, Pedersen AK, Andersen HR. 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. *J Am Coll Cardiol* 2000;**35**:1453–61.	Preclinical study
86. Nielsen JC. Mortality and incidence of atrial fibrillation in paced patients [review]. *J Cardiovasc Electrophysiol* 2002;**13**:Suppl 22.	Narrative, editorial or non-systematic review
87. Nishimura RA, Gersh BJ, Vlietstra RE, Osborn MJ, Ilstrup DM, Holmes DR Jr. Hemodynamic and symptomatic consequences of ventricular pacing. *Pacing Clin Electrophysiol* 1982;**5**:903–10.	Non-randomised study of two comparison groups
88. Nitsch J, Seiderer M, Bull U, Luderitz B. Evaluation of left ventricular performance by radionuclide ventriculography in patients with atrioventricular versus ventricular demand pacemakers. *Am Heart J* 1984;**107**:t-11.	Non-randomised study of two comparison groups

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
89. Nowak B, Voigtlander T, Himmrich E, Liebrich A, Poschmann G, Epperlein S, *et al*. Cardiac output in single-lead VDD pacing versus rate-matched VVIR pacing. *Am J Cardiol* 1995;**75**:904–7.	Study with less than 48 hours' follow-up
90. Ovsyshcher I, Gross JN, Blumberg S, Andrews C, Ritacco R, Furman S. Variability of cardiac output as determined by impedance cardiography in pacemaker patients. *Am J Cardiol* 1993;**72**:183–7.	Non-randomised study of two comparison groups
91. Ovsyshcher I, Zimlichman R, Katz A, Bondy C, Furman S. Measurements of cardiac output by impedance cardiography in pacemaker patients at rest: effects of various atrioventricular delays. *J Am Coll Cardiol* 1993;**21**:761–7.	Non-randomised study of two comparison groups and preclinical outcomes
92. Pace L, Betocchi S, Franculli F, Piscione F, Ciarmiello A, Sullo P, *et al*. Evaluation of left ventricular asynchrony by radionuclide angiography: comparison of phase and sector analysis. *J Nucl Med* 1994;**35**:1766–70.	Non-randomised study of two comparison groups and preclinical outcomes
93. Paridon SM, Karpawich PP, Pinsky WW. The effects of rate responsive pacing on exercise performance in the postoperative univentricular heart. *Pacing Clin Electrophysiol* 1993;**16**:1256–62.	Study with less than 48 hours' follow-up
94. Payne G, Spinelli J, Garratt CJ, Skehan JD. The optimal pacing rate: an unpredictable parameter. *Pacing Clin Electrophysiol* 1997;**20**:t-73.	Preclinical study
95. Payne GE, Williams H, Skehan JD. An approach in the assessment of pacing hemodynamics: a comparison of VVI and DDD. *Pacing Clin Electrophysiol* 1995; **18**:1861–8.	Non-randomised study of two comparison groups
96. Pehrsson SK, Hjemdahl P, Nordlander R, Astrom H. A comparison of sympathoadrenal activity and cardiac performance at rest and during exercise in patients with ventricular demand or atrial synchronous pacing. *British Heart Journal* 1988;**60**:212–20.	Preclinical study
97. Proctor EE, Leman RB, Mann DL, Kaiser J, Kratz J, Gillette P. Single- versus dual-chamber sensor-driven pacing: comparison of cardiac outputs. *Am Heart J* 1991; **122**:t-32.	Non-randomised study of two comparison groups and preclinical outcomes
98. Providencia LA, Paisana FM, Cristovao JL, Silva AM, Vinagre R, Faria H, *et al*. 'Physiological pacing': comparison of DDD and VVI programming by three different non-invasive methods. *Rev Port Cardiol* 1988;**7**:299–303.	Non-randomised study of two comparison groups
99. Raj SR, Brennan FJ, Abdollah H. Is there a sex bias in the selection of permanent pacemaker implantations? *Can J Cardiol* 1996;**12**:375–8.	Study with less than 48 hours' follow-up
100. Raza ST, Lajos TZ, Bhayana JN, Lee AB Jr, Lewin AN, Gehring B, *et al*. Improved cardiovascular hemodynamics with atrioventricular sequential pacing compared with ventricular demand pacing. *Ann Thorac Surg* 1984;**38**:260–4.	Study with less than 48 hours' follow-up
101. Romero LR, Haffajee CI, Levin W, Doherty PW, Berkovits BV, Alpert JS. Non-invasive evaluation of ventricular function and volumes during atrioventricular sequential and ventricular pacing. *Pacing Clin Electrophysiol* 1984;**7**:10–17.	Non-randomised study of two comparison groups and preclinical outcomes
102. Rosenqvist M, Isaaz K, Botvinick EH, Dae MW, Cockrell J, Abbott JA, *et al*. Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. *Am J Cardiol* 1991;**67**:148–56.	Non-randomised study of two comparison groups
103. Rosenqvist M, Nordlander R. Survival in patients with permanent pacemakers [Review]. *Cardiol Clin* 1992;**10**:691–703.	Non-randomised study of two comparison groups
104. Santini M, Alexidou G, Ansalone G, Cacciatore G, Cini R, Turitto G. Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. *Am J Cardiol* 1990;**65**:729–35.	Non-comparative study
105. Sasaki Y, Shimotori M, Akahane K, Yonekura H, Hirano K, Endoh R, *et al*. Long-term follow-up of patients with sick sinus syndrome: a comparison of clinical aspects among unpaced, ventricular inhibited paced, and physiologically paced groups. *Pacing Clin Electrophysiol* 1988;**11**:t-83.	Non-randomised study of two comparison groups
106. Sasaki Y, Furihata A, Suyama K, Furihata Y, Koike S, Kobayashi T, *et al*. Comparison between ventricular inhibited pacing and physiologic pacing in sick sinus syndrome. *Am J Cardiol* 1991;**67**:771–4.	Non-randomised study of two comparison groups

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
107. Sassone B, De Simone N, Parlangeli G, Tortorici R, Biancoli S, Di Pasquale G. Pacemaker-induced mitral regurgitation: prominent role of abnormal ventricular activation sequence versus altered atrioventricular synchrony. *Ital Heart J* 2001; **2**:441–8.	Non-randomised study of two comparison groups and preclinical outcomes
108. Sedney MI, Weijers E, Van Der Wall EE, Adipranoto JD, Camps J, Blokland JA, *et al*. Short-term and long-term changes of left ventricular volumes during rate-adaptive and single-rate pacing. *Pacing Clin Electrophysiol* 1989;**12**:1863–8.	Non-randomised study of two comparison groups and preclinical outcomes
109. Sethi KK, Bajaj V, Mohan JC, Arora R, Khalilullah M. Comparison of atrial and VVI pacing modes in symptomatic sinus node dysfunction without associated tachyarrhythmias. *Indian Heart J* 1990;**42**:143–7.	Non-randomised study of two comparison groups
110. Sgarbossa EB, Pinski SL, Jaeger FJ, Trohman RG, Maloney JD. Incidence and predictors of syncope in paced patients with sick sinus syndrome. *Pacing Clin Electrophysiol* 1992;**15**: t-60.	Non-randomised study of two comparison groups
111. Sgarbossa EB, Pinski SL, Castle LW, Trohman RG, Maloney JD. Incidence and predictors of loss of pacing in the atrium in patients with sick sinus syndrome. *Pacing Clin Electrophysiol* 1992;**15**:t-4.	Non-randomised study of two comparison groups
112. Sgarbossa EB, Pinski SL, Maloney JD. The role of pacing modality in determining long-term survival in the sick sinus syndrome. *Ann Intern Med* 1993;**119**:359–65.	Non-randomised study of two comparison groups
113. Simantirakis EN, Parthenakis FI, Chrysostomakis SI, Zuridakis EG, Igoumenidis NE, Vardas PE. Left atrial appendage function during DDD and VVI pacing. *Heart* 1997; **77**:428–31.	Non-randomised study of two comparison groups
114. Soussou AI, Helmy MG, Guindy RR. Preimplantation echo Doppler evaluation of VVI versus DDD pacing. *Echocardiography* 1995;**12**:335–49.	Study with less than 48 hours' follow-up
115. Sparks PB, Mond HG, Vohra JK, Yapanis AG, Grigg LE, Kalman JM. Mechanical remodeling of the left atrium after loss of atrioventricular synchrony. A long-term study in humans. *Circulation* 1999;**100**:1714–21.	Preclinical study
116. Sparks PB, Mond HG, Vohra JK, Jayaprakash S, Kalman JM. Electrical remodeling of the atria following loss of atrioventricular synchrony: a long-term study in humans. *Circulation* 1999;**100**:1894–900.	Non-randomised study of two comparison groups and preclinical outcomes
117. Stangl K, Weil J, Seitz K, Laule M, Gerzer R. Influence of AV synchrony on the plasma levels of atrial natriuretic peptide (ANP) in patients with total AV block. *Pacing Clin Electrophysiol* 1988;**11**:1176–81.	Non-randomised study of two comparison groups and preclinical outcomes
118. Stierle U, Kruger D, Mitusch R, Potratz J, Taubert G, Sheikhzadeh A. Adverse pacemaker hemodynamics evaluated by pulmonary venous flow monitoring. *Pacing Clin Electrophysiol* 1995;**18**:2028–34.	Non-randomised study of two comparison groups
119. Stojnic BB, Stojanov PL, Angelkov L, Pavlovic SU, Radjen GS, Velimirovic DB. Evaluation of asynchronous left ventricular relaxation by Doppler echocardiography during ventricular pacing with AV synchrony (VDD): comparison with atrial pacing (AAI). *Pacing Clin Electrophysiol* 1996;**19**:940–4.	Non-randomised study of two comparison groups and preclinical outcomes
120. Stone JM, Bhakta RD, Lutgen J. Dual chamber sequential pacing management of sinus node dysfunction: advantages over single-chamber pacing. *Am Heart J* 1982; **104**:1319–27.	Non-randomised study of two comparison groups
121. Sulke AN, Pipilis A, Henderson RA, Bucknall CA, Sowton E. Comparison of the normal sinus node with seven types of rate responsive pacemaker during everyday activity. *British Heart Journal* 1990;**64**:25–31.	Non-randomised study of two comparison groups
122. Sulke N, Dritsas A, Chambers J, Sowton E. Is accurate rate response programming necessary? *Pacing Clin Electrophysiol* 1990;**13**:1031–44.	Non-randomised study of two comparison groups
123. Sulke N, Chambers J, Sowton E. Variability of left atrial bloodflow predicts intolerance of ventricular demand pacing and may cause pacemaker syndrome. *Pacing Clin Electrophysiol* 1994;**17**:1149–59.	Non-randomised study of two comparison groups
124. Sutton R, Morley C, Chan SL, Perrins J. Physiological benefits of atrial synchrony in paced patients. *Pacing Clin Electrophysiol* 1983;**6**:t-8.	Non-randomised study of two comparison groups

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
125. Tang CY, Kerr CR, Connolly SJ. Clinical trials of pacing mode selection [review]. *Cardiol Clin* 2000;**18**:1–23.	Narrative, editorial or non-systematic review
126. Tani M, Fujiki A, Asanoi H, Yoshida S, Tsuji H, Mizumaki K, *et al*. Effects of chronotropic responsive cardiac pacing on ventilatory response to exercise in patients with complete AV block. *Pacing Clin Electrophysiol* 1992;**15**:t-91.	Non-randomised study of two comparison groups
127. Taylor JA, Morillo CA, Eckberg DL, Ellenbogen KA. Higher sympathetic nerve activity during ventricular (VVI) than during dual-chamber (DDD) pacing. *J Am Coll Cardiol* 1996;**28**:1753–8.	Non-randomised study of two comparison groups and preclinical outcomes
128. Thackray SD, Witte KK, Nikitin NP, Clark AL, Kaye GC, Cleland JG. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. *Eur Heart J* 2003;**24**:1143–52.	Non-comparative study
129. Theodorakis GN, Kremastinos DT, Markianos M, Livanis E, Karavolias G, Toutouzas PK. Total sympathetic activity and atrial natriuretic factor levels in VVI and DDD pacing with different atrioventricular delays during daily activity and exercise. *Eur Heart J* 1992;**13**:1477–81.	Preclinical study
130. Tung RT, Shen WK, Hayes DL, Hammill SC, Bailey KR, Gersh BJ. Long-term survival after permanent pacemaker implantation for sick sinus syndrome. *Am J Cardiol* 1994; **74**:1016–20.	Non-randomised study of two comparison groups
131. Vardas PE, Travill CM, Williams TD, Ingram AM, Lightman SL, Sutton R. Effect of dual chamber pacing on raised plasma atrial natriuretic peptide concentrations in complete atrioventricular block. *BMJ* 1988;**296**:94.	Non-randomised study of two comparison groups and preclinical outcomes
132. Vardas PE, Simantirakis EN, Parthenakis FI, Chrysostomakis SI, Skalidis EI, Zuridakis EG. AAIR versus DDDR pacing in patients with impaired sinus node chronotropy: an echocardiographic and cardiopulmonary study. *Pacing Clin Electrophysiol* 1997;**20**:1762–8.	Preclinical study
133. Vassolo M, Lamas GA. Dual-chamber vs. ventricular pacing in the elderly: quality of life and clinical outcomes [comment]. *Eur Heart J* 1999;**20**:1607–8.	Narrative, editorial or non-systematic review
134. Videen JS, Huang SK, Bazgan ID, Mechling E, Patton DD. Hemodynamic comparison of ventricular pacing, atrioventricular sequential pacing, and atrial synchronous ventricular pacing using radionuclide ventriculography. *Am J Cardiol* 1986;**57**:1305–8.	Study with less than 48 hours' follow-up
135. Vrouchos G, Kiupeloglou G, Laguvardos P, Kondopodis M, Fragiadulakis G. Prediction of permanent atrial sensing by preoperative esophageal atrial wave evaluation. *Pacing Clin Electrophysiol* 1992;**15**:t-61.	Preclinical study
136. Walsh CA, McAlister HF, Andrews CA, Steeg CN, Eisenberg R, Furman S. Pacemaker implantation in children: a 21-year experience. *Pacing Clin Electrophysiol* 1988;**11**:t-4.	Non-randomised study of two comparison groups
137. Whiting RB, Madigan NP, Heinemann FM, Curtis JJ, Reid J. Atrioventricular sequential pacing: comparison with ventricular pacing using systolic time intervals. *Pacing Clin Electrophysiol* 1983;**6**:t-6.	Non-randomised study of two comparison groups
138. Wish M, Fletcher RD, Gottdiener JS, Cohen AI. Importance of left atrial timing in the programming of dual-chamber pacemakers. *Am J Cardiol* 1987;**60**:566–71.	Non-randomised study of two comparison groups
139. Wong GC, Hadjis T. Single chamber ventricular compared with dual chamber pacing: a review [review]. *Can J Cardiol* 2002;**18**:301–7.	Other
140. Wu X, Seino Y, Ogura H, Fukuma N, Katoh T, Takano T. Plasma natriuretic peptide levels and daily physical activity in patients with pacemaker implantation. *Jpn Heart J* 2001;**42**:471–82.	Non-randomised study of two comparison groups and preclinical outcomes
141. Yee R, Benditt DG, Kostuk WJ, Ko PT, Purves P, Klein GJ. Comparative functional effects of chronic ventricular demand and atrial synchronous ventricular inhibited pacing. *Pacing Clin Electrophysiol* 1984;**7**:23–8.	Non-randomised study of two comparison groups
142. Wiegand UKH, Bode F, Bonnemeier H, Eberhard F, Schlei M, Peters W. Long-term complication rates in ventricular, single lead VDD, and dual chamber pacing. *Pacing Clin Electrophysiol* 2003;**26**:1961–9.	Non-randomised study of two comparison groups

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
143. Karagoz T, Celiker A. The influence of mental and physical stress on the autocapture function in children. *J Interv Card Electrophysiol* 2003;**9**:43–8.	Preclinical study
144. Lelakowski J, Majewski J, Szczepkowski J, Pasowicz M. The role of intrinsic atrioventricular conduction in paced patients with coronary artery disease and sick sinus syndrome. *Folia Cardiologica* 2002;**9**:253–8.	Non-randomised study of two comparison groups
145. Wiegand UKH. VVI versus physiologic pacing. New data on an old topic. *Herzschrittmachertherapie und Elektrophysiologie* 2000;**11**:1143–8.	Narrative, editorial or non-systematic review
146. Lukl J, Doupal V. Significance of atrioventricular synchrony at rest for quality-of-life in DDD patients with complete heart block. *European Journal of Cardiac Pacing and Electrophysiology* 1997.	Preclinical study
147. Rickli H, Rocca HPB, MacCarter DJ, Duru F, Candinas R. Importance of AV synchronous pacing during low intensity exercise evaluated by oxygen kinetics. *Pacing Clin Electrophysiol* 2000;**23**:174–9.	Preclinical study
148. Saccomanno G, Fraticelli A, Marini M, Spazzafumo L, Paciaroni E. Permanent ventricular and dual chamber cardiac stimulation: role of pacing mode in relation to chronic atrial fibrillation risk and stroke development. *Archives of Gerontology and Geriatrics* 1999;**29**:61–74.	Non-randomised study of two comparison groups
149. Horie H, Tsutamoto T, Ishimoto N, Minai K, Yokohama H, Nozawa M, *et al*. Plasma brain natriuretic peptide as a biochemical marker for atrioventricular sequence in patients with pacemakers. *Pacing Clin Electrophysiol* 1999;**22**:282–90.	Preclinical study
150. Yoshida H, Shirotani M, Mochizuki M, Sakata K. Assessment of myocardial fatty acid metabolism in atrioventricular synchronous pacing: analysis of iodine 123-labeled beta-methyl iodophenyl pentadecanoic acid SPECT. *J Nucl Cardiol* 1999;**6**:33–40.	Non-randomised study of two comparison groups and preclinical outcomes
151. Mayosi BM, Millar RS. The 1995 survey of cardiac pacing in South Africa. *Cardiovasc J S Afr* 1998;**88**:C207–11.	Non-randomised study of two comparison groups
152. Azam N, Chapman M, Roberts DH. 'Subclinical' pacemaker syndrome – further evidence using ambulatory blood pressure measurement to compare VVI and DDD pacing in asymptomatic patients. *European Journal of Cardiac Pacing and Electrophysiology* 1998;**8**:8–10.	Non-randomised study of two comparison groups
153. Crespo F, Lamas GA. Selecting the right pacemaker type of elderly patients. *Cardiol Rev* 1996;**13**:17–20.	Narrative, editorial or non-systematic review
154. Theodorakis GN, Panou F, Markianos M, Fragakis N, Livanis EG, Kremastinos DT. Left atrial function and atrial natriuretic factor/cyclic guanosine monophosphate changes in DDD and VVI pacing modes. *Am J Cardiol* 1997;**79**:366–70.	Preclinical study
155. Gillis AM, MacQuarrie DS, Wilson SL. The impact of pulse generator longevity on the long-term costs of cardiac pacing. *Pacing Clin Electrophysiol* 1996;**19**:1459–68.	Non-randomised study of two comparison groups
156. Bernstein AD,.Parsonnet V. Survey of cardiac pacing and defibrillation in the United States in 1993. *Am J Cardiol* 1996;**78**:187–96.	Non-randomised study of two comparison groups
157. Aggarwal RK, Connelly DT, Ray SG, Charles RG. Acute and early complications of permanent pacing: a prospective audit of 926 consecutive patients from a UK center. *International Journal of Angiology* 1996;**5**:78–81.	Non-randomised study of two comparison groups
158. Sgarbossa EB, Pinski SL, Maloney JD. Long-term survival in sick sinus syndrome: is one pacing mode better than another? *Cardiology Board Review* 1994;**11**:37–41.	Non-randomised study of two comparison groups
159. Steinbach KK, Nurnberg M. Sick sinus syndrome: incidence of embolic events and usefulness of different modes of stimulation. *Revista Latina de Cardiologia – Euroamericana* 1996;**17**:16–19.	Narrative, editorial or non-systematic review
160. Sweesy MW, Forney RC, Erickson SL, Batey RL. Pacemaker follow-up: complication frequency and time of detection. *European Journal of Cardiac Pacing and Electrophysiology* 1995;**5**:210–14.	Non-comparative study
161. Lo BF, Bianconi L, Altamura G, Mennuni M, Castro A, Magliocca M, *et al*. Atrial natriuretic factor levels during DDD and VVI pacing. *New Trends in Arrhythmias* 1993; **9**:651–3.	Preclinical study

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
162. Sgarbossa EB, Pinski SL, Trohman RG, Castle LW, Maloney JD. Single-chamber ventricular pacing is not associated with worsening heart failure in sick sinus syndrome. *Am J Cardiol* 1994;**73**:693–7.	Non-randomised study of two comparison groups
163. Bush DE, Finucane TE. Permanent cardiac pacemakers in the elderly. *J Am Geriatr Soc* 1994;**42**:326–34.	Narrative, editorial or non-systematic review
164. Chida K, Ohkawa SI, Imai T, Suzuki Y, Ishikawa K, Watanabe C, *et al*. Long-term follow-up study after permanent pacemaker implantation in patients aged 60 years or over with sick sinus syndrome. *Japanese Journal of Geriatrics* 1993;**30**:869–78.	Non-randomised study of two comparison groups
165. Lamaison D, Page E, Aupetit JF, Defaye P, Rozand JY, Mouton E, *et al*. A comparison between single atrial and dual chamber rate adaptive (AAIR and DDDR) and non adaptive AAI and DDD cardiac pacing using cardiopulmonary exercise testing in patients with atrial chronotropic incompetence. *European Journal of Cardiac Pacing and Electrophysiology* 1993;**3**:197–204.	Study with less than 48 hours' follow-up
166. Dretzke J, Toff WD, Lip GY, Raftery J, Fry Smith A, Taylor R. Dual versus single chamber ventricular pacemakers in sick sinus syndrome and atrioventricular block. In *The Cochrane Library* (Issue 4). Chichester: John Wiley; 2003.	Non-relevant outcomes This was the protocol of the Cochrane review considered in this review
167. Abe Y, Kadowaki K, Sato T, Nakagomi A, Kumagai T. Secretion of atrial natriuretic peptide during artificial pacing: assessments including the influence of ventriculoatrial conduction. *J Cardiol* 1992;**22**:265–70.	Preclinical study
168. Oie BK, Skadberg BT, Myking OL, Ohm OJ. Acute effects of different pacing modes on atrial natriuretic peptide, catecholamines and right atrial pressure in patients with complete atrioventricular block. *European Journal of Cardiac Pacing and Electrophysiology* 1993;**3**:29–35.	Preclinical study
169. Schucherr A, Kuck KH. Influence of the pulse generator on the rate response of activity modulated pacemakers. *European Journal of Cardiac Pacing and Electrophysiology* 1992;**2**:294–8.	Non-relevant outcomes
170. Ovsyshcher I, Gross JN, Blumberg S, Furman S. Precision of impedance cardiography measurements of cardiac output in pacemaker patients. *Pacing Clin Electrophysiol* 1992;**15**:1923–6.	Non-randomised study of two comparison groups and preclinical outcomes
171. Gross JN, Sackstein RD, Furman S. Cardiac pacing and atrial arrhythmias. *Cardiol Clin* 1992;**10**:609–17.	Narrative, editorial or non-systematic review
172. Jutzy RV, Feenstra L, Florio J, Hodgkin JE, Levine PA. Advantages of dual chamber rate adaptive pacing compared with ventricular rate adaptive pacing in patients with pulmonary disease. *J Cardiopulm Rehabil* 1992;**12**:270–6.	Non-randomised study of two comparison groups
173. Blanc JJ, Mansourati J, Ritter P, Nitzsche R, Pages Y, Genet L, *et al*. Atrial natriuretic factor release during exercise in patients successively paced in DDD and rate matched ventricular pacing. *Pacing Clin Electrophysiol* 1992;**15**:397–402.	Preclinical study
174. Fromer M, Kappenberger L, Babotai I. Subjective and objective response to single- versus dual-chamber pacing. *Journal of Electrophysiology* 1987;**1**:343–9.	Non-comparative study
175. Dretzke J, Toff WD, Lip GY, Raftery J, Fry Smith A, Taylor R. Dual versus single chamber ventricular pacemakers in sick sinus syndrome and atrioventricular block. In *The Cochrane Library* (Issue 4). Chichester: John Wiley; 2003.	Other (non-formally included since unpublished at the time of the search, but included as Birmingham WHMTAC Report)
176. Iwase M, Miyaguchi K, Aoki T, Kato K, Hatano K, Hayashi H, *et al*. Evaluation of maintenance of cardiac output during DDD and VVI pacing by exercise Doppler echocardiography. [in Japanese]. *J Cardiol Suppl* 1991;**21**:727–33.	Preclinical study
177. Lo BF, Altamura G, Bianconi L, Toscano S, Pandozi C, Castro A, *et al*. Effetti acuti della stimolazione ventricolare e bicamerale sui livelli plasmatici dell'ormone natriuretico (Acute effects of DDD and VVI stimulation on atrial natriuretic factor levels). *Giornale Italiano di Cardiologia* 1997;**27**:1019–23.	Study with less than 48 hours' follow-up

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
178. Lukl J, Doupal V, Heinc P. Which patients are indicated for replacement of ventricular pacing for dual chamber pacing? *Cor Vasa* 1994;**36**:77–80.	Other
179. Mizutani N, Kobayashi T, Kato I. Optimal pacing mode for sick sinus syndrome. *Japanese Journal of Artificial Organs* 1997;**26**:369–74.	Non-randomised study of two comparison groups
180. Schrepf R, Koller B, Pache J, Goedel ML, Schomig A. Atrial fibrillation in pace-maker therapy: results of a prospective randomised DDD vs. VVI crossover study in 54 patients. *Z Kardiol* 1997;**86** Suppl 2:109.	Other
181. Vogt P, Goy JJ, Kuhn M, Leuenberger P, Kappenberger L. Single versus double chamber rate responsive cardiac pacing: comparison by cardiopulmonary noninvasive exercise testing. *Pacing Clin Electrophysiol* 1988;**11**:1896–901.	Study with less than 48 hours' follow-up
182. Crowe MJ, Teo KK, Noel GJ, Lavan JN, Browne HI, Horgan JH. Pacing in geriatric patients – clinical experience and cost considerations. *Ir Med J* 1982;**75**:87–90.	Non-comparative study
183. de Belder MA, Linker NJ, Jones S, Camm AJ, Ward DE. Cost implications of the British Pacing and Electrophysiology Group's recommendations for pacing [comment]. *BMJ* 1992;**305**:861–5.	Non-comparative study
184. Ferguson TB Jr, Ferguson CL, Crites K, Crimmins-Reda P. The additional hospital costs generated in the management of complications of pacemaker and defibrillator implantations. *J Thorac Cardiovasc Surg* 1996;**111**:742–51.	Non-randomised study of two comparison groups
185. Griffin JC. VVIR or DDD(R): does it matter? [review]. *Clin Cardiol* 1991;**14**:257–60.	Narrative, editorial or non-systematic review
186. Johnson PM. Cardiac pacemaker implantation: costs, control and contribution to the heart patient. *Health Values* 1977;**1**:255–7.	Non-randomised study of two comparison groups
187. Stamato NJ, O'Toole MF, Enger EL. Permanent pacemaker implantation in the cardiac catheterization laboratory versus the operating room: an analysis of hospital charges and complications. *Pacing Clin Electrophysiol* 1992;**15**:2236–9.	Non-randomised study of two comparison groups
188. Tobin K, Stewart J, Westveer D, Frumin H. Acute complications of permanent pacemaker implantation: their financial implication and relation to volume and operator experience. *Am J Cardiol* 2000;**85**:774–6.	Non-randomised study of two comparison groups
189. Yamamura KH, Kloosterman EM, Alba J, Garcia F, Williams PL, Mitran RD, *et al*. Analysis of charges and complications of permanent pacemaker implantation in the cardiac catheterization laboratory versus the operating room [comment]. *Pacing Clin Electrophysiol* 1999;**22**:1820–4.	Non-randomised study of two comparison groups
190. Flaker G, Greenspon A, Tardiff B, Schron E, Goldman L, Hellkamp A, *et al*. Death in patients with permanent pacemakers for sick sinus syndrome. *Am Heart J* 2003; **146**:887–93.	Preclinical study
191. Sampietro-Colom L. *Cardiac pacemakers, electrodes and cardioverter defibrillators: health products comparison*. 3 Volumes. Barcelona: Catalan Agency for Health Technology Assessment and Research; 1996.	Non-randomised study of two comparison groups
192. Physiologic pacing vs. single chamber pacing. *J Cardiovasc Electrophysiol* 2000;**11**:945.	Narrative, editorial or non-systematic review
193. Alpert M, Curtis J, Sanfelippo J, Flaker G. Comparative survival following permanent AV sequential versus permanent ventricular demand pacing for sinus node dysfunction in patients with and without heart-failure. *Pacing Clin Electrophysiol* 1985;**8**:288.	Non-randomised study of two comparison groups
194. Alpert MA, Curtis JJ, Sanfelippo JF, Flaker GC. Comparative survival following permanent ventricular and dual chamber pacing for high degree AV block in patients with and without preexistent congestive-heart-failure. *J Am Coll Cardiol* 1986;**7**:A198.	Non-randomised study of two comparison groups
195. Altieri PI, Martinez JA, Banchs H. Improvement in left-ventricular function during physiologic pacing (ventricular rate responsive and DDD). *Clinical Research* 1988; **36**:A258.	Non-randomised study of two comparison groups
196. Andrews C, Klementowicz P, Oseroff O, Bohm A, Furman S. Follow-up of DVI and VDD pacemakers. *Pacing Clin Electrophysiol* 1987;**10**:635.	Non-randomised study of two comparison groups

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
197. Antonioli GE, Baggioni GF, Marzaloni M, Sermasi S, Rusconi L. Hemodynamics during AV sequential versus ventricular pacing in CHB and SSS patients. *Pacing Clin Electrophysiol* 1981;**4**:A80.	Preclinical study
198. Baller D, Wolpers HG, Zipfel J, Bretschneider HJ, Hellige G. Comparison of the effects of right atrial, right ventricular apex and atrioventricular sequential pacing on myocardial oxygen-consumption and cardiac efficiency – a laboratory investigation. *Pacing Clin Electrophysiol* 1988;**11**:394–403.	Non-randomised study of two comparison groups
199. Barshlomo B, Adelman AG, Goldman BS, Pym J, Mickleborough LL, Gilbert BW. Comparison of left-ventricular function during ventricular and sequential atrioventricular pacing – the effect of heart-rate on atrial contribution to ventricular performance. *Pacing Clin Electrophysiol* 1982;**5**:303.	Preclinical study
200. Batey R, Sweesy M, Scala J. Comparative-analysis of low rate dual chamber pacing to ventricular rate responsive pacing (Activitrax). *Pacing Clin Electrophysiol* 1987;**10**:642.	Non-randomised study of two comparison groups
201. Been M, deBono DP, Miller HC, Hillis WS. Afterload reduction in patients with ventricular and physiological pacing. *Scott Med J* 1984;**29**:46.	Preclinical study
202. Bennett TD. Dynamic characteristics of alternative physiological pacing modes. *Pacing Clin Electrophysiol* 1985;**8**:294.	Preclinical study
203. Binner L, Weismuller P, Mayer U, Richter P, Stauch M. Chest-wall stimulation for noninvasive electrophysiologic testing using implanted single or dual chamber pacemakers. *Pacing Clin Electrophysiol* 1987;**10**:609.	Study with less than 48 hours' follow-up
204. Binner L, Richter P, Mayer U, Weismuller P, Stauch M. Programmed ventricular and atrial stimulation in patients with implanted single or dual chamber pacemakers using the chest-wall stimulation technique. *Pacing Clin Electrophysiol* 1987;**10**:646.	Preclinical study
205. Blanksma PK, Hoorntje JCA, Knop N, Buurma AE. Pressure volume relationships in atrioventricular vs. ventricular pacing showing contribution of atrial-pacing to normal resting hemodynamics . *Pacing Clin Electrophysiol* 1987;**10**:647.	Preclinical study
206. Boon NA, Frew AJ, Cobbe SM. An intra-patient comparison of ambulatory blood-pressure during chronic DDD and VVI pacing. *British Heart Journal* 1986;**55**:508.	Preclinical study
207. Bren GB, Wasserman AG, Elbayoumi J, Ross AM. Comparison of DDD and rate responsive-VVI pacing during exercise. *Circulation* 1986;**74**:388.	Non-randomised study of two comparison groups
208. Brownlee WC, Hastings DL. Left-ventricular dynamics on exercise with physiological and non-physiological pacing using radionuclide angiography. *Pacing Clin Electrophysiol* 1985;**8**:A76.	Preclinical study
209. Brownlee WC, Hastings DL. Left-ventricular dynamics during exercise in physiological and non-physiological pacing modes using gated radionuclide angiography. *British Heart Journal* 1985;**53**:74–5.	Preclinical study
210. Cavichio L, Curimbaba J, Povoa R, Pimenta J. Ambulatory blood pressure monitoring in patients paced in mode DDD VDD versus VVI. *Am J Hypertens* 1999;**158**:167A.	Preclinical study
211. Chamberlainwebber R, Petersen MEV, Ingram A, Briers L, Sutton R. Reasons for reprogramming dual-chamber pacemakers to VVI-mode – a retrospective review using a computer database. *Pacing Clin Electrophysiol* 1994;**17**:1730–6.	Non-randomised study of two comparison groups
212. Chiladakis JA, Patsouras N, Manolis AS. Autonomic effects of pacing after cessation of single- and dual-chamber pacing. *Circulation* 2002;**106**:1614.	Preclinical study
213. Chirife R, Ortega DF, Salazar AI. Nonphysiological left heart AV intervals as a result of DDD and AAI physiological pacing. *Pacing Clin Electrophysiol* 1991;**14**:1752–6.	Preclinical study
214. Cobbe SM, Boon NA, Rajagopalan B. Intra-patient comparison of effects of DDD and VV1 pacing on supine, erect and exercise arterial blood-pressure and cerebral blood-flow. *Pacing Clin Electrophysiol* 1985;**8**:A68.	Preclinical study
215. Connolly SJ, Gent M, Kerr CR. Effects of physiologic pacing versus ventricular pacing – reply. *N Engl J Med* 2000;**343**:1418.	Non-randomised study of two comparison groups

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
216. Connolly SJ, Talajic M, Roy D, Tang ASL, Lau C, Bonilla L, *et al*. The effect of pacemaker selection on functional capacity in the Canadian Trial of Physiologic Pacing (CTOPP). *Circulation* 1999;**100**:2451.	Other
217. Curzi GF, Massacci C, Mocchegiani R, Fratadocchi GB, Berrettini U. Change of pacing mode (from VVI to AAI or DDD) – long-term hemodynamic and clinical results. *Pacing Clin Electrophysiol* 1987;**10**:662.	Preclinical study
218. D'Souza R, Dawson F, Kerr F. Experience of a small British pacing centre between 1994 and 2000: some answers to the problem of low UK implantation rates. *Scott Med J* 2001;**46**:173–5.	Non-randomised study of two comparison groups
219. Defilippi R, Bramucci E, Gavazzi A, Scuri PM, Mussini A, Zawaideh Z, *et al*. Acute and chronic hemodynamic aspects at rest and during exertion of patients using physiologic pacemakers (Funke Mod 5999) – comparison with synchronous ventricular pacing. *Pacing Clin Electrophysiol* 1981;**4**:A41.	Preclinical study
220. Dicarlo LA, Morady F, Krol R, Baerman JM, Debuitleir M, Schork A, *et al*. Role of the atrium during ventricular pacing – hemodynamic consequences of atrioventricular and ventriculoatrial pacing in humans. *Pacing Clin Electrophysiol* 1987;**10**:438.	Preclinical study
221. Dicola VC, Hand R, Boucher CA, Kanarek DJ, Okada R, Pohost GM, *et al*. Exercise cardiopulmonary assessment with dual chamber versus ventricular pacing. *Pacing Clin Electrophysiol* 1983;**6**:311.	Non-randomised study of two comparison groups
222. Eagle KA, Mulley AG, Singer DE, Harthorne JW, Thibault GE. Long-term cost comparison of single vs. dual chamber cardiac pacing. *Clinical Research* 1985;**33**:A249.	Other
223. Ellenbogen KA, Stambler BS, Orav EJ, Sgarbossa E, Tullo NG, Love C, *et al*. Clinical characterization of patient crossovers to DDDR pacing during DDDR versus VVIR pacing in the PASE trial: insights into pacemaker syndrome. *Circulation* 1996;**94**:793.	Other
224. Estrada JLN, Belziti C, Conde S, Corrado G, Piraino R, Contrucci V. Gated blood pool evaluation of left-ventricular function of patients with DDD vs. VVI pace makers. *Pacing Clin Electrophysiol* 1987;**10**:665.	Preclinical study
225. Faerestrand S, Ohm OJ. AV-valvular function during long-term dual chamber pacing (DDD) and activity-sensing rate-responsive ventricular pacing (RRP). *Pacing Clin Electrophysiol* 1987;**10**:673.	Preclinical study
226. Fetter J, Patterson D, Aram G, Hayes DL. Effects of extracorporeal shock-wave lithotripsy on single chamber rate response and dual chamber pacemakers. *Pacing Clin Electrophysiol* 1989;**12**:1494–501.	Other
227. Frey AW, Fischer W, Kellerer J. A resonance phenomenon of the arterial tree induces obvious beat to beat fluctuations of arterial blood-pressure during VVI but not during DDD pacing. *Circulation* 1992;**86**:585.	Preclinical study
228. Gillam LD, Homma S, Novick SS, Rediker DE, Eagle KA, Harthorne JW. Prediction of the degree of hemodynamic improvement achieved by DDD vs. VVI pacing – a doppler echocardiographic study. *Pacing Clin Electrophysiol* 1987;**10**:437.	Preclinical study
229. Godin JF, Potironjosse M, Lemarec H, Louvet S, Lhenaff HW, Moutel P, *et al*. Oxygen-uptake during stress-testing in DDD versus VVI pacing. *Pacing Clin Electrophysiol* 1985;**8**:A34.	Preclinical study
230. Gulamhusein S, McMeekin J, Garbe G, Mann S. Effect of AV sequential and VVI pacing on left-ventricular function using resting radionuclide ventriculography. *Clin Invest Med* 1985;**8**:A51.	Preclinical study
231. Harthorne JW. Effects of physiologic pacing versus ventricular pacing. *N Engl J Med* 2000;**343**:1417–18.	Narrative, editorial or non-systematic review
232. Hayes DL, Vlietstra RE, McGoon MD, Brown ML, Gersh BJ. Comparison of exercise responses during ventricular and physiologic pacing. *J Am Coll Cardiol* 1983;**1**:636.	Non-randomised study of two comparison groups
233. Hesselson AB, Parsonnet V, Bernstein AD, Bonavita GJ. Deleterious effects of long-term single-chamber ventricular pacing in patients with sick sinus syndrome – the hidden benefits of dual-chamber pacing. *J Am Coll Cardiol* 1992;**19**:1542–9.	Non-randomised study of two comparison groups

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
234. Jutila C, Klein R, Shively B. Deleterious long-term effects of single chamber as compared to dual chamber pacing. *Circulation* 1990;**82**:182.	Other
235. Karpawich PP, Perry BL, Farooki ZQ, Green EW. Comparative effects of single chamber ventricular and dual chamber sequential pacing in children. *Pediatr Res* 1986;**20**:A171.	Non-randomised study of two comparison groups
236. Karpawich PP, Perry BL, Farooki ZQ, Cicalese CA, Green EW. Comparative hemodynamic-response of ventricular and physiologic pacing in children with nonsurgical atrioventricular-block. *Circulation* 1985;**72**:196.	Non-randomised study of two comparison groups
237. Kertes P, Chan W, Mond H, Hunt D. Cardiac adaptation on exercise in ventricular compared to physiological pacing. *Eur Heart J* 1983;**4**:40.	Preclinical study
238. Kertesz NJ, Snyder C, Fenrich AL, Minor MC, Black HR, Friedman RA. Intermediate term comparison of DDD versus VVI(R) pacing in infants with congenital complete atrioventricular block. *Circulation* 2000;**102**:2271.	Non-randomised study of two comparison groups
239. Kolk R, Samarutel J, Vali J. Atrial versus ventricular pacing in sick sinus syndrome – the role of retrograde ventriculoatrial conduction. *Ann Chir Gynaecol* 1994;**83**:220–4.	Non-randomised study of two comparison groups and preclinical outcomes
240. Koller B, Pache J, Hofmann M, Goedelmeinen L. Atrial arrhythmias in pacemaker therapy: a randomized DDD vs. VVI crossover trial in 50 patients. *Circulation* 1996; **94**:388.	Study with less than 48 hours' follow-up
241. Koretsune Y, Nanto S, Ishikawa K, Taniura K, Uematsu M, Kohama A, *et al*. The clinical significance of atrial kick and synchronicity of ventricular contraction – atrial, ventricular vs. AV sequential pacing. *Japanese Circulation Journal – English Edition* 1982;**46**:888.	Non-randomised study of two comparison groups and preclinical outcomes
242. Koretsune Y, Kodama K, Nanto S, Taniura K, Mishima M, Inoue M, *et al*. The energy efficiency of atrial, ventricular and AV sequential pacing – the clinical significance of atrial kick and synchronicity of ventricular contraction. *Jpn Heart J* 1982;**23**:252–4.	Non-randomised study of two comparison groups and preclinical outcomes
243. Kristensson BE, Ryden L. Heart-rate and rhythm during physiological and single rate ventricular pacing. *Pacing Clin Electrophysiol* 1985;**8**:A32.	Preclinical study
244. Krol RB, Walton JA, Pitt B. Comparative effects of AV sequential and ventricle pacing on left-ventricular function at rest and exercise. *Circulation* 1984;**70**:408.	Non-randomised study of two comparison groups
245. Kyriakides ZS, Kremastinos DT, Kolettis TM, Livanis E, Apostolou T, Michelakakis N, *et al*. Short-term effects of atrial versus atrioventricular pacing on myocardial ischemia in coronary artery disease patients. *Eur Heart J* 1993;**14**:607–13.	Non-randomised study of two comparison groups
246. Kyriakides ZS, Antoniadis A, Iliodromitis E, Michelakakis N, Kremastinos DT. Short-term effects of right atrial, right-ventricular apical, and atrioventricular sequential pacing on myocardial oxygen consumption and cardiac efficiency in patients with coronary artery disease. *British Heart Journal* 1994;**72**:404 .	Non-randomised study of two comparison groups
247. Lamas GA, Ellenbogen KA, Griffin JJ, Wilkoff BL, Sgarbossa E, Huang S, *et al*. Quality-of-life and clinical events in DDDR versus VVIR paced patients – design and preliminary results of a randomized trial. *Circulation* 1995;**92**:2544.	Other
248. Leon AR, Marinchak R, Yee R, Mittleman R, Tolentino A, Montanez A, *et al*. Incidence of atrial fibrillation in patients with sinus node dysfunction treated with ventricular pacing as compared with dual chamber pacing. *Circulation* 2001;**104**:1823.	Non-randomised study of two comparison groups
249. Lindeedelstam C, Hjemdahl P, Pehrsson SK, Astrom H, Nordlander R. Is DDD pacing superior to VVI,R – a study on cardiac sympathetic-nerve activity and myocardial oxygen-consumption at rest and during exercise. *Pacing Clin Electrophysiol* 1992; **15**:425–34.	Preclinical study
250. Lotto A, Valentini R, Greco EM, Sernesi L, Arlotti M, Eriano G, *et al*. DDD and rate incremental VVI pacing – hemodynamic evaluation during exercise. *Pacing Clin Electrophysiol* 1985;**8**:A12.	Preclinical study
251. Mayer DA, Tsapogas MJ. Pacemakers – dual or single chamber implantation. *Vascular surgery* 1992;**26**:400–7.	Non-randomised study of two comparison groups and preclinical outcomes

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
252. Mayosi BM, Little F, Millar RNS. Long-term survival after permanent pacemaker implantation in young adults: 30 year experience. *Pacing Clin Electrophysiol* 1999; **22**:407–12.	Non-randomised study of two comparison groups
253. McMeekin JD, Gulamhusein SS, Hanson S, Lautner D, Bertoia F. Influence of ventricular rate at rest and exercise during AV sequential and ventricular pacing using radionuclide ventriculography. *J Am Coll Cardiol* 1987;**9**:A10.	Non-randomised study of two comparison groups and preclinical outcomes
254. McMeekin JD, Gulamhusein SS, Hanson S, Bertoia F. Resting and exercise hemodynamic variables during AV sequential (DDD) and ventricular (VVI) pacing using radionuclide ventriculography (RVG). *Clin Invest Med* 1986;**9**:B33.	Study with less than 48 hours' follow-up
255. Mitsuoka T, Kenny RA, Yeung TA, Chan SL, Perrins EJ, Sutton R. Benefits of DDD pacing in sick sinus syndrome. *Pacing Clin Electrophysiol* 1985;**8**:293.	Other
256. Morell S, Sanjuan R, Garciacivera R, Gonzalez E, Botella S, Llavador J. Ventricular versus AV sequential pacing – determinants of acute hemodynamic improvement. *Pacing Clin Electrophysiol* 1985;**8**:A7.	Preclinical study
257. Morillo CA, Taylor JA, Stambler BS, Wood MA, Eckberg DL, Ellenbogen KA. Differential effects of VVI and DDD pacing with variable atrioventricular delays on muscle sympathetic-nerve activity. *Circulation* 1994;**90**:71.	Preclinical study
258. Nielsen AP, Rokey R, Kuo LC, Verani MS, Quinones MA, Spencer WR, *et al*. A prospective comparison of DDD and VVI pacing in patients with non-fixed heart-rates at rest and during exercise. *Pacing Clin Electrophysiol* 1985;**8**:292.	Non-randomised study of two comparison groups and preclinical outcomes
259. Nielsen JR, Simonsen EH, Nielsen G, Tonnesen J. Maximum exercise capacity in 3 different pacing modes – a double-blind-study. *Pacing Clin Electrophysiol* 1987;**10**:1222.	Other
260. Parsonnet V. The cost-effectiveness of dual-chamber pacing. *Eur Heart J* 1996; **17**:495–6.	Narrative, editorial or non-systematic review
261. Perrins EJ, Hudson WM, Lahiri A, Raftery EB, Sutton R. A randomized controlled trial of DDD and incremental VVI-rate responsive pacing. *J Am Coll Cardiol* 1984;**3**:507.	Other
262. Perrins J, Morley C, Chan SL, Sutton R. A randomized controlled trial of physiological versus ventricular pacing. *Circulation* 1982;**66**:218.	Other
263. Rediker DE, Eagle KA, Homma S, Gillam LD, Harthorne JW. Clinical and hemodynamic superiority of dual-chamber cardiac pacing in a blinded crossover study. *Pacing Clin Electrophysiol* 1987;**10**:437.	Other
264. Reynolds DW, Olson EG, Burow BD, Thadani U, Lazzara R. Atrial vs. Atrioventricular pacing – a hemodynamic comparison. *Pacing Clin Electrophysiol* 1985;**8**:A37.	Preclinical study
265. Reynolds DW, Wilson MF, Burow RD, Schaefer CF, Lazzara R, Thadani U. Hemodynamic evaluation of atrioventricular sequential versus ventricular pacing in patients with normal and poor ventricular function at variable heart rates and posture. *J Am Coll Cardiol* 1983;**1**:636.	Preclinical study
266. Rodiger W, Darup J, Krebber HJ, Kreymann KG. Physiological versus ventricular pacing – comparison of the long-term results. *Pacing Clin Electrophysiol* 1981;**4**:A69.	Non-randomised study of two comparison groups
267. Romero LR, Haffajee CI, Doherty P, Levin W, Benotti JR, Vandersalm T, *et al*. Comparison of ventricular function and volume with AV sequential and ventricular pacing. *Chest* 1981;**80**:346.	Non-randomised study of two comparison groups and preclinical outcomes
268. Salachas A, Smith R, Oakley D, Peach M. A comparative study of atrial synchronous versus VVI pacing using both physiological and psychometric assessment. *Pacing Clin Electrophysiol* 1987;**10**: 738.	Non-randomised study of two comparison groups
269. Santini M, Rocchi M, Alliegro A, Masini V. Atrial and AV sequential pacing benefits and reliability. *Pacing Clin Electrophysiol* 1981;**4**:A71.	Non-randomised study of two comparison groups and preclinical outcomes
270. Sasaki Y, Akahane K, Hirano K, Yonekura H, Endoh R, Koike S, *et al*. Long-term follow-up of patients with sick sinus syndrome – a comparison of the clinical aspects among non-pacing, VVI and physiological pacing group. *Japanese Circulation Journal English Edition* 1987;**51**:728.	Other

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
271. Shefer A, Rosenman Y, Flugelman MY, Bendavid Y, Gotsman MS, Lewis BS. Hemodynamic effects of atrial, atrioventricular and ventricular pacing – a radionuclide ventriculographic study. *Israel Journal of Medical Sciences* 1983;**19**:399.	Preclinical study
272. Shibolet O, Amit G. Effects of physiologic pacing versus ventricular pacing. *N Engl J Med* 2000;**343**:1418.	Narrative, editorial or non-systematic review
273. Spencer RP. Cardiac physiologic versus ventricular pacing. Comparison by ventricular volumes and ejection fraction. *FASEB J* 2002;**16**:A1126.	Preclinical study
274. Stofmeel MAM, Post MWM, Kelder JC, Grobbee DE, Van Hemel NM. Quality-of-life of pacemaker patients: a reappraisal of current instruments. *Pacing Clin Electrophysiol* 2000;**23**:946–52.	Narrative, editorial or non-systematic review
275. Stone JM, Bhakta RD, Lutgen J. Dual chamber sequential pacing management of sinus node dysfunction – advantages over single chamber pacing. *Pacing Clin Electrophysiol* 1981;**4**:A76.	Narrative, editorial or non-systematic review
276. Swift PC, Cowell LC, Woollard KV. A comparison of the exercise response to DDD and activity response ventricular pacing. *Pacing Clin Electrophysiol* 1987;**10**:751.	Non-randomised study of two comparison groups and preclinical outcomes
277. Tang ASL, Green MS, Connolly SJ, Kerr C, Roberts RS. Effect of pacemaker dependency on the benefit of physiologic over ventricular pacing. *Circulation* 1999; **100**:3389.	Other
278. Theodorakis G, Kremastinos D, Livanis MME, Archontakis C, Karavolias G, Toutouzas P. cAMP and ANP levels in VVI and DDD pacing with different AV delays during daily activity and exercise. *Pacing Clin Electrophysiol* 1990;**13**:1773–8.	Non-randomised study of two comparison groups and preclinical outcomes
279. Toff WD, Tull SP, Broomes-Pakeerah GH, Lloyd AS, Skehan JD, Camm AJ, *et al*. Enhanced platelet activation in patients with single compared with dual chamber pacemakers. *Circulation* 1999;**100**:4149.	Non-randomised study of two comparison groups and preclinical outcomes
280. Toff WD, Broomes-Pakeerah GH, Skehan JD, Ng LL. Improved natriuretic peptide profile after dual compared with single chamber cardiac pacing in patients with high-grade atrioventricular (AV) block. *Heart* 2003;**89**:204.	Non-randomised study of two comparison groups and preclinical outcomes
281. Vardas P, Travill C, Williams M, Ingram A, Lightman S, Sutton R. Atrial-natriuretic-peptide in complete atrioventricular-block untreated and after VVI and DDD pacing. *Pacing Clin Electrophysiol* 1987;**10**:990.	Preclinical study
282. Vardas PE, Simantirakis EN, Parthenakis FI, Zuridakis EG, Chrysostomakis SI. Transoesophageal echocardiographic evaluation of left atrial appendage function during DDD and VVI pacing. *J Am Coll Cardiol* 1997;**29**:93574.	Preclinical study
283. Wharton JM, Criger DA, Sorrentino RA, Sharma A, Grill CR, Lee KL. Effect of underlying cardiovascular disease on mortality and atrial fibrillation in WI-R and DDD-R paced patients. *Circulation* 1999;**100**:353.	Other
284. Woodend K, Tang ASI, Irvine J, Connolly S, Lau C, Paquette M, *et al*. Pacemaker dependency conditions the QoL benefits of physiological over WI pacing: Canadian trial of physiologic pacing. *Circulation* 1999;**100**:101.	Other
285. Zabel M, Breitwieser C, Sancar D, Godde P, Behrens S. T-wave alternans in patients with dual-chamber pacemakers – comparison between atrial, ventricular, and AV sequential pacing. *Eur Heart J* 2001;**22**:437.	Preclinical study
286. Zugibe FT, Nanda NC, Akiyama T, Barold SS. Doppler detection and quantitation of mitral regurgitation during ventricular and atrioventricular sequential pacing. *J Am Coll Cardiol* 1984;**3**:508.	Non-randomised study of two comparison groups and preclinical outcomes
287. Lelakowski J, Majewski J, Machejek J, Bednarek J, Malecka B. QT dispersion during DDD and VVI pacing in hypertensive patients. *Europace* 2001;**2001**:405–12.	Preclinical study
288. Zagozdzon P, Swiatecka G, Radomski M, Zaborski L. Value of physiologic pacing mode depends on indication: more benefits on survival in sinus node disease than in atrioventricular block. *Heart Disease: New Trends in Research, Diagnosis and Treatment* 2001;665–70.	Narrative, editorial or non-systematic review

continued

TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
289. Kotsakis A, Kamalvand K, Tan K, Lloyd G, Birdi H, Bucknall C, *et al*. Dual chamber or single chamber ventricular pacing; which is the most appropriate in patients with a history of atrial tachyarrhythmias? *Europace '97 – the Official Meeting of the Working Groups on Cardiac Pacing and Arrhythmias of the European Society of Cardiology* 1997; 483–7.	Narrative, editorial or non-systematic review
290. Ueda K. Cost effectiveness of DDD pacemakers in geriatric patients with sick sinus syndrome. *Cardiac Pacing and Electrophysiology Today* 1993;192–3.	Narrative, editorial or non-systematic review
291. Antonioli GE, Barbieri D, Marzaloni M, Percoco GF, Pozzar C, Pradella A, *et al*. VDD single-lead versus VVI-RR. *Proceedings of the International Symposium on Progress in Clinical Pacing* 1988;**51**:39–52.	Non-randomised study of two comparison groups
292. Anzai N. Assessment of stable atrioventricular conduction and cost savings of single-chambered atrial paced patients with sinus bradycardia. 22–26, October 2000, San Francisco, CA, USA. *Chest* 2000;**118**:222S.	Narrative, editorial or non-systematic review
293. Bastani H. Prospective multicentre study of complications in first implant pacemaker systems during one year follow-up in a mid-Swedish area. *XXII Congress of the European Society of Cardiology*, 26–30 August 2000, Amsterdam, The Netherlands. *Eur Heart J* 2000;**21**:680.	Non-randomised study of two comparison groups
294. Capucci A, Ricci R, Spampinato A, Bellocci F, Dini P, Boriani G, *et al*. Does dual chamber pacing prevent paroxysmal atrial fibrillation in brady-tachy patients? *70th Scientific Sessions of the American Heart Association*, 9–12 November 1997, Orlando, FL, USA. *Circulation* 1997;**96**:I529.	Narrative, editorial or non-systematic review
295. Connolly SJ, Lau C, Bonilla L, Gillis A. The effect of pacemaker selection on functional capacity in the Canadian Trial of Physiologic Pacing (CTOPP). *72nd Scientific Sessions of the American Heart Association*, 7–10 November 1999, Atlanta, GA, USA. *Circulation* 1999;**100**:I.	Non-randomised study of two comparison groups
296. Cunningham A, Garratt C, Rickards AF. The effect on pacing practice in the United Kingdom following publication of clinical guidelines. *Joint XIIth World Congress of Cardiology and the XVIth Congress of the European Society of Cardiology*, 10–14 September 1994, Berlin, Germany. *Eur Heart J* 1994;**15**:271.	Narrative, editorial or non-systematic review
297. Down R, Logan T, Busse E, Burgess J, Haennel RG. Chronotropic response to exercise using three pacing modes versus a predictive heart rate. *44th Annual Meeting of the American College of Sports Medicine*, 28–31 May 1997, Denver, CO, USA. *Med Sci Sports Exerc* 1997;**29**:S167.	Preclinical study
298. Fletcher RD. Comparison of survival rates among single and dual-chamber pacing and heart failure. *71st Scientific Sessions of the American Heart Association*, 8–11 November 1998, Dallas, TX, USA. *Circulation* 1998:**98**:1713–14.	Non-randomised study of two comparison groups
299. Fletcher RD. Improved patient survival with increased use of dual and rate-responsive pacemakers in the VA system. *72nd Scientific Sessions of the American Heart Association*, 7–10 November 1999, Atlanta, GA, USA. *Circulation* 1999;**100**:I.	Non-randomised study of two comparison groups
300. Fletcher RD. Rate-responsive pacing improves longevity in single and dual chamber pacing. *48th Annual Scientific Session of the American College of Cardiology*, 7–10 March 1999, New Orleans, LA, USA. *J Am Coll Cardiol* 1999;**33**:154A.	Narrative, editorial or non-systematic review
301. Frielingsdorf J, Bertel O. Rate responsive single chamber (VVIR) versus dual chamber pacing (DDD) and work capacity: role of left ventricular function. *XVth Congress of the European Society of Cardiology*, 29 August–2 September 1993, Nice, France. *Eur Heart J* 1993;**14**:122.	Non-randomised study of two comparison groups
302. Iliev I. DDD pacing with optimal AV delay versus AAI pacing in patients with AV block I degree. *47th Annual Scientific Session of the American College of Cardiology*, 29 March–1 April 1998, Atlanta, GA, USA. *J Am Coll Cardiol* 1998;**31**:433A.	Non-randomised study of two comparison groups
303. Jahangir A. Differential impact of pacing mode on long-term survival in patients with conduction system disease. *44th Annual Scientific Session of the American College of Cardiology*, 19–22 March 1995, New Orleans, LA, USA. *J Am Coll Cardiol* 1995;152A.	Non-randomised study of two comparison groups

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
304. Krol RB. Comparative effects of atrioventricular sequential and ventricle pacing on left ventricular function at rest and exercise. *Am Heart Assoc Monogr* 1984; **12–15**:II–408.	Non-randomised study of two comparison groups
305. Lascault G. Comparison of av synchronous and asynchronous pacing on exercise by echo-Doppler. *XIIth Congress of the European Society of Cardiology*, 16–20 September 1990, Stockholm, Sweden. *Eur Heart J* 1990;**11**:312.	Preclinical study
306. Leon AR. Incidence of atrial fibrillation in patients with sinus node dysfunction treated with ventricular pacing as compared with dual chamber pacing. *Scientific Sessions of the American Heart Association*, 11–14 November 2001, Anaheim, CA, USA. *Circulation* 2001;**104**:II.	Non-randomised study of two comparison groups
307. Matsuura Y. How to choose the optimal pacemaker to minimize the occurrence of pulmonary embolism after pacing. *Cardiac Pacing and Electrophysiology Today* 1993;102–4.	Narrative, editorial or non-systematic review
308. Mitkowksi P. Atrial natriuretic peptide levels, natriuresis and haemodynamic response to volume overload in single-chamber ventricular versus dual-chamber pacing modes. *XXth Congress of the European Society of Cardiology*, 22–26 August 1998, Vienna, Austria. *Eur Heart J* 1998;**19**:251.	Preclinical study
309. Molin F. Risk factors of hospitalization for heart failure in the Canadian Trial of Physiologic Pacing. *72nd Scientific Sessions of the American Heart Association*, 7–10 November 1999, Atlanta, GA, USA. *Circulation* 1999;**100**:I.	Non-relevant outcomes
310. Nielsen JC. Atrioventricular conduction during long-term follow-up of patients with sick sinus syndrome randomized to single chamber atrial pacing. *71st Scientific Sessions of the American Heart Association*, 8–11 November 1998, Dallas, TX USA. *Circulation* 1998;**98**:1510.	Non-randomised study of two comparison groups
311. Sancho-Tello MJ. Atrioventricular sequential versus rate-responsive pacing the role of atrioventricular delay. *Xth Congress of the European Society of Cardiology*, 28 August–1 September 1988, Vienna, Austria. *Eur Heart J* 1988;**9**:269.	Non-randomised study of two comparison groups
312. Shigemura M. Comparison of cardiac output between in DDD and in VVI by pulsed Doppler echocardiographic method correlation with Swan-Ganz catheter method. *Japanese Circulation Journal* 1989;**53**:657.	Non-randomised study of two comparison groups
313. Spencer RP. Cardiac physiologic versus ventricular pacing: comparison by ventricular volumes and ejection fraction. *Annual Meeting of Professional Research Scientists on Experimental Biology*, 20–24 April 2002, New Orleans, LA, USA. *FASEB J* 2002; **16**:A1126.	Narrative, editorial or non-systematic review
314. Stewart WJ. Beat to beat changes in stroke volume between ventricular and dual chamber pacing assessment with Doppler echo cardiography. *Am Heart Assoc Monogr* 1983;**14–17**:111-241.	Preclinical study
315. Toda N, Ishikawa T, Kobayashi I, Tsunematsu T, Sumita S, Shindou T, *et al*. Crossover comparison of the effects of DDD and VVI in plasma level of B-type natriuretic peptide. *72nd Scientific Sessions of the American Heart Association*, 7–10 November 1999, Atlanta, GA, USA. *Circulation* 1999;**100**:I.	Preclinical study
316. Vardas P, Simantirakis E, Parthenakis F, Zuridakis E, Chrysostomakis SI. Transoesophageal echocardiographic evaluation of left atrial appendage function during DDD and VVI pacing. *46th Annual Scientific Session of the American College of Cardiology*, 16–19 March 1997, Anaheim, CA, USA. *J Am Coll Cardiol* 1997;**29**:112A.	Preclinical study
317. Vogt P. Simple versus double chamber rate responsive pacing comparison by exercise testing. *Xth Congress of the European Society of Cardiology*, 28 August–1 September 1988, Vienna, Austria. *Eur Heart J* 1988;**9**:269.	Non-randomised study of two comparison groups
318. Mahoney CB. Pacing modes and patient outcomes: the economic benefit of atrial-based pacing. *Pacing Clin Electrophysiol* 1994;**17**:x–xi.	Other
319. Stofmeel MA, Post MW, Kelder JC, Grobbee DE, Van Hemel NM. Psychometric properties of AQUAREL. A disease-specific quality of life questionnaire for pacemaker patients. *J Clin Epidemiol* 2001;**54**:157–65.	Non-relevant outcomes

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TABLE 59 *Excluded studies (cont'd)*

Study	Reason for exclusion (more than one is possible)
320. Hussein SJ, Hennekens CH, Lamas GA. An update on clinical trials in pacing: is dual chamber pacing better? *Curr Opin Cardiol* 2004;**19**:12–18.	Narrative, editorial or non-systematic review
321. Sweeney MO, Hellkamp AS, Ellenbogen KA, Glotzer TV, Silverman R, Yee R, *et al*. Prospective randomized study of mode switching in a clinical trial of pacemaker therapy for sinus node dysfunction. *J Cardiovasc Electrophysiol* 2004;**15**:153–60.	Non-relevant outcomes
322. Albertsen AE, Nielsen JC. Selecting the appropriate pacing mode for patients with sick sinus syndrome: evidence from randomized clinical trials. *Card Electrophysiol Rev* 2003;**7**:406–10.	Narrative, editorial or non-systematic review
323. Flaker G, Greenspon A, Tardiff B, Schron E, Goldman L, Hellkamp A, *et al*. Death in patients with permanent pacemakers for sick sinus syndrome. *Am Heart J* 2003; **146**:887–93.	Non-relevant outcomes
324. Horenstein MS, Karpawich PP, Tantengco MV. Single versus dual chamber pacing in the young: noninvasive comparative evaluation of cardiac function. *Pacing Clin Electrophysiol* 2003;**26**:1208–11.	Non-randomised study of two comparison groups

Appendix 5

Quality checklist, parallel RCTs

TABLE 60

Item	MOST[48]	PASE[35]	CTOPP[52]	Mattioli[46]	Nielsen[91]
Randomisation sequence generation	Central randomisation line	Block randomisation lists produced centrally for each centre	Not stated	Not stated	Not stated
Concealment of randomisation	Pacemaker mode is randomised at implant after positioning of leads and prior to insertion	Randomisation envelope opened at implant	Randomisation line. Up to 48 hours before implant	Randomisation list up to 24 hours from implant	Not stated
Similarity of groups at baseline	Trial arms differed in prior heart failure, diabetes, prior ventricular tachycardia or fibrillation (DDDR) and NYHA class I or II (VVIR). Analysis selectively adjusted only for characteristics higher in DDDR	Yes, but omitting number of patients with AVB or SSS in the two arms	Yes	Not stated	Not stated, reported to be comparable
Eligibility criteria specified (pre-stratification)	Yes	Yes	Yes	Yes	Yes
Care provider blinded	Unknown	Unknown	Unknown	Unknown	Unknown
Patient blinded	Yes	Yes	Yes	Not stated	Not stated
Blinding of assessors reported	Outcomes reviewed by a blinded committee	Not stated, except for outcomes collected with telephone interviews done by blinded interviewers after month 18 of follow-up	Outcomes reviewed by a blinded committee	CT reviewed by blinded neuroradiologist who adjudicated cerebrovascular events. Methods for measurement of AF not specified: AF was the only outcome reported by pacing mode	No
Co-intervention, equal at baseline	Not stated	Yes	Yes	Not stated	Yes
Co-intervention, equal during follow-up	Not stated	Not stated	Not stated	Not stated	Differential increase was observed in diuretics (ns)
Results for primary outcome measure	Results reported in full specification	Results are not fully reported (*p* but not SD)	Results partially detailed	Reported with adequate detail	Reported with adequate detail
ITT	No	No	Yes	States "Analysis was done regardless of re-programming"	States yes

continued

TABLE 60 *(cont'd)*

Item	MOST[48]	PASE[35]	CTOPP[52]	Mattioli[46]	Nielsen[91]
Missing values	LOCF was used. For QoL, LOCF (numbers of patients are not reported)	LOCF was used in the analyses		Patients' data censored at end of study, occurrence of end-point or death	
Loss to follow-up	None reported		Not stated		No loss to follow-up

Appendix 6

Summary table, quality of life

TABLE 61

Study	Instrument	Results
Hoijer, 2002[49]	Karolinska questionnaire	Values not reported, only significant differences in dyspnoea and mood (active/deactivated)
Linde-Edelstam, 1992[82]	Karolinska questionnaire	Symptoms: Activity: DDD 3.20 (SD 0.60), VVIR 3.20 (SD 0.40), ns Alertness: DDD 3.40 (SD 1.60), VVIR 3.50 (SD 1.20), ns Breathlessness: DDD 9.50 (SD 8.50), VVIR 18.10 (SD 14.30), $p = 0.02$ Calmness: DDD 3.30 (SD 0.50), VVIR 3.20 (SD 0.60), ns Chest pain: DDD 2.60 (SD 2.50), VVIR 6.80 (SD 8.90), $p = 0.06$ Concentration: DDD 2.60 (SD 2.50), VVIR 6.10 (SD 12.00), ns Decision-making: DDD 2.80 (SD 4.80), VVIR 4.00 (SD 6.00), ns Depressive score: DDD 1.20 (SD 2.10), VVIR 0.90 (SD 2.10), ns Dizziness: DDD 4.80 (SD 8.50), VVIR 15.20 (SD 22.60), $p = 0.04$ Memory: DDD 4.40 (SD 4.90), VVIR 10.50 (SD 12.00), $p < 0.001$ Palpitations: DDD 2.80 (SD 8.10), VVIR 6.30 (SD 15.20), $p = 0.03$ Physical ability: DDD 34.10 (SD 2.70), VVIR 34.60 (SD 2.40), ns Pleasantness: DDD 3.30 (SD 0.60), VVIR 3.30 (SD 0.60), ns Self-perceived health A: DDD 1.40 (SD 0.50), VVIR 1.60 (SD 0.80), ns Self-perceived health B: DDD 1.50 (SD 0.80), VVIR 1.70 (SD 1.00), ns Sleep: DDD 24.20 (SD 7.40), VVIR 26.00 (SD 7.00), ns Social participation: DDD 11.60 (SD 1.10), VVIR 11.90 (SD 0.30), ns
Lau, 1994[78]	General Health Questionnaire, 12 items Bradford Somatic Inventory (adapted)	DDDR 14.3 (SD 2.2), VVIR 14.9 (SD 2.0) Somatic symptoms: Total score (range 41–82): DDDR 71.5 (SD 3.3), VVIR 67.7 (SD 3.6), ns Activities of daily living: DDDR 31.2 (SD 2), VVIR 31.3 (SD 2.2), ns Emotional adjustment: DDDR 24.2 (SD 1.7), VVIR 23.5 (SD 1.9) (lower score better), ns Social interactions, frequency: DDDR 11.3 (SD 1.1), VVIR 11 (SD 1), ns 11.6.1.1 Social interaction, range: DDDR 2.1 (SD 0.2), VVIR 1.3 (SD 0.2), $p < 0.02$ Social interaction, quality: DDDR 21.5 (SD 1.2), VVIR 21.1 (SD 1.3) (lower score better), ns Work adjustment: DDDR 0.4 (SD 0.1), VVIR 0.4 (SD 0.1) (lower score better), ns Sleep: DDDR 0.3 (SD 0.1), VVIR 0.7 (SD 0.1) (lower score better), ns Fatigue: DDDR 1.6 (SD 0.1), VVIR 0.8 (SD 0.1) (lower score better), ns Appetite: DDDR 1.2 (SD 0.1), VVIR 1.1 (SD 0.1) (lower score better), ns
Lau, 1994[79]	Physical malaise score (41 items), adapted from Bradford Somatic Inventory	Significant differences in 4/41 scores only for DDDR: dyspnoea (DDD 1.7, DDDR, 2, VVIR 1.66, $p < 0.01$), temperature intolerance (DDDR 1.87, DDD 1.28, VVIR 1.28, $p < 0.01$), epigastric pain (DDDR 2, DDD 1.91, VVIR 1.73, $p < 0.05$), palpitations (DDDR 2.02, DDD 1.75, VVIR 1.66, $p < 0.01$). No significant differences between DDD and VVIR

continued

TABLE 61 *(cont'd)*

Study	Instrument	Results
	Illness perception score (43 items)	Significant differences in diet (DDDR 1, VVIR 1.3, $p < 0.01$), volition (DDDR 1.15, VVIR 1.86, $p < 0.01$), concentration (DDDR 2.3, VVIR 3.3, $p < 0.05$), work (DDDR 1.3, VVIR 1.9, $p < 0.05$). Significant difference in contentment only between DDD 1.71, VVIR 2.15, $p < 0.05$)
	QoL (48 items)	Total sum VVIR 116, DDDR 104, DDD 107, $p < 0.003$. Individual significant scores: stress (VVIR 1.8, DDDR 1.3, DDD 1.9, $p < 0.018$), mobility (VVIR 2, DDDR 1.21, DDD 1.7, $p < 0.01$), illness impact (VVIR 3.2, DDDR 2.8, DDD 3.07, $p < 0.05$), worries (VVIR 2.05, DDDR 1.72, DDD 1.3, $p < 0.002$)
Lukl, 1994[83]	QoL (19 items): scores 0–5, 0 optimal, 5 worst, with total score calculated as the sum of scores	Significant differences in the symptom scores included in the QoL measure Breathlessness: DDD 1.00 (SD 1.30), VVIR 0.60 (SD 1.30), ns Breathlessness during exertion: DDD 2.20 (SD 1.60), VVIR 3.20 (SD 1.50), $p < 0.02$ Dizziness: DDD 0.30 (SD 0.80), VVIR 1.70 (SD 1.60), $p < 0.05$ Oedema: DDD 1.00 (SD 1.30), VVIR 0.90 (SD 1.30), ns Fatigue: DDD 1.70 (SD 1.60), VVIR 2.70 (SD 1.50), $p < 0.02$ Memory: DDD 1.00 (SD 1.20), VVIR 0.60 (SD 0.90), ns Overexertion: DDD 1.60 (SD 1.30), VVIR 2.60 (SD 1.40), $p < 0.01$ Palpitations: DDD 0.90 (SD 1.20), VVIR 3.20 (SD 1.80), $p < 0.05$ Sleep: DDD 1.90 (SD 1.70), VVIR 1.70 (SD 1.50), ns Sweating: DDD 1.30 (SD 1.30), VVIR 2.40 (SD 1.80), $p < 0.05$ Tightness in chest: DDD 1.30 (SD 1.70), VVIR 0.80 (SD 1.30), ns Chronotropic incompetence ($n = 9$): VVI 16.56/32/17.75 Without chronotropic incompetence: 23.5/15.8 vs 36.92/17.69, $p < 0.05$ SSS ($n = 8$): 23.25/12.16 vs 36.25/14.68, $p < 0.05$ CHB: 18.85/16.67 vs 33.92/19.47, $p < 0.01$
Saner, 1996[73]	Self-perceived emotional well-being, VAS, 10 cm	Emotional well-being: VVIR 68/28%, DDD 89/79%, DDDR 92/12%
CTOPP[52]	SF-36	Differences in SF-36 at month 6, dual chamber compared to ventricular: Physical function –2 Physical role –1 Social function –1 Energy 6 Mental health +4 Emotional role –3 Pain –3 Health perception –3 All differences were significant ($p < 0.05$) for scores between baseline and month 6 with the exception of general health, and of physical function for dual chamber only

continued

TABLE 61 *(cont'd)*

Study	Instrument	Results
	SF-6	Differences in SF-6 between baseline and month 6 were non-significant for activity limitation, difficulty with work, emotional problems, social activity and bodily pain, and were significant for general health
	QLAP	Scores for the QLAP were significantly better between baseline and month 6 for total score and single items, activity, physical and social, and no different for psychological
PASE[35]	SF-36	Difference in QoL scores at month 18, dual chamber compared to ventricular: Physical function –1.5 Physical role –0.2 Social function –1.1 Energy 7.9 Mental health 4.6 Emotional role 1.6 Pain 3.6 Health perception –2.1 Significant differences only for mental health between ventricular and dual at month 9 ($p = 0.03$). Borderline significant difference in physical role and emotional role between ventricular and dual at month 3 ($p = 0.051$ and 0.052). Overall gap is significantly higher in QoL between baseline and 3 months for social function, physical role emotional role, mental health and energy (all $p < 0.001$)
MOST[48]	SF-36	Difference in QoL scores at month 48, dual chamber compared to ventricular: Physical function +1.9, $p = 0.04$ Physical role +8.6, $p < 0.01$ Social function +2.5, $p < 0.01$ Energy +4.1, $p < 0.01$ Mental health +1.2, $p = 0.05$ Emotional role +3.6, $p < 0.01$ Pain +0.5, $p = 0.57$ Health perception +1.1, $p = 0.09$ Mental component summary +1.1, $p < 0.01$ Physical component summary +1.2, $p < 0.01$

Appendix 7

Meta-analyses of individual symptom scores, cross-over trials

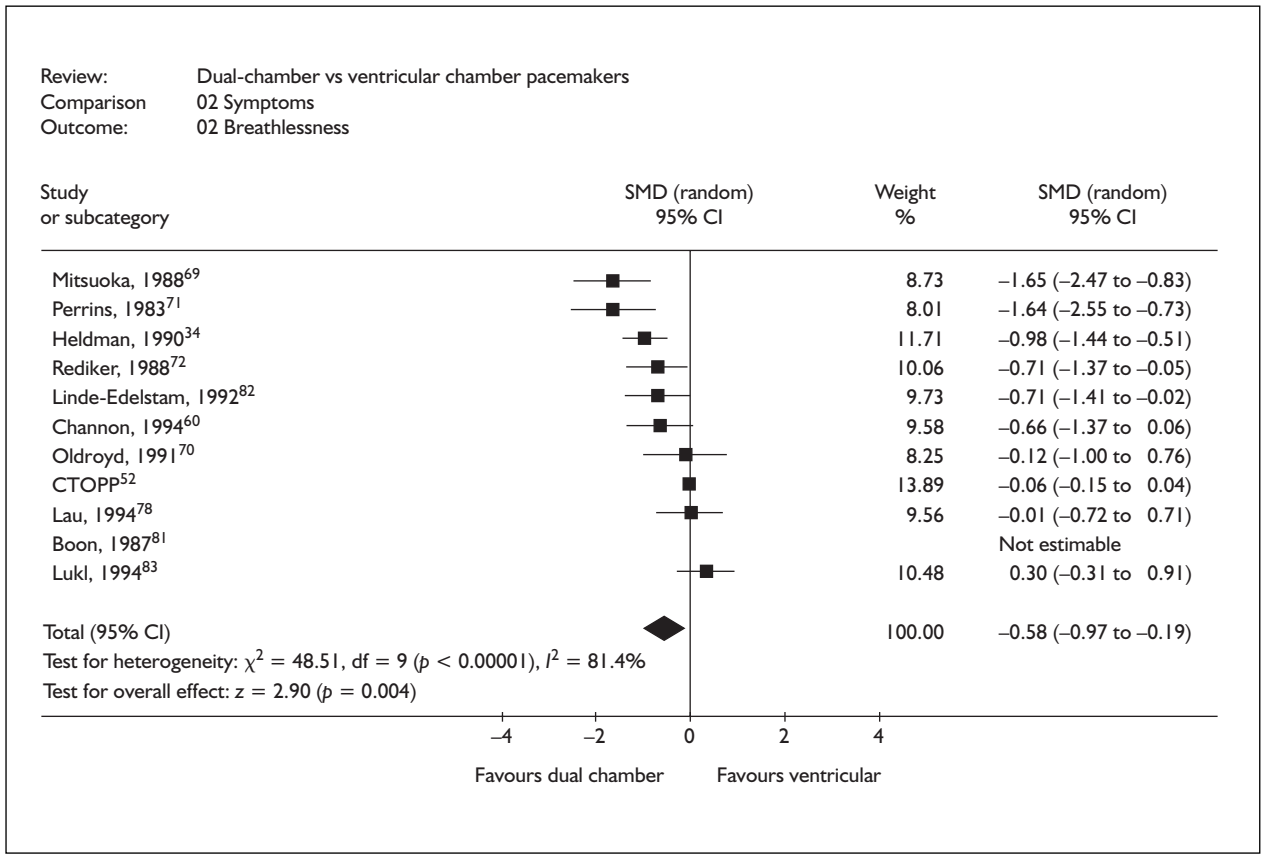

FIGURE 40 *Meta-analysis of individual symptoms: breathlessness*

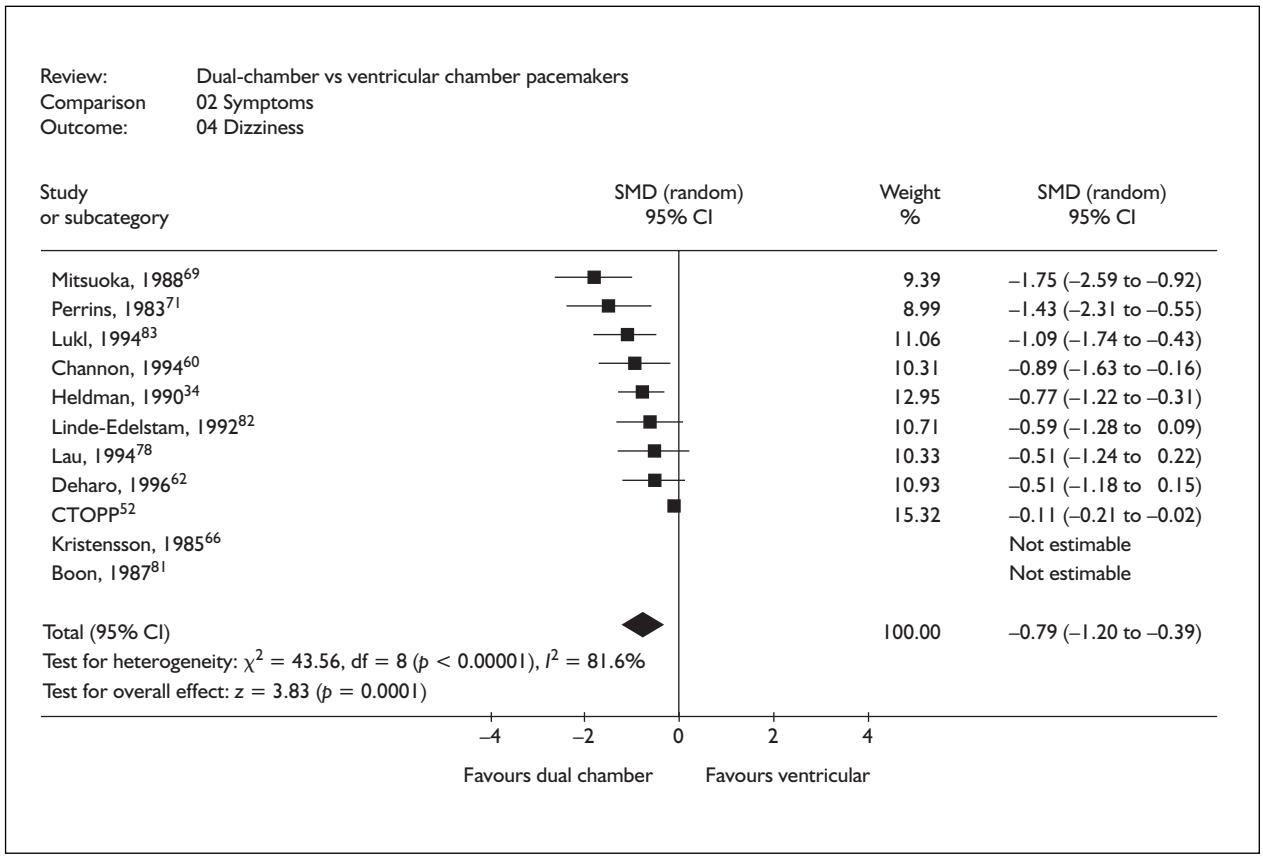

FIGURE 41 *Meta-analysis of individual symptoms: dizziness*

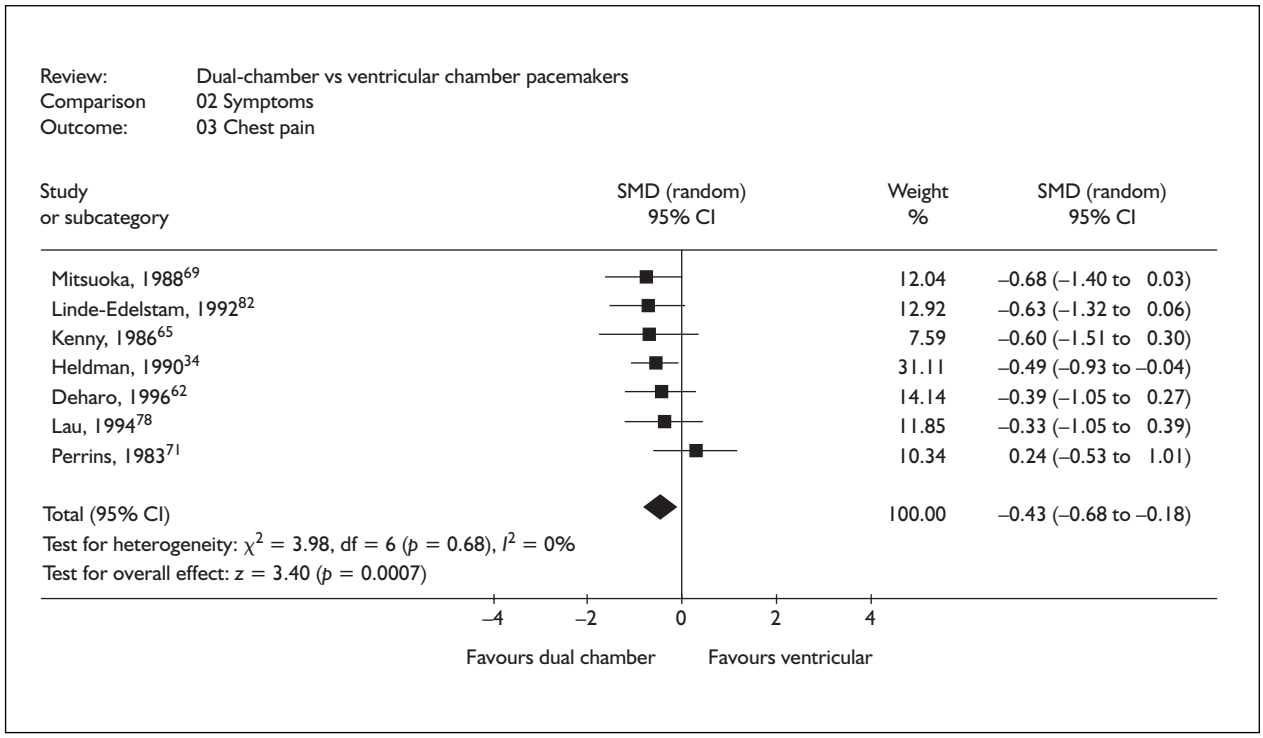

FIGURE 42 *Meta-analysis of individual symptoms: chest pain*

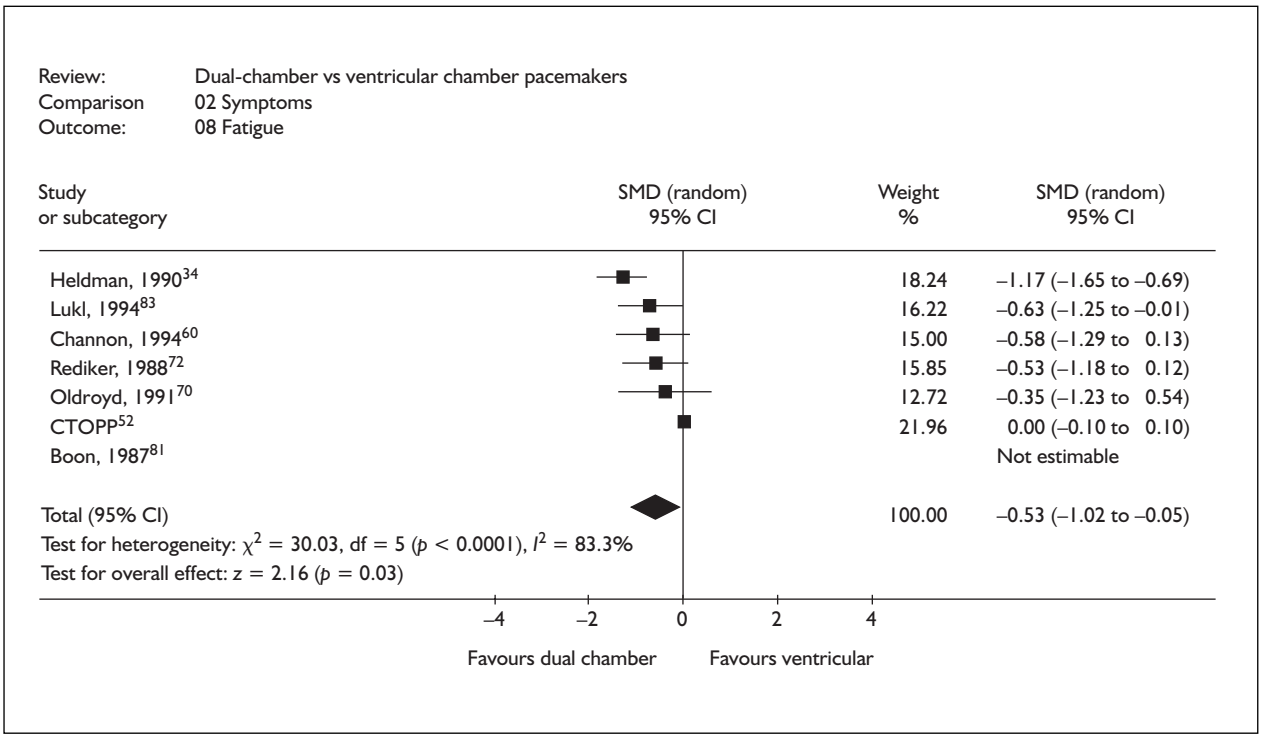

FIGURE 43 *Meta-analysis of individual symptoms: fatigue*

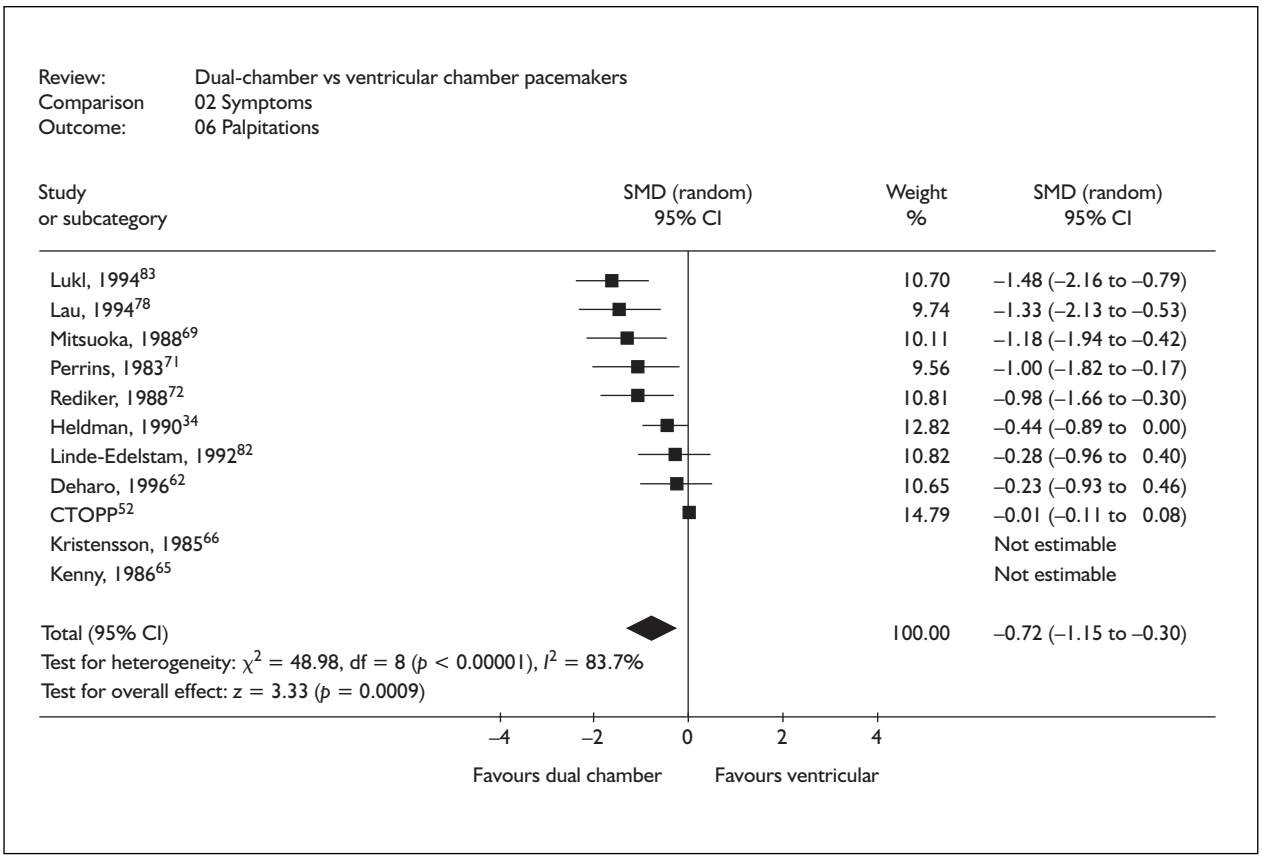

FIGURE 44 *Meta-analysis of individual symptoms: palpitations*

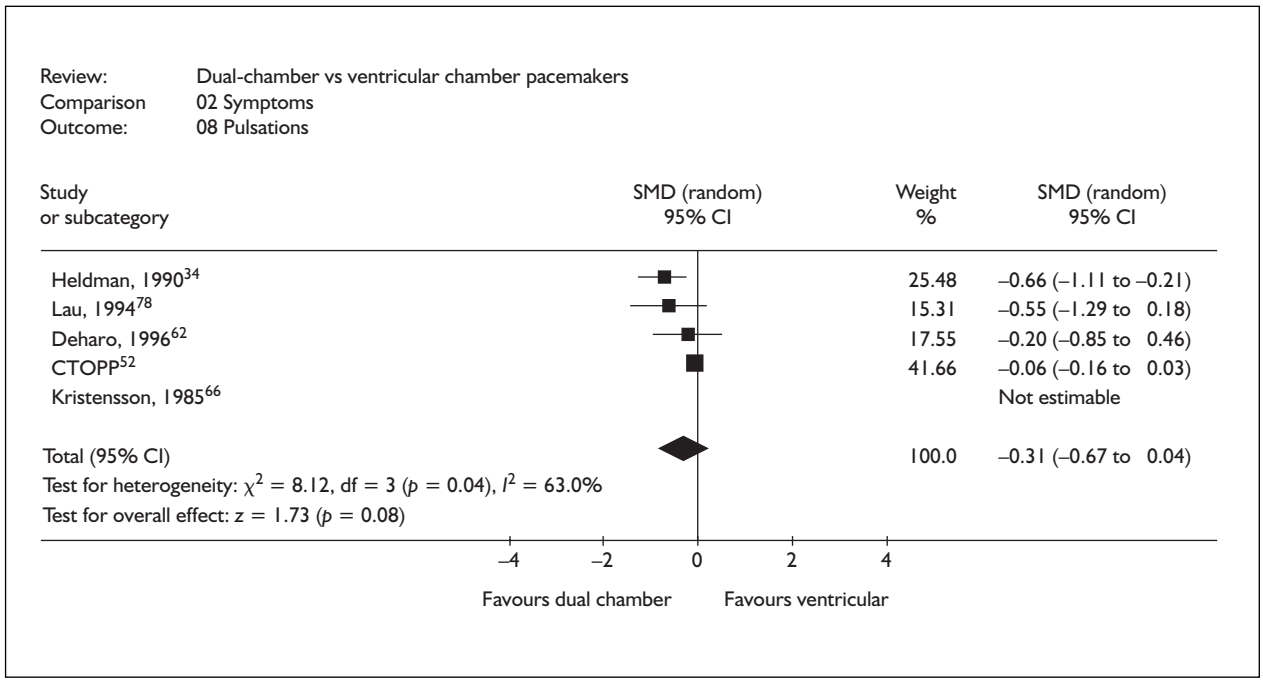

FIGURE 45 *Meta-analysis of individual symptoms: pulsations*

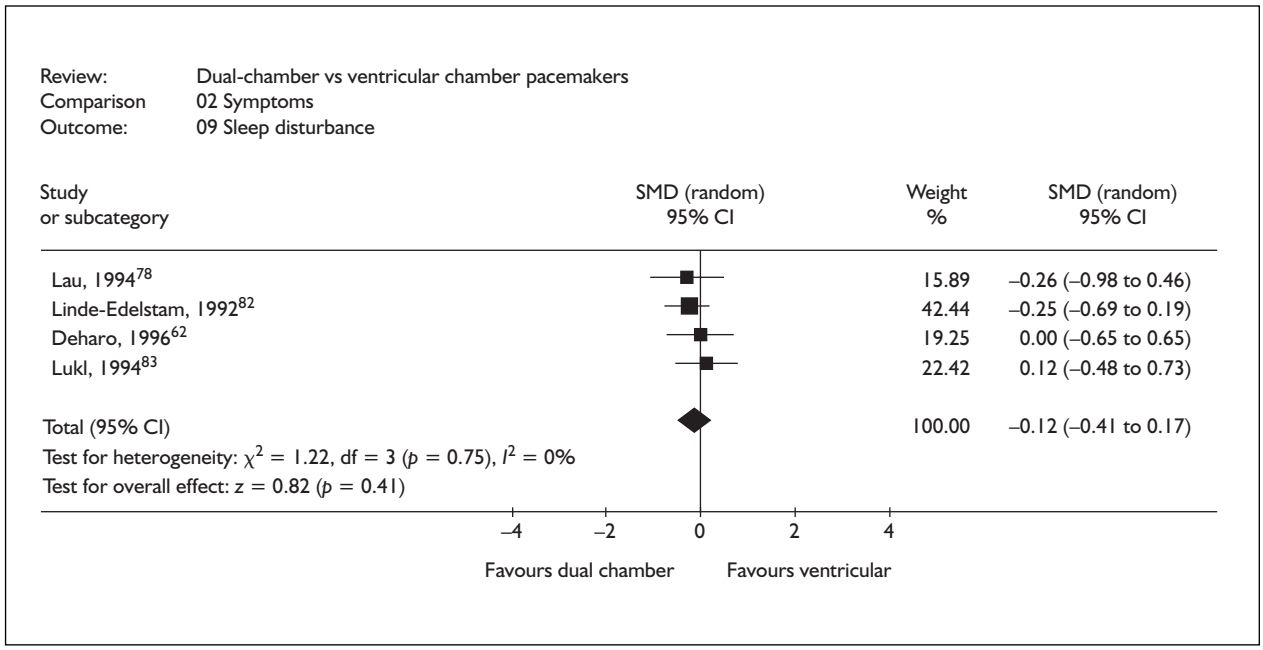

FIGURE 46 *Meta-analysis of individual symptoms: sleep disturbance*

Appendix 8

Data extraction sheets

Birmingham review

Authors:	Dretzke *et al.*[43]
Date:	2002
Type of study:	systematic review
Country:	UK
Period covered:	Clinical effectiveness: 1966 to 30 May 2001 Cost-effectiveness: 1966 to 12 July 2001
Intervention: permanent rate-adaptive or non-rate-adaptive dual-chamber pacemakers capable of sensing and pacing in both atrium and ventricle (codes DDD, DDDR, DDI, DDIR, VDD, VVDR)	
Comparator: permanent rate-adaptive or non-rate-adaptive single-chamber pacemakers capable of sensing and pacing either the ventricle or the atrium (VVI, VVIR, AAI, AAIR)	
Explicit clinical problem: addressing short- and long-term clinical and cost-effectiveness of dual versus ventricular pacing Biological rationale for the intervention: Rationale for review	
	Searching: information sources for clinical effectiveness: 1966 to 30 May 2001 (MEDLINE-OVID), 1993 to 19 February 2001 (Systematic Reviews, MEDLINE), 1980 to 30 May 2001 (EMBASE–OVID), 1980 to 30 May 2001 (Science Citation Index – Web of Science). Cochrane Controlled Trial Register (2001, Issue 2) Cost-effectiveness: 1966 to 12 July 2001 (MEDLINE–OVID) 1980 to 19 July 2001 (EMBASE–OVID), 1980 to 12 May 2001 (Science Citation Index – Web of Science) Other sources searched were: NNR, MRC-funded projects, UK Department of Health Research, British Heart Foundation, clinicaltrials.gov, www.controlled-trials.com, www.CentrWatch.com, UK Pacing Society and AHA, patients' sites and manufacturers' sites were searched using 'pacemaker(s)' and 'pacing' Any restrictions: atrial pacing compared to ventricular pacing was not investigated
	Inclusion criteria: studies were assessed by the main author, with 10% random sample of the potentially relevant studies checked for inclusion/exclusion by the information scientist. A weighted kappa score was calculated ($\kappa = 0.66$) with disagreement resolved by a third party
	Exclusion criteria: studies with pacing for less than 48 hours
	Data abstraction: data extraction form provided. The form was piloted on a subsample of studies; data were extracted by one reviewer and a 10% subsample was extracted independently by another reviewer
Definition of population	Individuals aged 18 years or older, with SSS, AV (any, total), third degree AVB, SSS+AVB, other diagnoses
Definition of main outcomes	Cardiovascular mortality, symptoms of pacemaker syndrome (as defined by the author of the trial) onset of AF, stroke, thromboembolic events, heart failure Patients' related QoL, including measurement of psychological/mental functioning, social functioning, physical status including ability to undertake everyday activities, symptoms caused by disease or treatment Exercise assessment, measurement of exercise duration or walking distance Complication rates, including device complications severe enough to warrant an additional visit to the hospital, surgical procedure or reimplantation of pacemaker
Definition of study design	RCTs of parallel or cross-over design
Validity assessment	Masked conditions: not stated **Quality assessment**: checklist based on Jadad Scale, including method of randomisation, concealment, blinding, completeness and ITT.

continued

	Added criteria: time of assessment of outcomes; for parallel trials, mode or device randomisation, comparability of study arms throughout the trial, adequacy of statistical power; for cross-over trials, washout periods (not included in effect estimate), period effect tests and unscheduled cross-over rates Findings: the recommendation for the preferential use of dual-chamber pacemakers over single-chamber pacemakers for AVB and SSS is borderline. While evidence is of a variable nature in terms of quality and effectiveness, there is a trend towards greater effectiveness in dual pacing, which supports the current BPEG guidelines for AVB
Principal measures of effect used	Odds ratios were used for binary data and standardised mean differences for continuous outcomes. Two-sided confidence intervals were calculated with 95% confidence
Quantitative data synthesis/methods of combining results	Summaries of results tabulated by study and outcome type; description of direction of effect (vote counting) and where data were available, pooling with fixed-effect meta-analysis
Handling of missing data	Not stated
Test of statistical heterogeneity	Statement of data homogeneity, with χ^2 statistic presented for each pooled estimate
Rationale for a priori sensitivity and subgroup analyses	Not stated
Assessment of publication bias	Yes

MRC, Medical Research Council.

Results, trial flow	
Total number of hits	1813
Total number of references (excluding duplicates)	1098
Excluded because non-relevant	875
Remaining studies for potential inclusion	223
Excluded, non-randomised	63
Excluded, non-relevant outcome	102
Excluded, non-relevant indication	21
Excluded, pacing period <48 hours	50
Excluded, after translation	3
Excluded, unobtainable	3
Included studies identified after review	1
Total studies included	30
Studies included: RCTs	4
Studies included: cross-over trials	26

Studies included, parallel trials	Intervention and comparator	Indication for pacing	No. of participants	Outcomes measured	Length of follow-up	Quality score (Jadad score, 0 low, 5 high)
Connolly, 2000[52]	Physiological (DDDR +AAIR) vs ventricular (VVIR)	SSS, AV or both	2568 (1094 physiological, 1474 ventricular)	AF, mortality, stroke, heart failure, QoL, complications	36 months (range 24–60)	1
Lamas, 1998[35]	Dual chamber (DDDR) vs ventricular (VVIR)	SSS or AV	407 (203 dual, 204 ventricular)	AF, stroke, mortality, heart failure, pacemaker syndrome, QoL	18.3 months average (range 7.2–33.2)	1
Mattioli, 1998[46]	Physiological (DDD, VDD, AAI) vs ventricular (VVI, VVIR)	SSS or AV	210 (105 physiological, 105 ventricular)	AF, stroke	24 months	2
Wharton, 1998[47]	Dual chamber (DDIR) vs ventricular (VVIR)	SSS (with brady–tachy syndrome)	198 (100 dual, 98 ventricular)	AF, stroke, mortality, heart failure, pacemaker syndrome, QoL	23.7 months (median)	1

Studies included, cross-over studies	Intervention and comparator	Indication for pacing	No. of participants	Outcomes measured	Length of follow-up	Jadad score (0 low, 5 high)
Avery, 1994[58]	Dual chamber (DDD) vs ventricular (VVI)	AVB	13	Pacemaker syndrome, walking distance	1 month	4
Boon, 1987[81]	Dual chamber (DDD) vs ventricular (VVI)	SSS or AVB	15	Pacemaker syndrome	4 weeks	2
Capucci, 1993[59]	Dual chamber (DDD, DDDR) vs ventricular (VVI)	SSS, AVB or both	14	Pacemaker syndrome, exercise	1 month	2
Channon, 1994[60]	Dual chamber (DDD) vs ventricular (VVI)	AVB	16	Pacemaker syndrome, walking distance	7 days	4
Davis, 1985[61]	Dual chamber (VDD) vs ventricular (VVI)	AVB	14	Pacemaker syndrome, exercise	3 weeks	4
Deharo, 1996[62]	Dual chamber (DDD) vs ventricular (VVIR)	AVB	18	Pacemaker syndrome, exercise	1 month	2
Hargreaves, 1995[63]	Dual chamber (DDD) vs ventricular (VVIR)	AVB	20	Pacemaker syndrome, walking distance	2 weeks	2
Heldman, 1990[34]	Dual chamber (DDD, DDI) vs ventricular (VVI)	SSS, AVB or both	40	Pacemaker syndrome	1 week	2

continued

Studies included, cross-over studies	Intervention and comparator	Indication for pacing	No. of participants	Outcomes measured	Length of follow-up	Jadad score (0 low, 5 high)
Kamalvand, 1997[64]	Dual chamber (DDDR and DDDR with mode switch) vs ventricular (VVIR)	SSS, AVB or both	48	Pacemaker syndrome, exercise	4 weeks	2
Kenny, 1986[65]	Dual chamber (DDD) vs ventricular (VVI)	SSS, AVB or both	10	Pacemaker syndrome	1 month	4
Kristensson, 1985[66]	Dual chamber (VDD) vs ventricular (VVI)	AVB	44	Pacemaker syndrome	3 weeks	4
Lau, 1994 (1)[78]	Dual chamber (DDDR) vs atrial (AAIR) and ventricular (VVIR)	SSS	15	Pacemaker syndrome, QoL	4 weeks	2
Lau, 1994 (2)[79]	Dual chamber (DDD, DDDR) vs ventricular (VVI)	SSS or AVB	33	Pacemaker syndrome, QoL	8 weeks	2
Linde-Edelstam, 1992 (1)[82]	Dual chamber (DDD) vs ventricular (VVIR)	AVB	17	Pacemaker syndrome, QoL	2 months	2
Linde-Edelstam, 1992 (2)[67]	Dual chamber (DDD) vs ventricular (VVIR)	AVB	17	Exercise	2 months	4
Lukl, 1994[83]	Dual chamber (DDD) vs ventricular (VVIR)	SSS or AVB	21	Pacemaker syndrome, QoL	2 weeks	4
Menozzi, 1990[68]	Dual chamber (DDD) vs ventricular (VVIR)	AVB	14	Pacemaker syndrome	6 weeks	4
Mitsuoka, 1988[69]	Dual chamber (DDD) vs ventricular (VVI)	SSS or AVB	16	Pacemaker syndrome	1 month	4
Oldroyd, 1991[70]	Dual chamber (DDD) vs ventricular (VVIR)	AVB	10	Pacemaker syndrome, exercise	1 month	2
Perrins, 1983[71]	Dual chamber (VDD) vs ventricular (VVI)	AVB	13	Pacemaker syndrome	1 month	4
Rediker, 1988[72]	Dual chamber (DDD) vs ventricular (VVI)	SSS or AVB	19	Pacemaker syndrome, exercise	6 weeks	2
Saner, 1996[73]	Dual chamber (DDD) vs ventricular (VVIR)	SSS or AVB	12	Pacemaker syndrome, exercise	6 weeks	2
Sulke, 1994[76]	Dual chamber (DDDR) vs ventricular (VVIR)	AVB or SSS and AVB	10	Pacemaker syndrome	4 weeks	2
Sulke, 1992[75]	Dual chamber (DDD) vs ventricular (VVI)	AVB or SSS and AVB	16	Pacemaker syndrome, exercise	4 weeks	4

continued

Studies included, cross-over studies	Intervention and comparator	Indication for pacing	No. of participants	Outcomes measured	Length of follow-up	Jadad score (0 low, 5 high)
Sulke, 1991[74]	Dual chamber (DDD, DDIR, DDDR) vs ventricular (VVI)	AVB or SSS and AVB	22	Pacemaker syndrome, exercise	4 weeks	4
Yee, 1984[77]	Dual chamber (VDD) vs ventricular (VVI)	AVB	8	Pacemaker syndrome, exercise	3 months	2

Results

Parallel studies	DCP	SCP	*p*-Value	Source
Pacemaker syndrome	0/203	53/204 (26%)	<0.0001	Lamas, 1998[35]
	0/100	27/98 (27.6%)	<0.0001	Wharton, 1998[47]
Pacemaker syndrome, pooled OR (95% CI)	0/303 0.10 (0.06 to 0.16)	80/302	<0.00001	Dretzke, 2002[43]
AF	58/1094 5.30% (annual rate)	97/1474 6.60% (annual rate)	Significant reduction in RR 18% (0.3 to 32.6%), $p = 0.05$	Connolly, 2000[52]
	35/203	38/204	0.08	Lamas, 1998[35]
	48/100 (tachyarrhythmia)	42/98 (tachyarrythmia)	0.09	Wharton, 1998[47]
AF in SSS patients	17/90	24/85	0.06	Lamas, 1998[35]
	0% (12 months) 3.5% (24 months)	7% (12 months) 20% (24 months)	<0.05, ns SSS vs AV	Mattioli, 1998[46]
AF in AVB group	16/99	11/102	0.26	Lamas, 1998[35]
AVB, pooled OR (95% CI)	141/1397 0.90 (0.7 to 1.15)	177/1776	0.08	Dretzke, 2002[43]
Stroke	11/1094 1% (annual rate)	16/1474 1.1% (annual rate)	ns	Connolly, 2000[52]
	3/203	5/204	ns	Lamas, 1998[35]
	10/105	19/105	<0.05	Mattioli, 1998[46]
Stroke in SSS patients	1/90	2/85	ns	Lamas, 1998[35]
Stroke in AVB group	1/99	3/102	ns	Lamas, 1998[35]
Stroke, pooled OR (95% CI)	24/1402 0.66 (0.39 to 1.12)	40/1783	0.17	Dretzke, 2002[43]
Heart failure	34/1094 3.1% (annual rate)	52/1474 3.50%	Reduction in RR 7.9% (18.5 to 28.3%), $p = 0.52$	Connolly, 2000[52]
	9/203	17/204	ns	Lamas, 1998[35]
HF in SSS patients	6/90	7/85	ns	Lamas, 1998[35]

continued

Parallel studies	DCP	SCP	*p*-Value	Source
HF in AV group	3/99	9/102	ns	Lamas, 1998[35]
HF, pooled OR (95% CI)	43/1297 0.78 (0.53 to 1.14)	69/1678	 0.2	Dretzke, 2002[43]
Mortality, all causes	69/1094 6.3% (annual rate)	97/1474 6.6% (annual rate)	Reduction in RR 9.4% (–10.5 to 25.7%), $p = 0.3392$	Connolly, 2000[52]
	32/203	34/204	0.95	Lamas, 1998[35]
Mortality in paced population	3/100	6/98	0.007	Wharton, 1998[47]
Mortality in SSS patients	11/90	17/85	0.09	Lamas, 1998[35]
Mortality in AVB group	17/99	15/102	0.41	Lamas, 1998[35]
Cardiovascular mortality and stroke combined	4.9% (annual rate)	5.5% (annual rate)	Reduction in RR 9.4% (–10.5 to 25.7%), $p = 0.33$	Connolly, 2000[52]
Mortality, all cause, pooled OR (95% CI)	104/1397 0.93 (0.71 to1.21)	137/1776	 0.4	Dretzke, 2002[43]

DCP, dual-chamber pacing; SCP, single-chamber pacing; HF, heart failure.

Cross-over studies	DCP, mean (SD)	*n*	SCP, mean (SD)	*n*	SMD	(95% CI)	Source
Pacemaker syndrome	19 (5)	13	28 (10)	13	–1.1	(–1.94 to –0.27)	Avery, 1994[58]
	4.73 (4.4)	16	9.4 (5.67)	16	–0.9	(–1.63 to –0.17)	Channon, 1994[60]
	2.9 (3.85)	20	5.2 (3.85)	20	–0.59	(–1.22 to 0.05)	Hargreaves, 1995[63]
	7.3 (12.4)	40	29 (26.1)	40	–1.05	(–1.52 to –0.58)	Heldman, 1990[34]
	22.3 (12.2)	48	26.8 (15.3)	48	–0.32	(–0.73 to 0.08)	Kamalvand, 1997[64]
	2.7 (1.6)	12	5.7 (3.2)	12	–1.14	(–2.02 to –0.27)	Saner, 1996[73]
	14.4 (8.1)	22	23.5 (11.5)	22	–0.9	(–1.52 to –0.28)	Sulke, 1991[74]
	10.5 (5.5)	10	23.7 (9.8)	10	–1.59	(–2.63 to –0.56)	Sulke, 1994[76]
	–46.9 (8.9)	8	–50.1 (8.4)	8	0.35	(–0.64 to 1.34)	Yee, 1984[77]
Pacemaker syndrome, pooled		189		189	–0.74 ($p < 0.0001$)	(–0.95 to –0,52)	Dretzke, 2002[43]
Exercise capacity	–360 (65)	13	–327 (69)	13	–0.48	(–1.26 to 0.3)	Avery, 1994[58]
	–18.7 (15.8)	16	–16.43 (22.72)	16	–0.11	(–0.81 to 0.58)	Channon, 1994[60]
	–8.4 (3)	14	–7.2 (3)	14	–0.39	(–1.14 to 0.36)	Davis, 1985[61]
	–10 (3.6)	18	–10 (3.8)	18	0.00	(–0.65 to 0.65)	Deharo, 1996[62]
	–20 (4.47)	20	–19 (4.47)	20	–0.22	(–0.84 to 0.4)	Hargreaves, 1995[63]
	–7.6 (3.6)	48	–7 (3.8)	48	–0.16	(–0.56 to 0.24)	Kamalvand, 1997[64]
	–8.15 (1.68)	10	–7.95 (1.64)	10	–0.12	(–0.99 to 0.76)	Oldroyd, 1991[70]
	–11.3 (3.7)	19	–10.1 (3.7)	19	–0.32	(–0.96 to 0.32)	Rediker, 1988[72]
	–15.83 (6.45)	12	–12.55 (5.82)	12	–0.52	(–1.33 to 0.30)	Saner, 1996[73]
	–6.9 (3.1)	8	–5.3 (2.9)	8	–0.50	(–1.5 to 0.5)	Yee, 1984[77]
Exercise capacity, pooled		178		178	–0.24 ($p = 0.02$)	(–0.45 to –0.03)	Dretzke, 2002[43]

SMD, standardised mean difference.

Subgroup analysis reported in cross-over trials	SSS group			AVB group			Source
Mean symptoms score (SD), higher score implies improvement	**DCP**	**SCP**	**Significance**	**DCP**	**SCP**	**Significance**	
Shortness of breath	3.37 (0.74)	2 (1.06)	ns	3.5 (0.75)	1.87 (0.64)	$p < 0.05$	Mitsuoka, 1998[69]
General well-being	3.25 (0.7)	2 (0.75)	$p < 0.05$	3.5 (0.92)	2.12 (0.64)	$p < 0.05$	
Palpitations	3.6 (0.91)	2.12 (0.38)	$p < 0.05$	2.87 (0.35)	2.75 (0.88)	ns	
Dizziness	3.25 (0.46)	2.5 (0.53)	ns	3.12 (0.35)	2.75 (0.46)	ns	
Chest pain	3.12 (0.35)	2.75 (0.46)	ns	2.62 (0.74)	3.37 (1.3)	ns	
Attacks per week of:							
Palpitations	0.12 (0.35)	5.6 (9.68)	$p < 0.05$	0.53 (1.08)	1.71 (3.48)	ns	
Dizziness	0.59 (1.25)	0.62 (0.65)	ns	0.15 (0.29)	0.37 (0.74)	ns	
Chest pain	0.68 (1.38)	1.25 (2.29)	ns	2.5 (4.68)	1.68 (2.77)	ns	
Patients with symptoms, % Symptom questionnaire: 16 scored items (0 = no symptoms, 10 = worst symptoms)	No results reported	38% (no/mild symptoms) 62% (moderate/severe) ns		No results reported	36% (mild/no symptoms) 64% (moderate/severe) ns		Heldman, 1990[34]

Complication rates	DCP	SCP	*p*-Value	Source
Any perioperative complication	9.0%	3.8%	<0.001	Connolly, 2000[52]
Pneumothorax	1.8%	1.4%	0.42	
Haemorrhage	0.2%	0.4%	0.32	
Inadequate pacing	1.3%	0.3%	0.002	
Inadequate sensing	2.2%	0.5%	<0.001	
Device malfunctioning	0.2%	0.1%	0.4	
Lead dislodgement	4.2%	1.4%	<0.001	

Quality of life: parallel and cross-over studies	Population size (*n*)	Statistically significant improvement in QoL in dual mode	No significant difference in QoL in either dual or single mode	Comments by the authors	Source
VVIR vs DDDR	407	Mental health at 9 months; cardiovascular functional status at 18 months	All QoL items at 3 months, 8/9 items at 9 and 18 months	Assessed by 8-item SF-36 and SAS for cardiovascular assessment	Lamas, 1998[35]
VVIR vs DDDR	33	4/5 items of physical malaise questionnaire, 3/4 items QoL, total score for QoL, 4/5 items illness perception	1/4 item of QoL and 1/5 items each of physical malaise and illness perception	Assessed by physical malaise questionnaire, QoL and illness perception questionnaire; papers report significantly different items only	Lau, 1994 (2)[79]
VVIR vs DDD		1/4 items QoL and total score for QoL, 1/5 items illness perception	All items of physical malaise, 4/5 items of illness perception and 3/4 items of QoL		
	21	12/19 items	7/19 items	19 items of the QoL questionnaire	Lukl, 1994[83]
	17	4/4 items cardiovascular symptomatology, 1/3 cognitive functioning	2/2 items of sleep disturbance, physical and social functioning, self-perceived health status; 2/3 cognitive functioning, 1/1 depressive score, 3/3 mood states	7 sets of items assessed: cardiovascular symptomatology, sleep disturbance, cognitive functioning, physical and social functioning, depressive score, mood states, self-perceived health status	Linde-Edelstam, 1992 (1)[82]
VVIR vs DDDR	15	1/1 of general well-being, 1/6 incidence and frequency of symptoms, 1/11 psychologist's assessment	5/6 incidence and frequency of symptoms, 1/1 cardiovascular functional status, 10/11 psychologist's assessment	DDDR, AAIR, VVIR modes compared. 4 sets of items assessed, including general well-being, incidence and frequency of symptoms, cardiovascular functional status, psychologist's assessment	Lau, 1994 (1)[78]
AAIR vs DDDR			1/1 general well-being, 6/6 incidence and frequency of symptoms, 1/1 cardiovascular functional status, 11/11 psychologist's assessment		Lau, 1994 (1)[78]

Randomised controlled trials

MOST

MOST: Lamas et al. *(2002)*[48]

Acronym	**MOST**	**Inclusion criteria:**
Authors:	Lamas *et al.*	Age ≥ 21 years
Date	2002	First implant of dual-chamber pacemaker
		Clinical diagnosis of SSS
Type of study:	parallel RCT	Indications for pacing, including one or more of:
Country:	USA and Canada	Symptomatic SSS with documented sinus pause >3 s; asymptomatic sinus pause >5 s
No. of centres:	91	Chronic sinus bradycardia with rates <50 bpm, inability to increase rate above 80 bpm on exercise, symptoms of fatigue or dyspnoea on exertion referable to chronotropic incompetence
Protocol presented in separate publication:	Lamas *et al.*, 2000	Sinus bradycardia with a rate <50 bpm restricting use of long-term medications for angina, hypertension or supraventricular tachyarrhythmia
Recruitment period:	25 September 1995 to 13 October 1999	Sinus mechanism or standstill at time of implant
Follow-up period:	5 years (end 31 January 2001)	Pacemaker being implanted with endocardial approach
Average follow-up: 33.1 months, with follow-up evaluation four times during the first year and twice a year from the second year. QoL assessment was done at months 3 and 12, and once a year from the second year		Informed consent
		Exclusion criteria:
		Inadequate acute atrial endocardial capture or sensing threshold, with P-wave amplitude <1.5 mV or atrial capture threshold >2.5 V at 0.5 pulse amplitude
		Documented chronic AF without sinus mechanism for longer than 6 months
		Clinically overt congestive heart failure
		Malignancy expected to limit patients' life expectancy
		Patients with serious concurrent illness (determined by investigator)
		Severe psychiatric illness (Mini-mental score of <17)

Intervention:	dual chamber modulated	**Primary and secondary outcomes:**	**Outcome measurement:**
Comparison:	ventricular modulated	All-cause and cardiovascular mortality	First occurrence of all-cause mortality and non-fatal stroke
Pacing indications:	SSS	Occurrence of death, stroke and heart failure	All-cause mortality
No. of patients:	2010	Occurrence of AF	Rate of non-fatal stroke
Intervention:	1014	Pacemaker syndrome	Mortality for cardiovascular causes
Comparison:	996	Quality of life	Incidence of AF (ECG)
			SAS
			SF-36 and summary scores for physical and mental component
			TTO utility score and VAS
			Changes in Minnesota Living with Heart Failure score
			Hospitalisation for heart failure

Diagnostic criteria	Definition of retrograde activation: recording of blood pressure while the patient is in sinus rhythm or atrially paced and in ventricular pacing; presence or absence of retrograde activation is recorded at heart rates of 70 and 100 bpm
	Definition of pacemaker syndrome: fulfilment of either (a) retrograde P waves present on ECG or atrial endocardial electrocardiography AND one symptom among dyspnoea at rest or on mild exertion, orthopnoea, paroxysmal nocturnal dyspnoea; AND the new occurrence of at least one symptom among jugular venous pressure >8 cm at 30°, rales to the inferior border of the scapula or greater than 1+ pedal oedema; and (b) reduction of systolic blood pressure when standing >20 mmHg with VVIR compared to atrial pacing or sinus mechanism AND a new occurrence of at least one symptom among dizziness, weakness, presyncope, syncope reproducible with ventricular pacing

continued

	Hospitalisation for heart failure defined as need for supplemental oxygen, repeated doses of intravenous diuretics, intravenous pressors or inotropes, poor response to more conservative outpatient therapy. Subsequent hospitalisations for heart failure were defined by a primary DRG code for heart failure for each hospitalisation
Characteristics of programming provided?	Patients receive same device? Each centre selects appropriate/available type of PM provided functions are similar
	Lower rate: ≥ 60; upper rate: ≥ 110 (120–140 in protocol)
	Other programming features: NA

TTO, time trade-off; DRG, Diagnostic Resource Group.

MOST (Lamas): Results

Patients' baseline characteristics	Intervention		Comparison		*p*-Value
	n = 1014	%	*n* = 996	%	
Age (years) (median, IQR)	74	(67–80)	74	(68–80)	0.58
Gender (female)	478	47%	477	48%	0.74
Race (non-white)	162	16%	144	14%	0.34
Hypertension	640	63%	608	61%	0.34
Cholesterolaemia	376	37%	340	34%	0.17
Smokers (current)	84	8%	85	9%	0.87
Prior MI	279	28%	243	24%	0.11
Prior heart failure	221	22%	183	18%	0.05
NYHA class I or II heart failure	822	81%	841	84%	0.05
Cardiomyopathy	133	13%	106	11%	0.09
Prior stroke	116	11%	108	11%	0.67
Diabetes	246	24%	204	20%	0.04
COPD	109	11%	109	11%	0.89
PTCA	131	13%	119	12%	0.05
CABG	222	22%	215	22%	0.87
Other cardiac surgery	83	8%	88	9%	0.63
Cardioverter defibrillator	13	1%	6	1%	0.17
Any supraventricular tachycardia	545	54%	514	52%	0.34
AF	477	47%	440	44%	0.2
Other atrial tachycardia	94	9%	92	9%	0.99
Any AVB	204	20%	209	21%	0.62
Complete heart block	39	4%	52	5%	0.16
Second degree heart block	72	7%	62	6%	0.48
Prolonged AV interval	101	10%	102	10%	0.83
Other heart block	25	2%	23	2%	0.88
Vasovagal syndrome	28	3%	33	3%	0.52
Ventricular tachycardia, ventricular fibrillation	42	4%	24	2%	0.03

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PTCA, percutaneous transluminal coronary angioplasty.

Clinical end-points	Intervention (n = 1014)	Comparison (n = 996)	Unadjusted HR (95% CI)	p-Value
Death or stroke	21.50%	23%	0.93 (0.78 to 1.13)	0.48
Combined all-cause death, first non-fatal stroke, first hospitalisation	27.60%	29.90%	0.9 (0.77 to 1.06)	0.23
Death	19.70%	20.50%	0.97 (0.8 to 1.18)	0.78
Stroke	4%	4.90%	0.82 (0.54 to 1.25)	0.36
Cardiovascular death	8.50%	9.20%	0.93 (0.69 to 1.24)	0.61
Hospitalisation from heart failure	10.30%	12.30%	0.82 (0.63 to 1.06)	0.13
AF	21.40%	27.10%	0.79 (0.66 to 0.94)	0.008
			Adjusted HR (95% CI)	
Death or stroke			0.91 (0.75 to 1.1)	0.32
Combined all-cause death, first non-fatal stroke, first hospitalisation			0.85 (0.72 to 1.0)	0.05
Death			0.95 (0.78 to 1.16)	0.64
Stroke			0.81 (0.54 to 1.23)	0.33
Cardiovascular death			0.87 (0.65 to 1.18)	0.37
Hospitalisation from heart failure			0.73 (0.56 to 0.95)	0.02
AF			0.77 (0.64 to 0.92)	0.004
Combined all-cause death, first non-fatal stroke, first hospitalisation by subgroup				
Men (n = 1055)			0.91 (0.73 to 1.15)	
Women (n = 955)			0.89 (0.71 to 1.13)	
≥75 years (n = 987)			0.97 (0.79 to 1.21)	
<75 years (n = 1023)			0.83 (0.65 to 1.07)	
White (n = 1704)			0.88 (0.73 to 1.05)	
Non-white (n = 306)			1 (0.68 to 1.46)	
History of supraventricular tachycardia (n = 1059)			0.92 (0.74 to 1.14)	
No history of supraventricular tachycardia (n = 951)			0.88 (0.69 to 1.13)	

No. of patients with VVIR switching to DDDR	**313 (31.4%)**
Mean time to cross-over	58 days
Reasons:	
Severe pacemaker syndrome requiring reprogramming	182
Patients meeting pacemaker syndrome definition	113
Refractory heart failure	39
Chronotropic incompetence	27
Physician preference or refusal	22
Supraventricular arrhythmia	19
Possible pacemaker syndrome	8
Patient's refusal	4
Rate response causing angina	2
Vasovagal syndrome	2
Programming error	1
Recurrent syncope	1
Unknown	6
Complications (summarised in this paper and reported in Sweeney, 2003[56])	
Occurrence of complications (total)	4.80%
Dislodgement or failure of atrial lead	1.80%
Pneumothorax	1.50%
Complications of left ventricular lead	1.10%

Quality of life	Intervention at baseline, intervention changes							
Changes in QoL from baseline	**Baseline**	**Month 3**	**Month 12**	**Month 24**	**Month 36**	**Month 48**		
Physical function	58.9	4.3	1.8	0.7	–0.7	–0.1		
Physical role	34.6	25.5	27.7	28.4	32.7	26.7		
Social function	62.6	9.1	9.3	6.3	7.8	9.8		
Energy	42.6	11.6	9.3	7.1	8.3	5.2		
Mental health	72	2.8	3.1	3.2	5.6	4.6		
Emotional role	74	6.9	9.1	9.2	11.4	12.3		
Pain	67.0	4.4	3.7	2.4	4.6	5.1		
Health perception	60.2	1.9	–0.2	3.1	–3.1	–2.5		
Mental component summary	48.4	2.6	2.8	2.3	3.6	3.5		
Physical component summary	38.4	3.7	2.7	2	2.3	2.2		
Specific activity scale	1.97	–0.06	0.02	0.05	0.11	0.13		
TTO utility	72	8	8	7	8	6		
		Comparison at baseline, comparison changes					**Difference in change from baseline between DDD and VVIR**	***p*-Value**
Changes in QoL from baseline		**Month 3**	**Month 12**	**Month 24**	**Month 36**	**Month 48**		
Physical function	58.8	1.9	0.5	–1.7	–2.9	–3.2	1.9	0.04
Physical role	35.7	17.8	21.5	17.1	17.1	18	8.6	<0.01
Social function	63.5	6.3	6.7	4.3	4.3	6.4	2.5	<0.01
Energy	41.9	7.1	6.3	4	1.7	3.6	4.1	<0.01
Mental health	72	2.2	1.7	1.6	1.6	4.7	1.2	0.05
Emotional role	74	5	4.6	4.3	4.7	4.8	3.6	<0.01
Pain	67.5	4.2	3.3	0.4	3.5	6.9	0.5	0.57
Health perception	60	0	–0.8	–3.4	–3.4	–3.5	1.1	0.09
Mental component summary	48.4	1.8	1.5	1.4	1.4	2.4	1.1	<0.01
Physical component summary	38.5	2.2	2.1	0.6	0.7	1	1.2	<0.01
Specific activity scale	2.01	–0.04	0	0.03	0.04	0.16	0.002	0.94
TTO utility	73	7	5	4	4	6	2	0.06

MOST (Lamas): methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	Enrolment and selection process not described. Patients were included if eligible for dual-chamber pacing. Patients excluded at the discretion of the investigator were not described. No information on consecutive enrolment
Unit of randomisation	Patient
Randomisation method	After atrial and ventricular placement, patients were randomised by calling a 24-hour randomisation line. Stratified by history of stroke and clinical site. Randomisation of programming
Randomisation results	Trial arms differed in prior heart failure (higher in DDDR), NYHA class I or II heart failure (higher in VVIR), diabetes (higher in DDDR) and ventricular tachycardia or ventricular fibrillation (higher in DDDR); the analysis was subsequently adjusted for prior MI (non-significantly higher in DDDR), any supraventricular tachycardia (non-significantly higher in DDDR), prior heart failure and diabetes (significantly higher in DDDR)
Blinding method	Patients were blinded, but not investigators. Prognostic characteristics of patients were determined by investigators (not blinded). Actions were taken to blind measurement of some outcomes, i.e. cause of death, suspected strokes, first hospitalisation for heart failure were classified by a blinded clinical events committee. Subsequent hospitalisations for heart failure were classified by ICD codes. Recording of retrograde activation was done immediately after randomisation with the physician blinded to results (methods not detailed). An ECG core laboratory reviewed and confirmed cases of AF diagnosed by investigators (concordance not reported)
ITT	States yes. Results are presented as hazard functions with decreasing population at risk. A randomly selected subsample of 1400 patients was planned for the QoL study at a protocol stage, but there is no further detail on the actual number of patients included and surveyed.
Power calculation	The trial was powered on detection of effect in primary end-point (first non-fatal stroke and death), overall and by age and gender, changes in the physical and health perception components of the SF-36 and the SAS, total and cardiovascular death. Based on an expected 11.9% occurrence of death and non-fatal stroke, the trial was designed to have 90% power to detect 25% reduction in primary end-point, and 80% power to detect 30% difference in the subgroup analyses based on age and gender. For secondary end-points, the trial was powered to detect a 6-point difference in physical functioning, 5-point difference in health perception and 0.2-point difference in SAS with 90% confidence. Based on expected death rate of 8.4% in control group, the trial was powered to detect 25% difference in mortality between groups with 80% confidence
Data analysis	For baseline values, Fisher exact tests for categorical variables present in less than 10% of patients, likelihood ratio χ^2 test for others; continuous variables Wilcoxon sum-rank test. All tests were two-tailed. Kaplan–Mayer methods used for cumulative event rates, with differences between treatment groups assessed with log-rank test. Relative risk expressed as HR (95% CI). Supplemental analyses with Cox proportional hazard models were adjusted for patients' characteristics at baseline. Heart failure scores were tested with Wilcoxon sum-rank test. ANOVA was used for SF-36 summary scores, utilities and SAS. Generalised model adjusted for dependence across time-points (unstructured correlation matrix) and with age, group, gender and QoL at baseline. For patients who crossed over to DDDR, LOCF before cross-over was used for QoL
Adjustment by centre	No
Loss to follow-up	None declared

continued

Generalisability	Selected sample? Yes Complete description of baseline sample/patients characteristics provided? Yes Evidence of unequal non-intervention treatment? Data not provided Subgroup analysis? Gender (HR favours dual chamber, 0.89 females, 0.91 males), age (HR favours dual chamber, ≥ 75 years 0.97, < 75 years 0.83), race (HR favours dual-chamber white 0.88, non-white 1), history of supraventricular tachycardia (HR favours dual chamber, with history 0.92, without history 0.88). All values were not statistically significant. Ancillary study on selected outcomes (heart failure and AF) on patients with normal baseline QRS complex
Main/secondary outcome measured independently	Partially
Conflict of interest	The study was funded by National Heart, Lung and Blood Institute, Medtronic, Guidant and St Jude Medical. Some authors have conflicts of interest (equity interest in M, G, SJM: Flaker; research support: Lamas, Ellenbogen, Freedman, Leon, Marinchak, Silverman, Sweeney; consulting: Greer, Lon; membership in speakers' bureau: Ellenbogen, Marinchak)

ICD, International Classification of Diseases; ANOVA, analysis of variance.

MOST: Sweeney et al. *(2003)*[56]

Acronym:	**MOST**	**Inclusion criteria:** Subsample of population from trial MOST #19 with baseline normal QRS complex. QRS was determined from 12-lead ECG at baseline, with normal QRS duration < 120 ms **Exclusion criteria:** Serious concurrent illness expected to affect longevity during trial Had not signed informed consent Clinically overt congestive heart failure Lacking adequate endocardial atrial and ventricular capture	
Authors:	Sweeney *et al*.		
Date:	2003		
Type of study:	ancillary analysis of MOST (protocol in Lamas, 2000[51])		
Country:	USA and Canada		
No. of centres:	91		
Recruitment period:	25 September 1995 to 13 October 1999		
Follow-up period:	6 years (end 31 January 2001)		
Average follow-up:	33.1 months, with follow-up evaluation four times during the first year and twice a year from the second year. QoL assessment was done at months 3 and 12, and once a year from the second year		
Intervention:	DDDR	**Primary and secondary outcomes:** Hospitalisation for heart failure and AF, defined and obtained from the primary study	**Outcome measurement:** Time to hospitalisation for heart failure Time to AF
Comparison:	VVIR		
Pacing indications:	SSS		
No. of patients:	1339		
Intervention:	707		
Comparison:	632		
Diagnostic criteria		Definition of retrograde activation: Definition of pacemaker syndrome: as in parent study Hospitalisation for heart failure: as in parent study	
Characteristics of programming provided?		Patients receive same device? Each centre selects appropriate/available type of PM provided functions are similar Lower rate: ≥ 60; upper rate: ≥ 110 Other programming features: NA	

Most (Sweeney): Results

Patients' baseline characteristics	Intervention		Comparison	
	***n* = 707**	**%**	***n* = 632**	**%**
Age (years) (median, IQR)	73 (66–79)		74 (67–80)	
Gender (male)	351	50%	308	49%
Prior MI	185	26%	133	21%
EF (median, IQR)	57 (50–62)		55 (50–63)	
Prior CHF	125	18%	100	16%
NYHA class I or II heart failure	580	83%	541	87%
PCI	93	13%	79	13%
CABG	131	19%	115	18%
Prior atrial tachycardia	399	56%	329	52%
AF	331	47%	254	40%
Other atrial tachycardia	142	20%	131	21%
Abnormal AV conduction		16%		20%
PR interval, ms (median, IQR)	180 (160–200)		190 (160–220)	

CHF, congestive heart failure.

Frequency of events by pacemaker dependency

No. of cases of heart failure by cumulative % time paced				
<10%	1/48	2%	7/97	7%
≥ 10–50%	10/110	9%	12/200	6%
>50–90%	16/188	9%	17/203	8%
>90%	44/361	12%	21/132	16%
Total	71/707	10%	57/632	9%
No. of cases of AF by cumulative % time paced				
<10%	8/49	16%	22/103	21%
≥ 10–50%	21/112	19%	44/191	23%
>50–90%	61/193	32%	63/215	29%
>90%	60/347	17%	22/123	18%
Total	150/701	21%	151/632	24%

Model end-point	Intervention		Comparison		*p*-Value
	n	%	*n*	%	
% cumulative time of ventricular pacing (median, IQR)		90% (57–99%)		58% (20–86%)	0.001
% individuals continuously ventricular paced (>90% time)		50%		20%	
% individuals infrequently ventricular paced (<10% time)		7%		15%	
Rates of hospitalisation for heart failure	71	10%	57	9%	
AF	150	21%	151	24%	
Risk of hospitalisation for heart failure by classes of time paced, compared to lower class of time paced					
	Intervention		**Comparison**		***p*-Value**
	HR	**(95% CI)**	**HR**	**(95% CI)**	
Up to 40% of time paced	1.54	(1.01 to 2.36)	0		0.0460
40–80% time paced	2.6	(1.05 to 6.47)			0.0400
>80% time paced			1.96	(1.39 to 2.77)	<0.0012
First HF >40% vs ≤40% unadjusted model	3.01	(1.12 to 7.46)			0.018
All HF >40% vs ≤40% unadjusted model	3.66	(1.44 to 9.3)			0.006
First HF, >40% vs ≤40% adjusted model	2.6	(1.05 to 6.47)			0.040
All HF >40% vs ≤40% adjusted model	2.99	(1.15 to 7.75)			0.024
First HF >80% vs ≤80% unadjusted model			3.13	(1.86 to 5.28)	0.0001
All HF >80% vs ≤80% unadjusted model			3.6	(1.93 to 6.7)	0.0001
First HF, >80% vs ≤80% adjusted model			2.5	(1.44 to 4.36)	0.0012
All HF >80% vs ≤80% adjusted model			2.56	(1.48 to 4.43)	0.0007
Risk of AF by classes of time paced, compared to lower class of time paced					
1% increase in cumulative % ventricle paced up to 85% (unadjusted)	1.018	(1.01 to 1.026)			0.0001
1% increase in cumulative % ventricle paced up to 85% (adjusted)	1.01	(1.002 to 1.018)			0.0120
1% increase in cumulative % ventricle paced up to 80% (adjusted)			1.008	(1.002 to 1.015)	0.0140
1% increase in cumulative % ventricle paced up to 80% (adjusted)			1.007	(1 to 1.014)	0.0390

MOST (Sweeney): methodological characteristics

Prospective	Unsure
Selection/consecutive enrolment	Patients from parent study were selected if they had baseline QRS values (1732/2010). This value was evaluated before implantation. Patients with normal QRS (<120 ms) were selected
Unit of randomisation	As in parent study
Randomisation method	As in parent study
Blinding method	As in parent study. Patients were selected after measurement of the relevant baseline characteristic (this was not a requisite for eligibility)
ITT	DAF was analysed for 701 of 707 patients in the DDD arm since they developed AF during implant
Power calculation	No information provided/NA
Data analysis	Cumulative time in ventricular pacing was compared between pacing modes with Wilcoxon sum-rank test. Cox proportional hazard model to assess time to heart failure hospitalisation and time to atrial fibrillation, with time to event as dependent variable and cumulative time of ventricular pacing as dependent covariate. Model of heart failure hospitalisation was extended to include multiple hospitalisation. The model was extended to include baseline values of prior heart failure, ejection fraction, arrhythmic therapy and Karnofsky scores. AF models were adjusted for prior AF, antiarrhythmic therapy, congestive heart failure, mitral regurgitation and AVB. The relationship between cum vP% and both end-points was estimated using a two-part linear spline function with the point of discontinuity chosen as to provide the best fit. The model was tested under an alternative hypothesis for truncation of data. Data from patients who crossed over were censored at the cross-over time. Per cent pacing groups were defined on the % time paced during the first 30 days (correlation to overall time paced $r = 0.76$). For the HFH, groups were defined by the points of change in the slope of the risk relation. In the AF, groups were defined as ≤ 40%, 40–70% and 70–90%
Adjustment by centre	No
Loss to follow-up	NA
Generalisability	Selected sample? Yes Complete description of baseline sample/patients' characteristics provided? No information on comparability at baseline, but the analysis was adjusted for some of the values Evidence of unequal non-intervention treatment? Data not provided Subgroup analysis? No
Main/secondary outcome measured independently	A clinical event committee blinded to pacing mode adjudicated first hospitalisation for heart failure; AF was confirmed by reading of ECG by a Core Laboratory blinded to pacing mode
Conflict of interest	Funded by the National Heart Lung and Blood Institute of the NIH

NIH, National Institutes of Health.

MOST: Glotzer et al. *(2003)*[54]

Acronym:	**MOST**	**Inclusion criteria:**
Authors:	Glotzer *et al*.	Patients with implanted ancillary study capable pacemakers
Date:	2003	Patients with at least one episode of spontaneous atrial arrhythmia (AHRE) longer than 5 minutes
Type of study:	ancillary study of MOST (RCT)	
Country:	USA and Canada	**Exclusion criteria:**
No. of centres:	91	

Recruitment period: not stated; 70% of patients were recruited concurrently with MOST patients, 30% in the 2 subsequent years

Follow-up period: median follow-up 27 months

Average follow-up: data were downloaded from pacemaker at months 1, 3 and 6 after enrolment, and every 6 months thereafter

Intervention:	DDDR	**Primary and secondary outcomes:**	**Outcome measurement:**
Comparison:	VVIR	Incidence of episodes of AF lasting for at least 5 minutes	Symptoms of AF: Symptoms Burden Index questionnaire, including ranking of palpitation, chest pain or tightness, shortness of breath, dizziness or light-headedness, nausea, sweating or perspiring, and tiredness or fatigue, on a scale from 1 (none) to 5 (incapacitating)
Pacing indications:	SSS	Symptoms of AF	
No. of patients:	312		
Patients with AHRE:	160		
Patients without AHRE:	152		

Diagnostic criteria:	Definition of AHRE (spontaneous atrial tachyarrhythmia, AF): atrial rate >220 bpm for 10 consecutive beats detected by pacemaker, and terminated after 20 spontaneous consecutive beats under the threshold Symptomatic patients were those reporting score of at least 3 on any one item of the Symptoms Burden Index
Characteristics of programming provided?	Patients receive same device? No, provided the pacemaker could record atrial rates Lower rate: as in parent study; upper rate: as in parent study Other programming features: in order to capture atrial rates, patients randomised to ventricular devices were programmed in VDIR

MOST (Glotzer): Results

Patients' baseline characteristics	Patients with AHRE			Patients without AHRE			*p*-Value
	n = 160	%		*n* = 152	%		
Age (years) (median, 25–75th percentile)	75		(68–81)	73		(68–79)	0.16
Gender (male)	72	45%		83	55%		0.94
Caucasian	149	93%		133	88%		0.091
Weight (lb) (median, 25–75th percentile)	164		(140–192)	157		(134–185)	0.067
Prior stroke/TIA/embolism	32	20%		23	15%		0.26
Charlson co-morbidity index:							0.11
0	48	30%		55	36%		
1–2	76	48%		77	51%		
3–4	22	14%		15	10%		
≥ 5	14	9%		5	3%		
Diabetes	37	23%		27	18%		0.24
Systolic blood pressure (mmHg) (median, 25–75th percentile)	133		(120–150)	140		(124–150)	0.24
Diastolic blood pressure (mmHg) (median, 25–75th percentile)	70		(62–80)	73		(68–82)	0.036
Prior supraventricular arrhythmia	129	81%		59	39%		0.001
Prior ventricular arrhythmia	4	3%		7	5%		0.31
Prior AVB	57	36%		27	18%		0.001
Antiarrhythmic on admission	46	29%			16	11%	0.001
Hypertension	98	61%			88	58%	0.55
Hypercholesterolaemia	68	43%			52	34%	0.13
Prior angina	49	31%			37	24%	0.21
Prior MI	37	23%			42	28%	0.36
Prior CHF	35	22%			16	11%	0.006
Prior CABG	29	18%			28	18%	0.95
Prior PTCA	20	13%			14	9%	0.36
NYHA CHF class:							0.51
I	68	43%			73	48%	
II	71	44%			56	37%	
III	19	12%			22	14%	
IV	2	1%			1	1%	

Clinical end-points	Patients with AHRE		Patients without AHRE		*p*-Value
	n = 160	%	*n* = 152	%	
ECG-documented AF	56/144	38.90%	3/146	2.10%	
Death or non-fatal stroke	33/160	20.60%	16/152	10.5%	
Symptoms	131/159	82.40%	92/149	61.70%	
Patients with dual pacemakers	95/190	50%	95	???	Log-rank $p = 0.79$
Patients with ventricular pacemakers	65/122	53%	57	???	
Death	28/160	17.5%	16/152	10.5%	
	HR of AHRE vs no AHRE population		**95% CI**		
Total mortality	2.48		1.25 to 4.91		0.0092
Death or non-fatal stroke	2.79		1.51 to 5.15		0.0011
AF	5.93		2.88 to 12.2		0.0001

MOST (Glotzer): methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	Patients were recruited within approved sites; eligible if they had a recording-capable pacemaker, with separate consent form signed prior to implantation
Unit of randomisation	Patient
Randomisation method	24-hour central randomisation line called after implantation of AV leads
Randomisation results	Differences in prior AVB, antiarrhythmic therapy, prior CHF (higher in patients with AHRE, $p = 0.001$)
Blinding method	Patients were blinded to mode assigned. Clinicians were blinded to the results of the atrial diagnostics data, but not to the inclusion of patients into the study. A blinded clinical events committee adjudicated all suspected strokes and causes of death. An ECG core laboratory reviewed all ECGs and confirmed diagnoses of AF. Some actions were taken to cross-validate rating of diagnostic tests. Recordings of pacemakers were compared to a 24-hour ambulatory ECG obtained at 6 months in 47 patients, of whom 41 had no AF on both recordings, six had AF episodes, with five having AF on ambulatory monitoring too and one having AF on pacemaker downloads but not on ambulatory recording. The sensitivity and specificity of AHRE used to detect AF were 100% and 97.6%, with a rate of false-positives of 2.4%. Sensitivity and specificity of symptoms for assessing AF were 82.4% and 38.3%, with a rate of false-positives of 58.7%
ITT	NA
Power calculation	Not reported
Data analysis	Baseline categorical variables were summarised with percentage and compared with likelihood ratio χ^2 test. Baseline continuous variables were summarised with median (25–75th percentile), intergroup comparisons with Wilcoxon sum-rank test. Cox proportional hazard models were used for the main analysis, adjusted for other known predictors and for variables that differed compared to the parent study (gender, race and prior AF, 60% vs 50%, $p = 0.003$). AHRE were entered as time-dependent covariate. Patients were divided into two groups based on reaching the AF end-point by the end of year 1 and Kaplan–Mayer estimates were derived for primary end-points for each of the two groups. The association between AHRE and pacing mode was examined using an unadjusted log-rank test
Adjustment by centre	Not stated
Loss to follow-up	22 patients were excluded from the study after they had reached the AF end-point in the parent study. No other information stated
Generalisability	Selected sample? Yes, according to postrandomisation criteria Complete description baseline sample/patients characteristics provided? Yes Evidence of unequal non-treatment intervention? Limited to antiarrhythmic therapy Subgroup analysis? No
Main/secondary outcome measured independently	Yes
Conflict of interest	Grants from the National Heart and Lung and Blood Institute of the NIH Bethseda supported MOST. Medtronic, Guidant and St Jude Medical donated additional support for the parent trial. The ancillary study received major support from Medtronic and other support from Guidant

CTOPP
CTOPP: Connolly et al. *(2000)*[52]

Acronym:	**CTOPP**	**Inclusion criteria:**	
Authors:	Connolly *et al*.	Patients scheduled for pacemaker with a diagnosis of bradycardia	
Date:	2000	Age ≥ 18 years	
Type of study:	RCT	Without chronic AF	
Country:	Canada	**Exclusion criteria:**	
No. of centres:	32	Previous atrioventricular nodal ablation	
Recruitment period:	3 years	Life expectancy of <2 years because of non-cardiovascular cause	
Follow-up period:	2 years		
Average follow-up:	3.5 expected (range 2–5 years)		
First follow-up between months 2 and 8 and yearly thereafter			
Intervention:	physiological pacing	**Primary and secondary outcomes:**	**Outcome measurement:**
Comparison:	ventricular pacing	Stroke and cardiovascular death	First occurrence of either cardiovascular death or stroke
Pacing indications:	SAN disease and AVB or both	Stroke, death from any cause, hospitalisation for HF and AF	Cardiovascular death
No. of patients:	2568		Death from any cause
Intervention:	1094		Stroke or systemic emboli
Comparison:	1474		Documented AF lasting for >15 minutes
			Admission to hospital for CHF
Diagnostic criteria		Cardiovascular death: death with a clearly attributable non-cardiovascular cause (trauma, cancer, infection, respiratory failure). Stroke was defined as neurological deficit, which did not resolve within 24 hours; only the first stroke was counted; AF lasting for >15 minutes, admission to hospital for CHF was ascertained by evidence of interstitial or alveolar oedema on chest radiography	
Characteristics of programming provided?		Patients receive same device? Patients assigned to dual-chamber arm could receive an atrial pacemaker if an optional intraoperative test demonstrated 1:1 AV conduction up to 130 bpm. Rate-adaptive pacemakers were implanted if there was evidence of chronotropic incompetence or in patients assigned to the ventricular pacing group if they had third degree AVB Lower rate, upper rate: not stated Other programming features: not stated	

CTOPP (Connolly): Results

Patients' baseline characteristics	Physiological pacing	Ventricular pacing
Mean age (years) (±SD)	73 ± 10	73 ± 10
Gender (male)	57	60.2
NYHA class ≥ II (%)	41.5	37.2
Indication for pacing:		
SA node disease	33.4	33.9
AV node disease	50.8	52.2
Both AV and SN node disease	8.5	8.1
Other	4.8	3.7
Unknown	2.6	2.1
Medical history:		
MI	26	24.5
Documented CAD	17.4	17.5
Stroke or TIA	9.7	9.3
Intermittent AF	21.4	20.9
Diabetes	13.8	15.5
Systemic hypertension	35.2	35.2
Medication:		
Anticoagulant drugs	11.9	10.4
Antiplatelet drugs	33.7	34.9
Antiarrhythmic drugs	12.6	11.5
Left ventricular function (clinical assessment):		
Normal	51.1	51.4
Abnormal	12.2	11.6
Objective assessment:		
Normal	17.5	19.4
Abnormal	16.8	15.5
Unknown	2.4	2.1
Symptoms of bradycardia:		
Ever had syncope	40.7	42.8
Ever had presyncope	58	61.3
Fatigue	59.3	63.4

Clinical end-points	Physiological pacing	Ventricular pacing	*p*-Value
First occurrence of stroke or cardiovascular death	4.9%	5.5%	0.33
Annual rate of death from all causes	6.3%	6.6%	0.92
Annual rate of AF	5.3%	6.6%	0.05
Hospitalisation for CHF	3.1%	3.5%	0.52
Annual rate of stroke	1%	1.1%	
Incidence of perioperative complications	9.0%	3.8%	<0.001

Subgroup analysis	HR, end-point, risk of stroke or cardiovascular death, physiological vs ventricular pacing		*p*-Value
Age: <74/≥74 years	0.65	1.00	0.054
Gender, M/F	0.98	0.84	0.52
MI or documented CAD: Y/N	0.89	0.91	0.9
Left ventricular function: normal/abnormal	0.93	0.84	0.61
SAN disease: Y/N	1.09	0.78	0.1
AV node block: Y/N	0.82	1.02	0.29
AF: Y/N	0.97	0.89	0.72
Stroke: Y/N	0.74	0.94	0.38
Anticoagulant therapy: Y/N	0.79	0.92	0.6
Antiarrhythmic therapy: Y/N	0.81	0.92	0.66
Third degree heart block: Y/N	0.87	0.94	0.74

CTOPP (Connolly): Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	A total of 7734 patients received a pacemaker in the centres over the enrolment period; of these 4499 were eligible, 2568 gave informed consent and were randomised. Of the 1931 excluded, 72% were because of refusal and 28% for technical reasons (unspecified)
Unit of randomisation	Patient
Randomisation method	Patients were randomly assigned up to 48 hours prior to implantation. The principal investigator in each centre chose a randomisation ratio in advance (67:33; 60:40; 50:50; 40:60; 33:67)
Randomisation results	Baseline characteristics are presented without further details
Blinding method	All reported primary and secondary events reviewed by a blinded adjudication committee. Disagreement with the report of the treating centre was solved with request for further evidence from the investigator and a final decision taken by AG
ITT	Unclear. Of the 1474 randomised to ventricular pacing, 99.1% remained in the original mode, 0.7% crossed over to physiological pacing, 0.2% received no pacing; at discharge from hospital, 99.2% remained in ventricular; cumulative percentage of patients who cross over to physiological pacing was 2.1% (year 1), 2.7% (year 2) and 4.3% (year 3) Of the 1094 randomised to physiological pacing, 93.5% received physiological pacing, 5.6% received ventricular pacing and 0.9% received no pacemaker; at discharge, 91.7% remained in physiological pacing, cumulative rates of cross-over were 10.8% (year 1), 12.8% (year 2) and 17.1% (year 3)
Power calculation	With annual rate of stroke or cardiovascular death of 5% in the ventricular group, 2550 patients were necessary to detect a 30% reduction in the relative risk of primary outcome with 90% power and 95% confidence
Data analysis	Kaplan–Mayer estimates of the risk of outcome events compared with log-rank test. The effect of baseline variables was analysed with Cox proportional hazard models. All statistical tests stratified by centre. Proportional hazard assumption tested with Grambsch and Therneau methods. All *p*-values are two-sided
Adjustment by centre	Yes
Loss to follow-up	None declared
Generalisability	Selected sample? Yes Complete description baseline sample/patients' characteristics provided? Yes Evidence of unequal non-intervention treatment? No Subgroup analysis? Yes
Main/secondary outcome measured independently	Yes
Conflict of interest	Supported by the Medical Research Council of Canada

CTOPP: Skanes et al. (2001)[55]

Acronym:	**CTOPP**
Authors:	Skanes
Date:	2003
Type of study:	detailed analysis of AF outcome in RCT
Country:	Canada
No. of centres:	32

Protocol presented in separate publication (Connolly *et al*.)

CTOPP (Skanes): Results

Patients' baseline characteristics	All patients (n = 2568)
Mean age (years)	72.7 ± 10.3
Gender (male)	58.8%
NYHA class ≥ II	39%
Pacing indication	
SA node disease	33.7%
AV node disease	51.6%
Both	8.3%
Other	4.2%
Unknown	2.3%
Medical history	
MI	25.1%
Documented CAD	17.5%
Stroke or TIA	9.5%
Prior AF	21.1%
Diabetes	14.8%
Systemic hypertension	35.2%
LVF (clinical assessment)	
Normal	51.3%
Abnormal	11.9%
Objective assessment	
Normal	18.6%
Abnormal	16.1%

Clinical end-points	Physiological pacing	Atrial pacing	RR reduction (95% CI)	p-Value
Cumulative risk reduction of AF	2.8% annual rate	3.84% annual rate	27.1% (5.5 to 43.6%)	0.016

Clinical predictors of AF	Chronic AF				p-Value (for HR)
	No. of events		Rate/year		
Treatment: ventricular vs physiological	167	92	3.84	2.8	0.016
Age: <74/≥74 years	112	147	2.95	3.83	0.057
SAN disease: Y/N	171	82	5.66	1.86	<0.001
Prior AF: Y/N	131	128	9.64	2.04	<0.001
MI or documented CAD: Y/N	84	175	3.79	3.23	0.425
Hypertension	101	158	3.85	3.16	0.261
Diabetes	36	223	3.5	3.37	0.715
LVF: normal/abnormal	188	71	3.3	3.65	0.473

Subgroup analysis	HR (95% CI) for AF, physiological vs ventricular pacing, by subgroup characteristic				*p*-Value (test of interaction between treatment and risk factors)
Age: <74/≥74 years	0.65	(0.43 to 0.97)	0.78	(0.56 to 1.09)	0.47
SAN disease: Y/N	0.75	(0.54 to 1.03)	0.66	(0.41 to 1.04)	0.65
Prior AF: Y/N	0.8	(0.56 to 1.15)	0.65	(0.45 to 0.95)	0.45
MI or documented CAD: Y/N	1.0	(0.64 to 1.55)	0.62	(0.45 to 0.86)	0.09
Hypertension	0.76	(0.5 to 1.15)	0.71	(0.51 to 0.99)	0.8
Diabetes	0.57	(0.27 to 1.19)	0.76	(0.57 to 1.0)	0.47
LVF: normal/abnormal	0.64	(0.47 to 0.87)	1.01	(0.63 to 1.62)	0.11

CTOPP (Skanes): methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	As in main study
Unit of randomisation	Patient
Randomisation method	As in main study
Randomisation results	Baseline description is reported for a partial list of characteristics for the overall group
Blinding method	As in main study
ITT	Not stated
Power calculation	Not stated
Data analysis	Cumulative risk of developing AF estimated with Kaplan–Mayer compared between treatments with Mantel–Henszel test stratified by centre. Data analysed with Cox proportional hazard model; results are expressed as hazard ratios and relative risk reduction (1-HR) with CI and *p*-values. Cox model was used to explore potential risk factors (age ≥74, history of MI or CAD, prior AF, history of hypertension, diabetes, SSS, normal or abnormal LVF) and subgroups of interest. Annualised event rates are also presented
Adjustment by centre	Yes
Loss to follow-up	Not stated
Generalisability	Selected sample? As in parent study Complete description baseline sample/patients' characteristics provided? No Evidence of unequal non-intervention treatment? None stated Subgroup analysis? Yes
Main/secondary outcome measured independently	As in main study
Conflict of interest	Supported by Medical Research Council of Canada

CTOPP: Newman et al. (2003)[80]

Acronym:	**CTOPP**	**Inclusion criteria:** in addition to requisite of the main study, English speakers; Having a completed parent study QoL available **Exclusion criteria**: no additional exclusion criteria stated	
Authors:	Newman *et al*.		
Date:	2002		
Type of study:	quality of life substudy in RCT		
Country:	Canada		
No. of centres:	32		
Recruitment period: as in main study			
Follow-up period: as in main study			
Average follow-up: values for QoL in the substudy were collected at baseline, within 48 hours from implantation and at month 6. All patients were interviewed at month 6 (main study)			
Intervention:	physiological pacing	**Primary and secondary outcomes:** Quality of life Physical functioning	**Outcome measurement:** Self-reported QoL administered in two separate protocols: (1) Substudy: Medical Outcome Study SF-36, QLAP, Goldman SAS (2) Main study: SF-6 (shorter version of SF-36), Pacemaker Syndrome Scale [including questions on symptoms clusters of palpitations, presyncope, pulsing and pounding, chest pain, dyspnoea with exertion. Each symptom cluster was treated as a separate domain (Likert scale) grouped together as 6-item Pacemaker Syndrome Scale] and Ladder of Life well-being scale. QoL (250 items in five instruments) for substudy and simplified 12-item QoL questionnaire for main study
Comparison:	ventricular pacing		
Pacing indications:	as in main study		
Substudy: 296 included, 207 analysed, 94 physiological pacing, 113 ventricular pacing			
Diagnostic criteria		Pacemaker dependency: heart rate <50 bpm determined at first postimplant visit (2–8 months)	
Characteristics of programming provided?		Patients receive same device? Patients in the physiological group received atrial and dual-chamber pacemakers (main study: 94% dual chamber and 6% atrial; substudy: 93% and 7%, respectively) Lower rate: NA; upper rate: NA Other programming features: NA	

CTOPP (Newman): Results

Patients' baseline characteristics	Physiological pacing, main study (n = 983)	Ventricular pacing, main study (n = 738)	Physiological pacing, substudy (n = 113)	Ventricular pacing, substudy (n = 94)
Gender (% male)	60	59	59	70
Age (years)	72 ± 10	72 ± 10	72 ± 10	71 ± 11
Sinus node disease (%)	43	44	42	37
AV node disease (%)	50	49	51	54
Taking arrhythmia drugs (%)	11	11	12	11
History of CAD (%)	20	18	18	20
Prior MI (%)	22	24	21	25
Diabetes (%)	15	12	10	16
Abnormal LVF (%)	24	27	26	19
Pacemaker dependent (%)	34	40	34	41

Subanalysis	
Pacemaker dependent, SSS patients (%)	29.6%
Pacemaker dependent, AVB patients (%)	40%

Quality of life	Physiological, baseline	Physiological, 6 months	p-Value	Ventricular, baseline	Ventricular, 6 months	p-Value
Substudy, SF-36 scores (0–100) at baseline and 6 months[a]						
Physical function	54	59	ns	55	62	<0.05
Physical role	25	52	<0.05	25	53	<0.05
Vitality	43	53	<0.05	47	58	<0.05
Emotional role	52	69	<0.05	58	69	<0.05
Mental health	69	75	<0.05	76	78	<0.05
Social function	59	76	<0.05	62	82	<0.05
Pain	60	68	<0.05	66	77	<0.05
General health	60	58	ns	64	65	ns
QLAP						
Total score	72	76	<0.01	72	77	<0.01
Activity	27	32	<0.01	27	30	<0.01
Physical	41	46	<0.01	41	47	<0.01
Psychological	93	93	ns	95	94	ns
Social	67	69	<0.01	68	72	<0.01
SAS						
Total score (higher values worse status)	30	23	<0.01	29	22	<0.01
Main study, SF-6 scores at 6 months (1–5)[a]						
Activity limitations		2.3			2.4	ns
Difficulty with work		2.3			2.35	ns
Emotional problems		2.15			2.1	ns
General health		2.8			2.9	<0.05
Social activities		1.78			1.8	ns
Bodily pain		2.3			2.4	ns
Main study, Pacemaker Syndrome Scale, at 6 months[a]						
Fatigue		2.8			2.8	ns
Shortness of breath		2.2			2.3	ns
Dizzy spells		1.5			1.6	<0.05
Palpitations		1.6			1.6	ns
Pulsation and pounding		1.4			1.4	ns
Activity limitations (scale 1–10)		7.1			6.93	ns
Patients < 70 years reported improvement in QoL score in three SF-6 domains (activity, general health, work difficulty) on average better by 0.2 SD unit difference (n = 645).						

[a] Values calculated from graph.

CTOPP (Newman): Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	Substudy was administered in six centres only
Unit of randomisation	Patient
Randomisation method	As in main study
Randomisation results	Baseline data are provided and tested, with all *p*-values non-significant after correction for multiple comparisons; however, there is a large difference in proportions of patients with SSS and AVB in the substudy compared to the parent study
Blinding method	None stated
ITT	No, only data from 207 patients in the substudy were analysed. ITT stated from main study
Power calculation	Power calculation was done for the substudy only, using general estimates of the effect size from the SF-36 for medical patients. Determination of sample was done with the multivariate sample size estimation function of SYSTAT based on the effect difference of 0.5 SD units of magnitude, based on a beta of 0.8, a sample of 48 patients was required. In addition, it was hypothesised that 40% of patients would be pacemaker dependent and with a dropout rate of 25%, so 250 patients were included in the substudy
Data analysis	Analysis of the substudy: covariance analysis was done on each of the QoL variables, with QoL at baseline, gender and NYHA scores used as covariates. Treatment assignment and pacemaker dependency were treated as between-subjects factors Analysis of the parent study: the three QoL instruments were analysed separately, with any pacemaker symptoms reported by <35% of patients dichotomised in present/absent and analysed with non-parametric techniques; other instruments analysed with standard ANOVA. Hochberg corrections for repeated measurement were utilised
Adjustment by centre	No
Loss to follow-up	Not detailed
Generalisability	Selected sample? Yes, by language. No explanation is provided of differences between included and excluded subgroups Complete description baseline values/patients' characteristics provided? Yes Evidence of unequal non-intervention treatment? No Subgroup analysis? Yes
Main/secondary outcome measured independently	Unclear
Conflict of interest	Supported by the Medical Research Council of Canada

CTOPP Tang et al. *(2001)*[57]

Acronym:	**CTOPP**	**Inclusion criteria:**
Authors:	Tang *et al*.	Pacing for symptomatic bradycardia
Date	2001	First implant
Type of study:	subanalysis of RCT	AF absent at time of implant
Country:	Canada	**Exclusion criteria:**
No. of centres:	32	Same as main study

Recruitment period: months 2–8 of the follow-up

Follow-up period: outcome data were obtained from CTOPP

Average follow-up: not stated

Intervention:	physiological pacing (DDD and AAI)	**Primary and secondary outcomes:**	**Outcome measurement:**
Comparison:	ventricular pacing	First occurrence of either cardiovascular death or stroke; cardiovascular death; death from any cause; stroke; AF, CHF	First occurrence of either cardiovascular death or stroke; cardiovascular death; death from any cause; stroke or systemic emboli; documented AF lasting for >15 minutes; admission to hospital for CHF
Pacing indications:	SSS, AVB, both		
No. of patients:	2244 (parent study 2568)		
Intervention:	942		
Comparison:	1302		

Diagnostic criteria: Definition of pacemaker dependency: presence of underlying rate of <60 bpm; for each patient, a point estimate of underlying heart rate was assessed during the first follow-up visit by setting the pacemaker to the VVI mode and a stable heart rate was recorded (UHR)

Characteristics of programming provided?

Patients receive same device? As in main study

Lower rate: NA; upper rate: NA

Other programming features: NA

CTOPP (Tang): Results

Patients baseline characteristics	Intervention	Comparison	*p*-Value
Mean age (years)	72.7 ± 10.1	72.5 ± 10.1	0.57
Gender (male)	57%	61%	0.11
NYHA class ≥ II	38%	37%	0.99
Pacing indication			
SSS	34%	34%	0.81
AVB	50%	52%	
SSS and AVB	9%	8%	
Unknown	7%	6%	
Rate-adaptive pacing	43%	76%	
Medical history:			
MI	25%	23%	0.16
Diabetes	13%	15%	0.43
Hypertension	35%	35%	0.82
Stroke or TIA	9%	8%	0.55
Paroxysmal AF	21%	20%	0.4
Medication:			
Anticoagulant	11%	10%	0.44
Antiplatelet agents	41%	42%	0.7
Arrhythmic drugs	12%	11%	0.28

Clinical end-points	Physiological pacing		Ventricular pacing		RR reduction (95% CI)	*p*-Value
	n	%	*n*	%		
UHR at first follow-up:						
≤40 bpm	209	22%	275	21%	NA	<0.0001
41–50 bpm	171	18%	164	13%		
51–60 bpm	188	20%	238	18%		
>60 bpm	374	40%	625	48%		
CV death or stroke by UHR:						
≤40 bpm	24	4.1% (annual rate)	51	6.9% (annual rate)	38.4 (–2 to 63)	0.089
41–50 bpm	20	4.2% (annual rate)	28	6.4% (annual rate)	37.8 (–13 to 65)	
51–60 bpm	20	3.9% (annual rate)	38	5.9% (annual rate)	40.3 (–6 to 66)	
>60 bpm	44	4.3% (annual rate)	70	4.1% (annual rate)	–1.9 (–50 to 31)	
Cardiovascular deaths:						
≤60 bpm		3.2%		5.9%	43.8 (21 to 60)	0.005
>60 bpm		4%		3.3%	–10.8 (–75 to 22)	
Any deaths:						
60 bpm		4.6%		7.8%	38.1 (18 to 53)	0.0008
>60 bpm		6.6%		5%	–29.1 (–79 to 67)	
Stroke/emboli:						
≤60 bpm		1%		0.9%	–0.9 (–105 to 50)	0.52
>60 bpm		0.7%		0.9%	35.8 (–60 to 74)	
CHF hospitalisation:						
≤60 bpm		2.8%		2.8%	0.9 (–51 to 35)	0.71
>60 bpm		2.6%		2.4%	13.3 (–88 to 32)	
AF:						
≤60 bpm		4.6%		7.3%	35.3 (12 to 53)	0.22
>60 bpm		4.6%		5.2%	16.2 (22 to 43)	

CTOPP (Tang): Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	In addition to selection from the main study, 324 patients were excluded from the study because the primary outcome had already occurred in 57 patients in the ventricular group and 47 patients in the outcome group; UHR was not assessed in the first follow-up visit (63 patients ventricular group, 49 in physiological group); first follow-up visit not attended (52 ventricular and 56 physiological)
Unit of randomisation	Patient
Randomisation method	As in main study
Randomisation results	Baseline values are reported and tested for equality. However, there appears to be a large difference in the proportion of patients with rate-adaptive pacing in the two groups; this characteristic is not tested
Blinding method	Not blinded to the investigators. An event adjudication committee reviewed any reported outcome event in a blinded fashion
ITT	NA
Power calculation	Not stated
Data analysis	Kaplan–Mayer estimates were calculated for cumulative risk by group (≤60 and >60)
Adjustment by centre	Not stated
Loss to follow-up	NA
Generalisability	Selected sample? The selection of patients is not independent from the outcome measured since patients with early occurrence of death and stroke do not enter the analysis Complete description baseline/patients characteristics provided? Yes Evidence of unequal non-treatment intervention? No
Main/secondary outcome measured independently	As in main study
Conflict of interest	Not stated

PASE

PASE: Lamas et al. *(1998)*[35]

Acronym:	**PASE**
Authors:	Lamas *et al*.
Date:	1998
Type of study:	single-blind RCT
Country:	USA
No. of centres:	29

Recruitment period: 26 February 1993 to 30 September 1994

Follow-up period: closeout procedure began 01 June 1995 and ended 31 August 1995. Follow-up ended 30 June 1996

Average follow-up: 550 days (range 216–996). Follow-up visits at months 3, 9 and 18, and at end of study. Clinical end-points were assessed until start of the closeout period; thereafter, QoL data were collected with telephone interviews

Inclusion criteria:
Age >65 years
Patients in sinus rhythm
Patients requiring permanent pacemaker for bradycardia

Exclusion criteria:
Serious non-cardiac illness
Unable to participate in the QoL assessment
Clinically overt CHF
Patients with inadequate endocardial atrial and ventricular capture and sensing threshold during implantation
Patients with AF for 6 months without any documented sinus mechanism

Intervention:	DDDR
Comparison:	VVIR

Pacing indications: provided for overall patients group: SSS 175, AVB (any, total) 201 (of which third degree AVB 119), other diagnoses 31

No of patients:	407
Intervention:	203
Comparison:	204

Primary and secondary outcomes:	**Outcome measurement:**
QoL	SF-36 including one multi-item scale measuring physical function, social function, physical role, emotional role, mental health, energy, pain, general health perceptions. Each item scores ranged from 0 (worst) to 100 (best) SAS with scores from 1 (best) to 4 (worst)
Disease-specific cardiovascular functional status	
Mortality	Deaths from all causes
Stroke	First stroke or death from any cause
AF	First stroke or hospitalisation for heart failure or death from any cause
Pacemaker syndrome	AF

Diagnostic criteria

Definition retrograde activation: assessed by ventricular pacing at 70 and 100 bpm

Definition of pacemaker syndrome: presence of left-sided or right-sided heart failure in association with ventricular pacing or of symptomatic hypotension with a drop in blood pressure of ≥ 20 mmHg during ventricular pacing

Characteristics of programming provided?

Patients receive same device? Yes
Lower rate: ≥ 50 bpm; upper rate: ≤ 130 bpm
Other programming features: left to discretion of investigators

PASE (Lamas): Results

Patients' baseline characteristics	Dual-chamber pacemakers	Ventricular pacemakers
No. of patients randomised	203	204
Age (years)	76 ± 7	76 ± 6
Gender (male)	57%	62%
Race (non-white)	12%	14%
NYHA class I or II	70%	73%
History of:		
Diabetes	29%	25%
Hypertension	52%	51%
Prior MI	33%	33%
Prior heart failure	26%	28%
Depressed EF	27%	25%
Supraventricular tachycardia	27%	30%
Cerebrovascular disease	12%	14%
Chronic lung disease	14%	13%
Any tumour	10%	8%
Prior procedures or operations:		
CABG	23%	22%
Mitral valve surgery	3%	3%
Aortic valve surgery	4%	4%
PTCA	10%	7%
Cardioverter defibrillator	1%	1%
Radiofrequency ablation	1%	1%
Concomitant medication:		
ACE inhibitors	31%	27%
Amiodarone	4%	5%
Aspirin	41%	37%
β-Adrenergic blockers	9%	16%
Calcium antagonists	26%	24%
Warfarin	6%	4%
Digitalis	17%	23%
Diuretics	34%	36%
Flecainide	2%	2%
Procainamide	7%	5%
Quinidine	2%	1%
Sotalol	4%	3%

Clinical end-points	Dual chamber		Ventricular		*p*-Value
	n	%	*n*	%	
Ventriculoatrial conduction at implantation		29%		29%	1
Death from all causes	32	16%	34	17%	0.95
Stroke or death from all causes[a]	35	17%	39	19%	0.75
Stroke or hospitalisation for heart failure or death from any cause	44	22%	56	27%	0.18
AF	35	17%	38	19%	0.8
Subgroup with SSS, total	*n* = 90		*n* = 85		
Death from all causes	11	12%	17	20%	0.09
Stroke or death from all causes	12	13%	19	22%	0.11
Stroke or hospitalisation for heart failure or death from any cause	18	20%	26	31%	0.07
AF	17	19%	24	28%	0.06
Subgroup with AVB, total	*n* = 99		*n* = 102		
Death from all causes	17	17%	15	15%	0.41
Stroke or death from all causes	18	18%	18	18%	0.68
Stroke or hospitalisation for heart failure or death from any cause	21	21%	27	26%	0.49
AF	16	16%	11	11%	0.26
Reprogramming from ventricular to dual chamber because of cross-over (all patients)			53	26%	
Patients with SSS			24	45%	
Patients with AVB			29	55%	
Cumulated time to cross-over:					
Within 1 month				44%	
Within 6 months				77%	
Manifestations:					
Fatigue				100%	
Dyspnoea or effort intolerance				67%	
Ortopnoea or paroxysmal nocturnal dyspnoea				24%	
Presyncope				33%	
Fullness of the neck				20%	
Reprogramming from dual to ventricular chamber	4	2%			

[a] Stambler *et al*. report four strokes in the DDDR (2%) and seven in the VVIR group (3.4%), $p = 0.54$.

Quality of life	Intervention				Comparison				*p*-Value
	Baseline	Month 3	Month 9	Month 18	Baseline	Month 3	Month 9	Month 18	
No. of patients	203	160	163	138	204	167	165	150	Significant differences only for mental health between ventricular and dual at month 9 ($p = 0.03$). Borderline significant difference in physical role and emotional role between ventricular and dual at month 3 ($p = 0.051$ and 0.052). Overall gap is significantly higher in QoL between baseline and 3 months for social function, physical role emotional role, mental health and energy (all $p < 0.001$)
% eligible patients evaluated	100%	81%	87%	88%	100%	85%	88%	92%	
Scores on SF-36 (by item)									
Physical function	54.4	59.6	57.5	58.4	52.9	53.9	54	58.4	
Physical role	63.4	75.3	69.2	69.9	61.3	73	67.3	68	
Social function	35.9	62.8	53.2	55.1	33.4	53.6	49	53.7	
Energy	67.2	90.6	81.1	80.6	70.6	83.8	76.5	76.1	
Mental health	71.9	77.6	79	76.5	73	77	75.2	73	
Emotional role	42.3	55	50.5	50.1	43.9	53	50.3	50.1	
Pain	66.1	69.4	70.9	70.6	67.3	69.7	72.1	68.2	
Health perception	60.3	62.2	58.3	56.2	60.3	62.3	58.4	58.3	
SAS									
No. of patients	203	158	161	136	204	159	155	141	
% eligible patients evaluated	100%	80%	86%	87%	100%	81%	83%	87%	
% patients by score on SAS (1 best, 4 worst)									
1	39%	44%	55%	60%	37%	41%	47%	46%	Significant differences for difference between ventricular and dual at 18 months ($p = 0.02$)
2	20%	27%	22%	15%	25%	22%	25%	23%	
3	38%	27%	23%	24%	37%	34%	26%	26%	
4	2%	3%	1%	1%	1%	3%	3%	6%	

Other subgroup analyses

Patients with heart failure had higher SF-36 physical function subscore than patients without heart failure (44 vs 57, $p < 0.001$) and on physical role (25 vs 38, $p = 0.004$)

Patients with angina had higher SF-36 physical function subscore than patients without angina (47 vs 57, $p = 0.001$) and on the physical role subscale (25 vs 39, $p = 0.002$).

The paper does not indicate what points in time are compared

Patients with AVB: no significant differences between groups in any of the SF-36 subscales, longitudinal analyses of SAS or any clinical end-points

Patients with SSS reported significantly higher scores at 3 months on physical role ($p = 0.02$), social function ($p = 0.03$) and emotional role ($p = 0.002$). Longitudinal analysis of SF-36 scores reported significant differences for emotional role ($p = 0.001$) and social function ($p = 0.02$) and SAS ($p = 0.02$)

PASE (Lamas): Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	No details provided
Unit of randomisation	Patient
Randomisation method	Blocked randomisation lists were produced centrally for each clinical site. After ventricular and atrial leads were placed, a randomisation envelope was opened. Pacemaker programmed to ventricular or dual chamber before implantation
Randomisation results	The equality of the distribution of AV and SSS patients in each group is not reported in the baseline values, with no recording of significance of the difference
Blinding method	Single-blind study
ITT	No, furthermore LOCF was used in some of the analyses
Power calculation	400 patients were deemed necessary for the study to have more than 80% power to detect meaningful difference in the quality of life between treatment groups
Data analysis	Wilcoxon sum-rank test (continuous variables) and Fisher exact test (categorical). Wilcoxon signed-rank test to test paired data for changes occurred after randomisation in all patients and changes that occurred after cross-over to dual-chamber pacing for patients in the single-chamber group. Scores for the SF-36 subscales were compared between modes at each period with multiple linear regression analysis adjusted for gender, quartile of age and baseline score for specific subscale. Scores for SAS compared between treatment groups with ordinal logistic regression adjusted for gender, quartile of age and baseline score. Longitudinal mode-related differences analysed with generalised estimating equations: SF-36, repeated-measures linear regression; SAS general estimating equation analogue of a binomial model. In patients who crossed over from ventricular to dual chamber, last measurement before cross-over was carried forward. Length of time before cross-over was analysed with Kaplan–Mayer curve
Adjustment by centre	No
Loss to follow-up	Loss to follow-up occurred, but not stated
Generalisability	Selected sample? Yes, inclusion criteria consider patients with adequate atrial capture or sensing threshold only, with inclusion of patients eligible for dual-chamber implantation only Complete description baseline sample/patients' characteristics reported? No Evidence of unequal non-intervention treatment? Baseline concomitant treatment is non-significantly different Subgroup analysis? Preplanned subgroup analysis of patients with AVB and SSS
Main/secondary outcome measured independently	No
Conflict of interest	Funded by a grant of Intermedics

PASE: Stambler et al. *(2003)*[53]

Acronym:	**PASE**	**Inclusion and exclusion criteria:**	
Authors:	Stambler *et al*.	As in main paper	
Date:	2003		
Type of study:	ancillary analysis of PASE (Lamas *et al*., 1998)[35]		
Country:	USA		
No. of centres:	29		
Recruitment period: As in main paper			
Follow-up period, average follow-up: as in main paper			
Intervention:	DDDR	**Primary and secondary outcomes:**	**Outcome measurement**
Comparison:	VVIR	AF Predictors of AF	AF
Pacing indications: provided for overall patients group: SSS 175, AVB (any, total) 201 (of which third degree AVB 119), other diagnoses 31			
No. of patients:	407		
Intervention:	203		
Comparison:	204		
Diagnostic criteria		Definition of retrograde activation: presence was determined during pacemaker implant pacing in ventricular mode at a rate 15 bpm above the intrinsic rate	
Characteristics of programming provided?		Patients receive same device? Yes Lower rate: ≥ 50 bpm; upper rate: none Other programming features: discretionary	

PASE (Stambler): Results

Time to AF (days)	216 (SD 209, range 0–811), time to onset: within 1 day (n = 5), within 1–30 days (n = 13)
Duration of AF episode	0–24 hours (n = 10), ≥ 24 hours (n = 20), chronic (n = 9)
Treatment for AF	Electrical cardioversion (n = 6), antiarrhythmic therapy (n = 25), hospitalised for AF (n = 20)

Clinical end-points	All patients	Dual chamber		Ventricular		*p*-Value
AF	73 (18%)	35	17%	38	19%	
Cumulative incidence of AF (Kaplan–Mayer estimates)			17%		18%	0.8
Patients with SSS		17/91	19%	24/85	28%	0.16
Cumulative incidence at 18 months, SSS patients (Kaplan–Mayer)			16%		28%	0.08
Patients with AVB		16/99	16%	11/102	11%	0.31
Cumulative incidence at 18 months, AV patients (Kaplan–Mayer)			17%		11%	0.22

Predictors of AF	RR (95% CI)	*p*-Value
VVIR vs DDDR in SSS patients	1.74 (0.93 to 3.24)	0.08
VVIR vs DDDR in SSS (Multivariate Cox model)	2.55 (1.23 to 5.29)	0.012
VVIR vs DDDR without SSS	0.60 (0.3 to 1.23)	0.17
Hypertension	1.63 (1.02 to 2.63)	0.043
Hypertension (multivariate Cox model)	1.85 (1.1 to 3.07)	0.018
Preimplant supraventricular tachycardia (last 3 weeks)	2.73 (1.69 to 4.41)	<0.001
Preimplant supraventricular arrhythmia (multivariate Cox model)	2.44 (1.06 to 5.62)	0.036
Preimplant supraventricular tachycardia (>3 weeks before)	3.2 (1.94 to 5.28)	<0.001
Preimplant history of supraventricular tachycardia	2.7 (1.71 to 4.27)	<0.001
Continued need for arrhythmic drugs after implant	2.45 (1.39 to 4.32)	0.002
Arrhythmic therapy 48 hours prior to implant	2.43 (1.49 to 3.96)	<0.001
Preimplant history of AF	2.4 (1.49 to 3.86)	<0.001
Digitalis therapy within 48 hours prior to implant	2.06 (1.25 to 3.41)	0.005
Chronic sinus bradycardia	1.84 (1.07 to 3.17)	0.028
Valvular heart disease	1.68 (1.01 to 2.8)	0.044
Impact of AF on main clinical end-points of the trial:		
Death from all causes (AF patients vs non-AF patients)	1.35	0.39
Death or stroke	1.08	0.83
Death stroke and heart failure hospitalisation	0.99	0.98
SF-36 scores	No difference reported	
SAS	No difference reported	

PASE (Stambler): Methodological characteristics

Prospective	Yes
Consecutive enrolment	Not stated
Unit of randomisation	Patient
Randomisation method	This paper reports that randomisation was directed by a coordinating centre; however, the main study reports randomisation with envelope
Blinding method	As in the main paper
ITT	The incidence of AF is analysed with ITT
Power calculation	The study had 90% power to detect a two-fold relative risk to develop AF between pacing modes
Data analysis	Patients' data were censored at the end of the study or at death. Baseline clinical and implant characteristics were compared between groups and between patients with or without AF with the Wilcoxon sum-rank test for continuous variables and the Fisher exact test for categorical variables. Time to AF was calculated with Kaplan–Mayer estimates and compared with log-rank test. Cox proportional hazard was used to identify independent predictors of AF, and those with $p < 0.1$ were combined into a Cox regression model, as well as baseline characteristics not balanced with randomisation ($p < 0.2$). These were age, COPD, use of β-blockers, use of warfarin, sinus pauses, fatigue and social function on the SF-36 scale. Interactions were tested for pacing mode and pacing indication, with the interaction between pacing mode and SSS significant ($p < 0.01$) and included in the multivariate model. QoL scores at month 18 were compared for patients with and without AF with multiple linear regression analysis and ordinal logistic regression, adjusted for gender quartiles of age, assigned pacing mode and baseline functional status. *p*-Values were two-tailed and considered significant at a confidence level $\leq 5\%$. Continuous variables are presented as mean $\pm$ 1 SD.
Adjustment by centre	Not stated
Loss to follow-up/cross-over	Five of the 38 patients in VVIR crossed over to DDR before developing AF, no patients in DDR crossed over to VVIR
Generalisability	Selected sample? As in main study Complete description baseline sample/patients' characteristics reported? Yes Evidence of unequal non-intervention treatment? Reported and adjusted for Subgroup analysis? NA
Main/secondary outcome measured independently	As in main study
Conflict of interest	Funded by a grant of Intermedics

PASE: Link et al. *(1998)*[29]

Acronym:	**PASE**	**Inclusion and exclusion criteria:**	
Authors:	Link *et al*.	As in the main paper	
Date:	1998		
Type of study:	single-blind RCT		
Country:	USA		
No. of centres:	29		
Recruitment period: February 1993 to September 1994			
Follow-up period: ended 30 June 1996			
Average follow-up: 550 days, with assessments prior to implantation and at 3, 9 and 18 months			
Intervention:	DDDR	**Primary and secondary outcomes:**	**Outcome measurement:**
Comparison:	VVIR	Rates of complications Hospital length of stay	Serious complications were defined as pneumothorax, cardiac perforation without or with cardiac tamponade, infection, erosion, atrial lead dislodgement, ventricular lead dislodgement, perioperative mortality. Total hospital length of stay, length of stay after pacemaker implant Health status assessment was done prior to operation
Pacing indications: provided for overall patients group: SSS 175, AVB (any, total) 201 (of which third degree AVB 119), other diagnoses 31			
No. of patients:	407		
Intervention:	203		
Comparison:	204		
Diagnostic criteria		Patients' general health was rated with Karnofsky scores (scores 1–10, 1 moribund state, 10 normal activity)	
Characteristics of programming provided?		Patients receive same device? Yes Lower rate, upper rate: as in the main study Other programming features: as in the main study	

PASE (Link): Results

Type of complication	Dual chamber
Any	6.1%
Pneumothorax	2%
Lead dislodgement	Atrial 0.5%, ventricular 1.7%
Subclavian vein thrombosis	1.5%
Erosion	0.25%
Infection	0.25%
Cardiac perforation	1%

Confidential: *UKPACE*

UKPACE: Toff et al. *(unpublished)*[45]

Acronym:	*UKPACE*	***Inclusion criteria:***	
Authors:	*Toff* et al.	*CiC removed – inclusion and exclusion criteria*	
Date:	*unpublished*		
Type of study:	*RCT*		
CiC removed – recruitment and follow-up criteria			
Intervention:	*DDD or DDDR*	*CiC removed – information on the outcome measures*	*CiC removed – information on the outcome measures*
Comparison:	*VVI or VVIR*		
Pacing indications: high-grade heart block (second degree or complete heart block)			
No. of patients:	*2021*		
Intervention:	*1012*		
Comparison:	*1009 [CiC removed]*		
Diagnostic criteria		*CiC removed* *CiC removed*	
Characteristics of programming provided?		*CiC removed* *CiC removed* *CiC removed*	

UKPACE: Results

Patients' baseline characteristics	*Dual chamber (DDD and DDDR)*	*Ventricular (VVI)*	*Ventricular (VVIR)*
	n = *1012*	**n = *504***	**n = *505***
Age (years) (mean ± SD)	*CiC removed*	*CiC removed*	*CiC removed*
Gender (% male)	*CiC removed*	*CiC removed*	*CiC removed*
Caucasian (%)	*CiC removed*	*CiC removed*	*CiC removed*
NYHA class I or II (%)	*CiC removed*	*CiC removed*	*CiC removed*
NYHA class III or IV (%)	*CiC removed*	*CiC removed*	*CiC removed*
Unknown	*CiC removed*	*CiC removed*	*CiC removed*
Primary ECG indication for implant (%)	*CiC removed*	*CiC removed*	*CiC removed*
Second degree	*CiC removed*	*CiC removed*	*CiC removed*
Complete	*CiC removed*	*CiC removed*	*CiC removed*
Other or unknown	*CiC removed*	*CiC removed*	*CiC removed*
Presenting bradycardia (%)	*CiC removed*	*CiC removed*	*CiC removed*
Intermittent	*CiC removed*	*CiC removed*	*CiC removed*
Constant	*CiC removed*	*CiC removed*	*CiC removed*
Unknown	*CiC removed*	*CiC removed*	*CiC removed*
Symptoms of bradycardia (%)	*CiC removed*	*CiC removed*	*CiC removed*
Symptomatic	*CiC removed*	*CiC removed*	*CiC removed*
Asymptomatic	*CiC removed*	*CiC removed*	*CiC removed*
Unknown	*CiC removed*	*CiC removed*	*CiC removed*
Medical history (%)	*CiC removed*	*CiC removed*	*CiC removed*
Hypertension	*CiC removed*	*CiC removed*	*CiC removed*
Diabetes	*CiC removed*	*CiC removed*	*CiC removed*
Angina	*CiC removed*	*CiC removed*	*CiC removed*
Prior MI	*CiC removed*	*CiC removed*	*CiC removed*
Prior heart failure	*CiC removed*	*CiC removed*	*CiC removed*
Cardiac surgery	*CiC removed*	*CiC removed*	*CiC removed*
PTCA	*CiC removed*	*CiC removed*	*CiC removed*
Paroxysmal AF	*CiC removed*	*CiC removed*	*CiC removed*
Other arrhythmia	*CiC removed*	*CiC removed*	*CiC removed*
Stroke	*CiC removed*	*CiC removed*	*CiC removed*
Prior TIA	*CiC removed*	*CiC removed*	*CiC removed*
Concomitant medication at randomisation	*CiC removed*	*CiC removed*	*CiC removed*
Aspirin	*CiC removed*	*CiC removed*	*CiC removed*
Warfarin or other anticoagulant	*CiC removed*	*CiC removed*	*CiC removed*
ACE inhibitor	*CiC removed*	*CiC removed*	*CiC removed*
Diuretic	*CiC removed*	*CiC removed*	*CiC removed*
Nitrate or other vasodilator	*CiC removed*	*CiC removed*	*CiC removed*
β-Blocker	*CiC removed*	*CiC removed*	*CiC removed*
Calcium-channel blocker	*CiC removed*	*CiC removed*	*CiC removed*
Digoxin	*CiC removed*	*CiC removed*	*CiC removed*
Other antiarrhythmic	*CiC removed*	*CiC removed*	*CiC removed*
Lipid-lowering agent	*CiC removed*	*CiC removed*	*CiC removed*
Oral hypoglycaemic	*CiC removed*	*CiC removed*	*CiC removed*
Insulin	*CiC removed*	*CiC removed*	*CiC removed*
Non-steroidal anti-inflammatory drug	*CiC removed*	*CiC removed*	*CiC removed*
Antidepressant	*CiC removed*	*CiC removed*	*CiC removed*

Dual chamber versus ventricular, all modes

Clinical end-points	*Dual chamber (DDD and DDDR)* n = *1012*	*Ventricular (VVI)* n = *504*	*Ventricular (VVIR)* n = *505*	*Dual vs ventricular (All) HR (95% CI),* p-*value*	*Dual vs ventricular (VVI) HR (95% CI),* p-*value*	*Dual vs ventricular (VVIR) HR (95% CI),* p-*value*
All-cause death at year 5	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
All-cause death at year 3	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
AF (3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
Stroke, TIA, thromboembolism (3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
Heart failure (3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
New-onset angina or IHD (3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
MI (3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
Pacemaker revision (3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*
Composite end-point (all events, 3 years)	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*	*CiC removed*

Cumulative Kaplan–Mayer estimates indicate event-free survival

Clinical end-points	***HR***	***95% CI***	**p-*Value***
Total	*CiC removed*	*CiC removed*	*CiC removed*
Age ≤ 75 years	*CiC removed*	*CiC removed*	*CiC removed*
Age >75 years	*CiC removed*	*CiC removed*	*CiC removed*
Male	*CiC removed*	*CiC removed*	*CiC removed*
Female	*CiC removed*	*CiC removed*	*CiC removed*
NYHA I	*CiC removed*	*CiC removed*	*CiC removed*
NYHA II–IV	*CiC removed*	*CiC removed*	*CiC removed*
Second degree heart block	*CiC removed*	*CiC removed*	*CiC removed*
Complete heart block	*CiC removed*	*CiC removed*	*CiC removed*
History of CHF	*CiC removed*	*CiC removed*	*CiC removed*
No history of CHF	*CiC removed*	*CiC removed*	*CiC removed*
Known IHD	*CiC removed*	*CiC removed*	*CiC removed*
No known IHD	*CiC removed*	*CiC removed*	*CiC removed*
Hypertension	*CiC removed*	*CiC removed*	*CiC removed*
No hypertension	*CiC removed*	*CiC removed*	*CiC removed*
Diabetes	*CiC removed*	*CiC removed*	*CiC removed*
No diabetes	*CiC removed*	*CiC removed*	*CiC removed*
Aspirin	*CiC removed*	*CiC removed*	*CiC removed*
No aspirin	*CiC removed*	*CiC removed*	*CiC removed*
ACE inhibitor	*CiC removed*	*CiC removed*	*CiC removed*
No ACE inhibitor	*CiC removed*	*CiC removed*	*CiC removed*
Diuretic	*CiC removed*	*CiC removed*	*CiC removed*
No diuretic	*CiC removed*	*CiC removed*	*CiC removed*

Complications

Clinical end-points	***Dual chamber (DDD and DDDR)* n = *1012***	***Ventricular (VVI and VVIR)* n = *1009***	**p-*Value***
Procedural complications	*CiC removed*	*CiC removed*	*<0.001*
Predischarge complications	*CiC removed*	*CiC removed*	*<0.001*
Need for therapeutic interventions	*CiC removed*	*CiC removed*	*0.005*
[CiC removed – comment on the complication rate].			

UKPACE: Methodological characteristics

Prospective	*Yes*
Selection/consecutive enrolment	*CiC removed*
Unit of randomisation	*CiC removed*
Randomisation method	*CiC removed*
Randomisation results	*CiC removed*
Blinding method	*CiC removed*
ITT	*CiC removed*
Power calculation	*CiC removed*
Data analysis	*CiC removed*
Adjustment by centre	*CiC removed*
Loss to follow-up	*CiC removed*
Generalisability	*CiC removed*
Main/secondary outcome measured independently	*CiC removed*
Conflict of interest	*CiC removed*

Cross-over trials in addition to the Birmingham review

Hoijer et al. *(2002)*[49]

Authors:	Hoijer *et al*.	**Inclusion and exclusion criteria:**	
Date:	2002	None stated	
Type of study:	double-blind cross-over study		
Country:	Sweden		
No. of centres:	1		
Recruitment period: not stated			
Follow-up period: 8 weeks in each mode			
Data collection: QoL questionnaires administered at the end of each period; patients' preferences at the end of follow-up			
Intervention:	VVIR	**Outcomes**	**Outcome measurement**
Comparison:	DDDR	QoL	QoL was rated with the Karolinska questionnaire
Total no. of patients:	19	Patients' preferences	Patients' preferences rated by (1) asking patients to identify preferred period and (2) patients rating how their general well-being was affected in the preferred period on a 5-item scale (0 no difference, +1 slightly better, +2 much better, –1 slightly worse, –2 much worse)
Pacing indications: AVB 12/19, SSS 7/19			
No. of advanced cross-overs: 7 from VVIR to DDDR, 0 from DDDR to VVIR			
Diagnostic criteria		Definition of pacemaker syndrome: none provided	
Characteristics of programming provided?		Patients receive same device? Yes	
		Average programmed rate of pacing: 95 bpm	
		Other programming features: NA	

Hoijer: Results

Patients' baseline characteristics		***p*-Value**
Age (years) (mean ± SD)	75.5 ± 7.3	
Gender (*n* male)	13/19	
Time in VVIR before study (years) (mean ± SD)	6.8 ± 4.3	
Time in DDDR before study (years) (mean ± SD)	2.2 ± 1.1	
Results		
Early cross-over from VVIR to DDIR	7/19	0.003
Early cross-over from DDDR to VVIR	0/19	
Time to cross-over (days) (median, range)	4 (1–20)	
Reasons for cross-over:		
Dyspnoea (*n*)	4	
Fatigue (*n*)	3	
Dizziness (*n*)	2	
Chest pain (*n*)	1	
Median preference score for VVIR	–1	0.015
Symptoms of pacemaker syndrome	9 yes, 10 no	
Request of cross-over by pacemaker syndrome	3/9 symptomatic patients and 4/10 asymptomatic patients	0.14

Quality of life	Item	Significant difference (*p*-value) of scores comparison	Mode preferred
Symptoms	Dyspnoea	0.049	DDDR
	Dizziness	ns	DDDR
	Chest pain	ns	DDDR
	Palpitations	ns	DDDR
Sleep	Alertness	ns	DDDR
	Quality of sleep	ns	DDDR
Cognitive ability	Decision-making	ns	DDDR
	Memory	ns	VVIR
	Concentration	ns	VVIR
Physical and social ability	Physical ability	ns	0
	Social participation	ns	DDDR
Depression	Depressive score	ns	0
Health	Self-perceived health A	ns	0
	Self perceived health B	ns	0
Mood state	Activation/deactivation	0.034	DDDR
	Calmness/tension	ns	DDDR
	Pleasantness/unpleasantness	ns	DDDR

Hoijer: Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	Sample selected among all patients with a pacemaker followed up in one hospital; 19 patients were selected among 33 patients implanted with VVIR and upgraded to DDD or DDDR, the latter only were included in the study
Unit of randomisation	Mode of randomisation
Randomisation method	Not reported
Blinding method	An investigator blinded to the pacing mode administered the QoL questionnaire. Patients were also unaware of the pacing mode in each period
ITT	Cannot tell
Power calculation	Not reported
Data analysis	Paired data were analysed with Wilcoxon sign-rank test. Data are presented as medians and quartiles with differences shown as boxplots. Comparisons of early cross-over mode and patients' preferences were done with Fisher's exact test. Data are not presented in the paper; only the results of comparison tests are reported
Adjustment by centre	NA
Loss to follow-up	None stated
Generalisability	Selected sample? Yes Complete description of baseline sample/patients' characteristics provided? No Evidence of unequal non-intervention treatment? No information provided Subgroup analysis? No
Main/secondary outcome measured independently	No
Conflict of interest	Not stated

Jordaens et al. *(1988)*[50]

Authors:	Jordaens *et al*.	**Inclusion criteria:**	
Date:	1988	Age ≥ 65 years	
Type of study:	randomised cross-over trial	Patients with physically active life selected for implantation of dual-chamber pacemakers in stable synus rhythm 24–48 hours after admission	
Country:	Belgium	**Exclusion criteria:**	
No. of centres:	1	Not stated	
Protocol presented in separate publication? No			
Recruitment period: not stated			
Follow-up period: 48 hours			
Average follow-up: not stated			
Intervention:	DDD	**Primary and secondary outcomes:**	**Outcome measurement:**
Comparison:	VVI	Exercise duration	Total time of exercise (upright bicycle ergometer test)
Pacing indications: complete heart block			
No. of patients: 18			
Diagnostic criteria		Definition retrograde activation: NA	
		Definition of pacemaker syndrome: NA	
		Hospitalisation for heart failure: NA	
Characteristics of programming provided?		Patients receive same device? No	
		Lower rate: 70 bpm; upper rate: 140–150 bpm	
		Other programming features:	

Jordaens: Results

Patients' baseline characteristics	All patients	Patients included in analysis only
Age (years) (mean, all patients)	74.4 ± 3.7	74.4 ± 3.9
Patients with first implant	11	9
Patients with replacement of VVI pacemaker	7	6
Known CAD	2	
Severe hypertension	1	
Males (analysed patients)	12	

Clinical end-points	DDD mode	VVI mode	*p*-Value
Total exercise time (minutes)	5.5 ± 2.6	6.2 ± 2.3	<0.05
AF (lasting >1 minute)	1	1	
Atrial premature beats (episodes)	4	0	

Jordaens: Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	Not stated
Unit of randomisation	Patient
Randomisation method	Not stated
Randomisation results	NA
Blinding method	Not stated
ITT	No
Power calculation	No
Data analysis	Values are expressed as mean ± SD. Statistical analysis conducted with Wilcoxon's test for paired data
Adjustment by centre	NA
Loss to follow-up	Three patients excluded from analysis: one for occurrence of intermittent AF, one with normal AV conduction, one with second degree heart block
Generalisability	Selected sample? Yes Complete description baseline sample/patients' characteristics provided? Yes Evidence of unequal non-intervention treatment? Not stated Subgroup analysis? NA
Main/secondary outcome measured independently	Not stated
Conflict of interest	Not stated

Atrial versus dual-chamber pacing

***Nielsen* et al. *(2003)*[91]**

Authors:	Nielsen *et al*.	**Inclusion criteria:**
Date:	2003	First implant
Type of study:	parallel randomised trial	SSS with normal AV conduction (PQ interval ≤ 220 ms for patients ≤ 70 years and ≤ 260 for patients >70 years)
Country:	Denmark	Diagnosis of symptomatic bradycardia <40 bpm
No. of centres:	2	Symptomatic QRS pause >2
Recruitment period: December 1994 to March 1999 Follow-up period: follow-up ended March 2000 Average follow-up: mean follow-up 2.9 ± 1.1 years. Follow-up visits were done at months 3 and 12, then once a year		**Exclusion criteria:** AVB grade I (defined as PQ interval >0.22 s in patients ≤ 70 years and PQ interval >0.26 in patients >70 years), AVB grade II and II; bundle branch block, Wenckebach block <100 bpm known before implantation Chronic AF or AF >50% of the time or AF with QRS rates <40 bpm or AF with RR intervals >3 s Cerebral disease including dementia or cancer Planned cardiac surgery Follow-up not possible Pacing for hypertrophic obstructive cardiomyopathy, carotid sinus syndrome, prior heart transplant, major non-cardiac surgery, bradycardia and ventricular tachycardia Refusal or other reasons
Intervention:	DDDR	**Primary and secondary outcomes:** Changes in left atrial and left ventricular size LVF AF, thromboembolism All-cause and cardiovascular mortality CHF
Comparison:	AAIR	
Pacing indications:	SSS	
No. of patients:	177	
Intervention, DDDR-s:	60	
Intervention, DDDR-I:	63	
Comparison:	54	
		Outcome measurement: Cardiovascular deaths including sudden death, death due to CHF, arterial thromboembolism, pulmonary embolus Heart failure (NYHA criteria and daily dose of diuretics)
Diagnostic criteria (outcomes)		Cause of death was obtained from interview of doctors who assisted the dead and from review of hospital and necropsy reports; AF diagnosed by standard 12-lead ECG; stroke was diagnosed if neurological symptoms of presumably cerebral ischaemic origin persisted for more than 24 hours or if patient died from an acute cerebrovascular event within 24 hours; peripheral embolus was diagnosed by embolectomy or necropsy reports; heart failure was classified by NYHA and daily dose of diuretics
Characteristics of programming provided?		Patients receive same device? No Lower rate and upper rate: programmed individually Other programming features: the intervention group was randomised to conventional short rate adaptive AV delay (DDDR-s, ≤ 150 ms) or to fixed long AV delay (DDDR-I, 300 ms)

Nielsen: Results

Patients' baseline characteristics	DDDR-s	DDDR-l	AAIR	*p*-Value
No. of patients	60	63	54	
Age (years)	79 ± 9	74 ± 9	74 ± 9	
Gender (*n* male)	26	24	23	
Mean follow-up (years)	2.8 ± 1.5	2.8 ± 1.4	3.1 ± 1.3	
Blood pressure (mmHg):				
Systolic	139 ± 22	144 ± 22	145 ± 24	
Diastolic	75 ± 12	80 ± 10	80 ± 13	
Indications for pacing:				
Sinus bradycardia	5	11	8	
Sinoatrial block	17	16	19	
Brady–tachy syndrome	38	36	27	
Symptoms:				
Syncope	26	24	19	
Dizzy spells	32	34	34	
Heart failure	2	5	1	
CAD	25	22	21	
Diabetes	6	7	6	
NYHA class (*n*):				
I	38	46	32	
II	22	14	18	
III	0	3	2	
IV	0		1	
Electrocardiographic parameters:				
PQ intervals (ms)	183 ± 28	184 ± 27	186 ± 27	
Wenckebach block point (*n*):				
<100 bpm	5	3	2	
≥ 100 bpm	52	57	50	
Medication:				
β-Blocker	5	7	4	
Calcium-channel blocker	7	11	14	
Digoxin	9	11	11	
Sotalol	8	10	7	
Aspirin	40	36	35	
Warfarin	5	11	5	
Programmed minimum rate	60 ± 4	61 ± 5	63 ± 8	0.04
Programmed maximum rate	120 ± 5	108 ± 8	120 ± 8	0.01

Clinical end-points	DDDR-s	DDDR-l	AAIR	*p*-Value
Occurrence of AF (*n*, %)	14 (23.3%)	11 (17.5%)	4 (7.4%)	0.03
Proportion without AF at 1 year[a]	9.50%	95%	98%	
Proportion without AF at 2 years[a]	90%	92%	96%	
Proportion without AF at 3 years[a]	74%	86.30%	94.50%	
Proportion without AF at 4 years[a]	67.20%	80.50%	90.50%	
Proportion without AF at 5 years[a]	60.30%	67.20%	90%	
Patients experiencing stroke	7 (11.7%)	4 (6.3%)	3 (5.6%)	0.32
Deaths	14 (23.3%)	14 (22.2%)	9 (16.7%)	0.51
Annual rate of mortality	8.40%	8%	5.40%	
Cardiovascular mortality, total	11.70%	14.30%	7.40%	0.43
Patients increased at least one NYHA class	30%	46%	31%	0.17
Increase in consumption of diuretics	32%	21%	28%	0.34

[a] Data derived from graph.

Subgroup analyses	RR (95% CI)	*p*-Value
Risk of AF for presence/absence of brady–tachy syndrome	3.3 (1.3 to 8.1)	0.01
Risk of developing AF in AAIR adjusted for brady–tachy syndrome	0.27 (0.09 to 0.83)	0.02

No. of patients with AAIR switching to DDDR	**Six in total, three (implantation), one (before discharge) and two (by the end of follow-up)**
Reasons	Two Wenckebach block during implantation, one due to AF during implantation; three developed high-degree AVB (1.9% per year)
No. of patients in DDDR switching to VVI	Four (by the end of follow-up)
Reasons	Four because of development of persistent AF
No. of patients switching from DDDR to AAIR	One (by the end of follow-up)
Reasons	Malfunction of ventricular lead

Nielsen: Methodological criteria

Prospective	Yes
Selection/consecutive enrolment	The trial sample was selected from a population of 952 consecutive patients of whom 775 were excluded for causes. Documented in the paper
Unit of randomisation	Patient. Randomisation of devices
Randomisation method	Not stated
Randomisation results	Trial arms are reported to be comparable
Blinding method	Investigators were not blinded. During implantation, an atrial pacing test was performed with 1:1 AV conduction being required for an atrial pacemaker to be implanted. If Wenckebach point occurred at a rate of 100 bpm, the patient received a DDDR pacemaker
ITT	States yes; no length of total follow-up reported
Power calculation	The study is underpowered. Power calculation based on M-mode echocardiographic data from a previous AAI vs the VVI study; 450 patients were necessary to detect 10% difference of the left atrium diameter with 80% power and a confidence of 5%. However, the recruitment was stopped after randomisation of 177 patients since a national multicentre trial was initiated (DANPACE trial)
Data analysis	Continuous variables were summarised with mean and SD, with within-group comparisons done with two-tailed *t*-test for continuous variables. Comparisons between groups were tested with χ^2 test for discrete variables and ANOVA for continuous variables. Differences in occurrence of discrete events were calculated with log-rank test and Kaplan–Mayer plots were derived for the occurrence of AF. Cox regression analysis was done to calculate the relative risk proportion of AF adjusted for brady–tachy syndrome; differences in functional class (NYHA) and consumption of diuretics before and after the intervention were calculated from contingency tables and tested with χ^2 test. For all variables, 95% CI were computed
Adjustment by centre	No
Loss to follow-up	No patients were lost to follow-up
Generalisability	Selected sample? Yes Complete description baseline sample/patients' characteristics provided Evidence of unequal non-intervention treatment? Reported, but not tested for difference Subgroup analysis? No
Main/secondary outcome measured independently	Cannot tell
Conflict of interest	Not stated

Schwaab et al. *(2001)*[92]

Authors:	Schwaab *et al*.[92]	**Inclusion criteria:** Chronotropic incompetence criteria fulfilled	
Date:	2001		
Type of study:	randomised cross-over	**Exclusion criteria:** Complete bundle branch block Bifascicular block PQ interval > 240 ms during rhythm at rest Second or third degree heart block (24 Holter ECG) Significant valvular heart disease (echo or Doppler echocardiography)	
Country:	Germany		
No. of centres:	1		
Recruitment period: NA Follow-up period: 6 months Average follow-up: 6 months			
Intervention:	AAIR	**Primary and secondary outcomes:** QoL Recurrent atrial tachyarrythmia Exercise tolerance LVF Patients' preferences	**Outcome measurement:** QoL: four self-administered questionnaires: 1. General well-being and three dimensions of QoL, physical, emotional and cognitive functioning, measured using VAS (0–100, 0 very unwell, unable to exercise, symptoms present all the time, 100 very well, unlimited exercise, no symptoms at all). Questions referred to previous 3 months 2. Karolinska questionnaire (measurement with VAS as above) 3. SAS 4. Questionnaire assessing prevalence of specific symptoms (pacemaker syndrome) measured on 5-point category scale (1 severe or nearly persistent, 5 free of symptoms) Exercise testing by bicycle ergometry Atrial tachyarrythmia: number and total duration of episodes
Comparison:	DDDR		
Pacing indications: brady–tachy syndrome			
No. of patients: 21			
Diagnostic criteria		Definition of chronotropic incompetence provided Definition of pacemaker syndrome: not stated	
Characteristics of programming provided?		Patients receive same device? Yes, DDDR, trial of programming Lower rate and upper rate: individually programmed rates, average 119 ± 10 Other programming features: rate response individually programmed	

Schwaab: Results

Patients' baseline characteristics	
Gender (M/F)	11/8
Age (years) (mean ± SD)	70 ± 7
Concomitant medication:	
Sotalol	13
Flecainide	2
Amiodarone	5

Clinical end-points	AAIR	DDDR	*p*-Value
Overall no. of detected episodes	12 (2 patients)	22 (7 patients)	
Total duration of all registered episodes (minutes)	1 ± 0.9	85 ± 198	0.055
Patients reporting episodes of II or III AVB	7 (164 episodes)		
Exercise testing (time, maximum, in seconds)	423 ± 127	402 ± 102	<0.05
Results, QoL:			
General well-being (mean ± SD)	67 ± 23%	67 ± 20%	ns
Physical function (mean ± SD)	56 ± 25%	59 ± 25%	ns
Emotional function (mean ± SD)	63 ± 27%	63 ± 27%	ns
Cognitive function (mean ± SD)	51 ± 27%	56 ± 23%	ns
Karolinska questionnaire			
Chest pain (mean ± SD)	76 ± 19%	73 ± 20%	ns
Palpitations (mean ± SD)	79 ± 20%	78 ± 17%	ns
Dizziness (mean ± SD)	82 ± 11%	71 ± 16%	<0.05
Dyspnoea (mean ± SD)	71 ± 20%	67 ± 24%	ns
SAS	1.6 ± 0.67%	1.6 ± 0.74%	ns
Pacemaker Syndrome Scale	3.6 ± 0.64%	3.5 ± 0.6%	ns
Preferred pacing mode (no. of individuals)	8	11	ns
Clinical end-points by preferred mode:			
QoL, echo/Doppler electrocardiography, exercise testing			ns
Arrhythmia during preferred mode	All patients free of atrial tachyarrythmia	5 patients (45%) had AF	<0.05

Schwaab: Methodological characteristics

Prospective	Yes
Selection/consecutive enrolment	Not stated
Unit of randomisation	Patient
Randomisation method	Not stated
Randomisation results	NA
Blinding method	Patients and investigators were blinded, methods not stated
ITT	No. Data summarised only for patients who completed protocol
Power calculation	No
Data analysis	Comparisons were done with Wilcoxon test for paired and Mann–Whitney *U*-test for unpaired data
Adjustment by centre	NA
Loss to follow-up	21 patients randomised, one developed chronic AF in AAIR mode and was excluded, another died while in DDDR mode. No serious life-related events occurred during follow-up (death of spouse or child, divorce, accident, dismissal from work). No episodes of syncope were reported in either group
Generalisability	Selected sample? Yes. Complete description baseline sample/patients' characteristics provided? Yes Evidence of unequal non-intervention treatment? NA. Concomitant medication reported Subgroup analysis? A subgroup analysis was conducted by patients' preferences
Main/secondary outcome measured independently	Questionnaire on pacemaker syndrome not detailed. Authors report testing questions on general pacemaker population (no further details)
Conflict of interest	Not stated

Economic evaluation studies

Critical appraisal of the St Jude Medical economic evaluation (Drummond[41] framework for economic evaluation)

1. Was a well-defined question posed in answerable form?	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes. Ventricular single-chamber pacemakers only were considered
3. Was the effectiveness of the programmes or services established?	A comprehensive review of effectiveness was carried out, drawing substantially on the Birmingham HTA review cited elsewhere in this assessment. However, effectiveness data were used selectively
4. Were all the important costs and consequences for each alternative identified?	Yes, with important limitations. In the case of pacemaker syndrome there is inconsistency between the incidence of this event and consequent rates of reprogramming. This overestimates the relative cost of ventricular pacing and biases the model in favour of the dual-chamber option For AF, reprogramming of dual to ventricular chamber is not considered (resulting in underestimate of the cost of AF in dual chamber) For main events, costs were limited to hospital stays. Community care costs were included limited to the incident event, with no attempt to include the subsequent associated healthcare resource and longer term costs of follow-up and care of AF, heart failure and stroke (i.e. long-term GP costs, rehabilitation, long-term drug treatment, etc.)
5. Were costs and consequences measured accurately in appropriate units?	Partially. Costs of implants and hospitalisations relative to adverse events were calculated with a bottom–up method and appear justified, with the exception of the cost of pacemaker syndrome, which is always assumed to equal the cost of reimplant Mortality, stroke and heart failure are likely to have been overestimated, with no account taken of the uncertainty associated with these parameters Quality of life (utility) is not considered, despite this being feasible
6. Were costs and consequences valued credibly?	Yes. Unit costs are taken from standard published sources (see below)
7. Were costs and consequences adjusted for differential timing?	No
8. Was an incremental analysis performed?	Yes. The model estimates cost per number of adverse events avoided (AF, stroke and cases of pacemaker syndrome). An additional analysis presents costs per pacemaker syndrome event avoided
9. Was allowance made for uncertainty?	No
10. Did the presentation and discussion of study results include all issues of concern to users?	Partially. The model assumes that the survival time of the generator is equal in dual and ventricular types. The submission contains a discussion of the possible survival time of generators on behalf of the sponsor, but does not consider the implications of this on differential costs over the duration of the model

Critical appraisal of the St Jude Medical economic evaluation (Sculpher[40] framework for economic evaluation)

1.	Structure of the model Is there a clear statement on the decision problem, context and perspective?	Yes
	Theory of underlying disease?	Yes
	Assumptions in the model clearly specified? Justified? Relaxed?	No
2.	Disease states Model type appropriate for the time dimension of the disease?	No
	Justification of the choice of states provided	Yes
	Empirical evidence of the suitability of the states?	No
	Any important states omitted?	No
3.	Options and strategies Is there a clear statement of the options being evaluated?	Yes
	Cover full range of logical and feasible options	Yes, with important limitations (see above)
4.	Time horizon Exhaustive in time and coverage of option through time	No. Although there is a statement that the model covers 7.5 years, the timing of events is not incorporated in the model. No other details are provided on how time has been handled. In addition, event rates are derived from trials with a shorter duration than the time-framework stated without correction
	Justification based on disease and effect of interventions	Yes
5.	Cycle length Used if relevant? Justified? Related to disease?	No
6.	Data identification Sources of parameter values	Costs were determined with a bottom–up approach. Resource use was estimated by the authors and validated by clinical experts. However, the constituency of the group and the methods used for validation are not reported. Nevertheless, cost estimates appear valid. Unit (component) costs were retrieved from trust costs schedules, recognised published sources for the UK (NHS reference costs, British National Formulary, PSSRU). Prices of pacemakers are taken from one sponsor audit. Selective use of transition probabilities is reported elsewhere
	Is there reasonable empirical justification from early iterations of the model given that these data are obtained from all low-cost data sources (i.e. secondary data)?	No
	Are ranges specified for parameters?	No
	Evidence to suggest selective use of data?	Yes. Differences in all main outcomes may be overestimated in favour of dual chamber. Although the submission includes a thorough effectiveness review (drawing from the Birmingham review), the model uses only values that were found significantly different by mode in selected trials and does not consider the evidence from pooled results from the Birmingham HTA review In the SSS/AVB model, mortality is taken from the Wharton study (this is the only study to report a significant difference between dual chamber, 6.8%, and ventricular chamber, 3.2%, and has not been published in full). Progression to AF is taken from MOST for the SSS model (27.1% dual and 21.4% ventricular) and from

continued

	CTOPP for the SSS/AVB model (annual rates of 6.6% dual and 5.3% ventricular). Occurrence of AF is modelled at a fixed rate. Rates for stroke were from Mattioli and colleagues, the only trial to report a significant difference for this outcome: 18% dual versus 9.5% ventricular. The RR used is very high (close to 2.0), while other evidence suggests that the RR is, in fact, not different by pacing mode. In addition, these rates are very high compared to other trials (on average 2.4% dual and 2.7% ventricular, see Effectiveness section). Stroke rates are not considered in the SSS model (no difference by mode) Progression to heart failure is taken from MOST for the SSS model (12.3% ventricular and 10.3% dual), where significance was achieved only for the adjusted HR. In the AVB/SSS no significant difference was modelled For pacemaker syndrome, the model uses data from trials of programming only (26% in the SSS/AVB and 32.8% in the SSS model only). There is no discussion on the weakness of these estimates and the evidence from CTOPP is not considered
If parameters are valued based on elicitation of expert opinion methods, have methods been adequately described (inclusion criteria, sample size, elicitation methods?	No. Validation of resource consumption with clinical experts is reported
Are the claims made by model 'tempered' by limitations in the data?	No
7. Data incorporation For each parameter, is there a clear justification on how data have been incorporated into the model?	No
Has a stochastic analysis been undertaken? If so, do the distributions in parameters reflect second order uncertainty? Have appropriate distributions been selected for each parameter?	No
Have interval rates been translated into transition probability using the appropriate formula?	No
Has a half-time related estimate been applied?	No
8. Internal consistency Does it work? Is there a statement about internal consistency?	No statement is reported

Guidant (YHEC) evaluation of dual-chamber pacing (Drummond[41] framework for economic evaluation)

1. Was a well-defined question posed in answerable form?	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes, although it is not clear whether atrial or ventricular single-chamber pacemakers are considered
3. Was the effectiveness of the programmes or services established?	Effectiveness data were taken from a systematic review carried out by the Birmingham Technology Assessment Group (BTAG). Some cases where the transition probabilities used cannot be related to data reported in that review (see under decision analysis critical appraisal framework)
4. Were all the important costs and consequences for each alternative identified?	Yes, except for the therapeutic implications of AF Single-chamber patients who develop AF are changed to a dual-chamber pacemaker. This is contrary to the recommendations for pacemaker use, which specify that VVI(R) mode should be used in AF with AVB. In contrast, dual-chamber pacemaker patients are not reprogrammed to VVI(R) mode if

continued

	AF develops. Drug treatment is reportedly included in cases of AF, but this is not specified in the section on costs. Finally, all patients with AF move to the heart failure arm of the model, which is unlikely to be the case. The impact of this assumption is to substantially increase the costs of developing AF for single-chamber patients
	Modelling of heart failure is necessarily greatly simplified, and may be oversimplified. The impact of this is uncertain
5. Were costs and consequences measured accurately in appropriate units?	Mostly. Costs for AF appear high and sources are not reported. Emergency admission for 10 days, including 2 days in CCU is assumed. Cardioversion is assumed for heart failure but not transient or persistent AF. Increased costs for AF, which occurs more frequently with single-chamber pacing, biases in favour of dual-chamber pacing
	Source for biventricular pacemaker device cost is not given and basis for assumption of increased procedural costs (50% greater than single- or dual-chamber pacemaker insertion) not stated
	No differential cost for pacemaker insertion between dual- and single-pacemaker assumed, although dual-chamber pacemaker insertion takes longer. This biases costs in favour of dual chamber
	Pneumothorax costs are estimated arbitrarily as an additional day in hospital, but source not given. Admission likely to be longer than 1 day and procedural costs involved for drainage. This may bias costs in favour of dual chamber
	Costs are otherwise estimated from NHS national reference costs for 2002
6. Were costs and consequences valued credibly?	The methods used to obtain the utilities employed in the model are not stated clearly. EQ-5D scores for a sample of 1205 patients after percutaneous coronary intervention (for CHD) are used for the "well after pacing" states (0.86). Values were taken at 6 and 12 months, at which time a significant proportion of patients may have had recurrence of angina. On this basis, the 'well' utility may therefore be underestimated. However, the value from a community sample for people in this age group was 0.73 (as used in the present model), suggesting that the 'well' utility may be overestimated. These issues illustrate the considerable uncertainty around utility values
	These data have the useful property of reflecting community values, assuming that the tariffs for EQ-5D collected as part of the MVH study were used
	The other utility values are described as 'disutility weights' which are applied to the baseline 'well' value. These values are taken from studies in patients or were arbitrarily assigned by the researchers (transient AF only) and so do not reflect community preferences. The methods used in the original studies are not reported
	It is not clear whether the values for 'disutility weights' are subtracted from the 'well' state or whether they are the value used. For example, heart failure has a disutility weight of 0.71. It is not clear whether 0.71 is the value used for heart failure or whether this value is subtracted from 0.86, making the value for heart failure 0.15. It seems more likely that the former method is used. Since patient preferences are likely to be higher than those of the general public, the use of a community preference value for 'well' and patient values for other states may underestimate utility losses
7. Were costs and consequences adjusted for differential timing?	Yes
8. Was an incremental analysis performed?	Yes
9. Was allowance made for uncertainty?	Yes
10. Did the presentation and discussion of study results include all issues of concern to users?	

Guidant (YHEC) evaluation of dual-chamber pacing (Sculpher[40] framework for appraisal of decision-analytic models)

1. Structure	
Is there a clear statement of the decision problem, the context and the perspective?	Single vs dual pacing is compared. It is not clear whether single ventricular and/or single atrial pacing are being compared to dual-chamber devices
Is a theory of the underlying disease detailed?	• Association between initial and subsequent events is well understood for AF, stroke and death • The model does not accommodate the two underlying causes of bradycardia (SSS and AVB) • Link between heart failure and pacing mode is less well understood. One study (Sweeney, 2003) suggests that ventricular asynchrony is the cause of increased rates of AF and heart failure in both single- and dual-chamber pacing (in SND with normal QRS)
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	Most assumptions are stated clearly and justified. However, there are some issues where the source of assumption is not clear, or where the assumption appears to be unjustified: • AF: where this develops on DCP, the patient moves to the heart failure arm. This is likely to overestimate the disutility and costs associated with AF as not all people who develop AF will develop overt heart failure • AF: where this develops in VVIR mode, the patient has a dual-chamber pacemaker inserted. This is contrary to clinical advice received by the present authors and contrary to the recommendations of the BPEG which suggest that dual-chamber pacemakers should have the facility to be converted to VVIR mode in case of development of AF. This assumption will increase the cost in the single-chamber arm. It may be that a typographical error has occurred and this statement refers to biventricular pacing. The authors can see no reason to assume that access to biventricular pacing would vary depending on original pacing mode and this assumption biases the analysis in favour of dual chamber • Assumptions regarding the use of biventricular pacemakers are acknowledged to be speculative. Regardless of the impact of assuming differential use of this intervention, as noted above, the use of biventricular pacing increases the cost of treatment of heart failure, therefore increasing the influence of differential heart failure rates between pacing modes on model outputs Transition probabilities: choices made appear, in some cases, to favour dual-chamber pacing: • The annual rates for AF are almost identical between arms in the model (0.136 vs 0.135 per year: YHEC report Table 2.1), which is contrary to the evidence suggesting a difference in AF. The evidence for a time-dependent risk of AF is not incorporated in the model • Although absolute values are low, the annual *relative* risk of heart failure between the two arms is high (0.03 in DCP vs 0.045 in VVIR, RR = 0.66). Source is cited as BTAG review.[43] However, this suggests a relative risk of 0.80 in the meta-analysis over a longer period. The present meta-analysis suggests a higher value for heart failure, which is non-significant (OR = 0.90). The YHEC value appears to favour dual-chamber pacing. The assumptions regarding the use of biventricular pacemakers exacerbate the impact on model outputs • Cardiac deaths: a slightly higher risk of cardiac death is modelled in the single-chamber arm: a risk difference of 0.8%. Source is cited as BTAG review, but no data are reported in that review for cardiac deaths. Total mortality data reported by BTAG suggest a risk difference over longer than 1 year of 0.2%. Mortality difference appears to be overestimated. The importance of this parameter is demonstrated in the one-way sensitivity analysis which shows that an increase in annual probability of 1 SD in DCP will result in single-chamber pacing dominating

continued

	• The difference in stroke rates may be overestimated in the YHEC model. Annual rates of 2.2% in DCP vs 3.9% are modelled, i.e. an annual difference of 1.7%. Taking the crude data from studies included in the present review, which were all longer than 1 year, risk differences of 0.3% are suggested. The largest risk difference reported in this review was 1.4% in PASE (ns)	
2. Disease states		
Is the chosen model type appropriate for the time dimension of the disease process?		Yes
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?		Yes
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?		No
Have any important disease states been omitted from the model?		No
3. Options		
Is there a clear statement of the options being evaluated?		Yes
Do these appear to cover the range of logical and feasible options?	Yes. Scenario analyses consider younger patients, in which the lifetime of the generator may be an issue. Assumptions regarding the use of biventricular pacemakers in heart failure are open to question and the sources for the estimates are not detailed	
4. Time horizon		
Is the time horizon of the analysis stated?		Yes: 10 years
If so, is this justified in terms of the underlying disease and the effect of interventions?	Yes: justified by advanced average age at implantation and life expectancy of pacemaker generator	
5. Cycle length (if relevant)		
If relevant, is the cycle length used in the model stated?		Yes
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	No justification, but 1 month seems reasonable and is sufficient to reflect most changes that are likely to occur. Finer resolution might be justified given that some states are likely to last for less than 1 month (e.g. transient AF, implantation and its early complications), but the impact is likely to be minimal	
6. Data identification		
Are the sources of parameter values in the model clearly stated?	No. See above: transition probabilities are reportedly derived from the BTAG review, but in some cases are not found in that document	
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	No: time available to develop the model is limited	
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane Library)?	Details of the literature review are not given. However, the studies quoted constitute the main evidence base available to the researchers on the effectiveness of DCP	
Are ranges specified for parameters?		No
Is there evidence to suggest selective use of data?		Yes
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?		No: one expert acknowledged in the report
Are the claims made about the model results tempered by the limitations of the data?		In some respects only
7. Data incorporation		
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?		No
Has a stochastic analysis been undertaken?		Yes

continued

If so, do the distributions in parameter values reflect second order uncertainty?	Yes, although values used for distributions are not given
Have appropriate distributions been selected for each parameter?	Yes
Have interval rates been translated into transition probabilities using the appropriate formula?	Event rates are reported in Table 2.1 in the YHEC report, but transition probabilities not given
If appropriate, has a half-cycle correction been applied to adjust the time-related estimate in the model?	Not known
8. Internal consistency Is there a statement about the tests of internal consistency that were undertaken?	No
9. External consistency Are any relevant studies and/or models identified by the analyst for purpose of comparison?	No
Have any comparisons of the outputs of the model with independent external sources been reported?	No
If so, are the conclusions justified? Have discrepancies been investigated and explained?	No

Caro evaluation of dual-chamber pacing (Drummond[41] framework for economic evaluations)

1. Was a well-defined question posed in answerable form?	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes
3. Was the effectiveness of the programmes or services established?	Yes: the analysis rests on the findings of CTOPP and MOST
4. Were all the important costs and consequences for each alternative identified?	Two assumptions regarding effectiveness are reasonable given the absence of significant results from studies, although it might be argued that the differences observed in trials should be included in the model and the uncertainty associated with them modelled. The approach taken may bias the model slightly against dual-chamber pacing, although the impact would be limited in a stochastic analysis, i.e. taking account of the uncertainty in these factors: • mortality rates are assumed to be identical • heart failure is not considered Complication rates are based on data from CTOPP and MOST. MOST provided the baseline (lower than CTOPP but provides data beyond the perioperative period) and the RR from CTOPP was applied The probability of AF becoming chronic and of anticoagulation being given were included The type of pacemaker (VVI or VVIR, DDD or DDDR) implanted was taken from data on usage in the UK. Ratio of usage for DDD:DDDR was approximately 50:50, while VVI:VVIR was 35:65. Rate-responsive pacemakers cost less. MOST, which provided the effectiveness data used in the model, was a trial of DDDR vs VVIR modes and in CTOPP 75% of patients received a rate-responsive pacemaker. The model may therefore underestimate the relative cost of dual-chamber pacemakers in relation to the effects assumed, i.e. rate-responsive and non-rate-responsive devices are assumed to have the same effectiveness, but the costs of dual-chamber devices are reduced by the difference in the proportion of rate-responsive devices used

continued

5. Were costs and consequences measured accurately in appropriate units?	Limitations in costing of stroke Utility values for stroke, pacemaker syndrome and complications are not reported A utility difference of 0.02 is maintained between the cohorts, based on data from MOST. The difficulty in interpreting the MOST utility data are noted, since there was a high rate of cross-over from VVIR to DDDR and this dilutes the apparent effectiveness of dual-chamber pacing. This is therefore a conservative assumption
6. Were costs and consequences valued credibly?	Costs of stroke are reported as "initial costs of stroke" and derived from HRG data, which costs only length of initial hospital stay (9–13 days). Community costs of stroke to the NHS are therefore excluded. This biases the model in favour of single-chamber pacing, although the number of strokes is small (absolute difference of 2.6 events in 5 years) and so the impact minimal Utility values for stroke, pacemaker syndrome and complications are not reported Costs of anticoagulation in AF are important. Value assumed is £432 per patient per year, based on six physician visits per year, monitoring and cost of warfarin. Source for the relatively high rate of physician contact is not reported. The specific impact of varying the cost of AF in the model is not reported Pacemaker syndrome is modelled on the basis of data from MOST which, as a trial of mode, gives a higher rate for cross-over than seen in trials of device (CTOPP and UKPACE). Overall, 18% of patients had an upgrade from single- to dual-chamber devices The need to reprogramme dual-chamber pacemakers to single-chamber mode in the presence of AF is not included. This biases the analysis, to a small degree, in favour of dual-chamber pacing The benefits of anticoagulation in terms of avoidance of stroke are modelled but the disbenefits through major and minor bleeding episodes are not included. The benefits of dual-chamber pacing may therefore be slightly overestimated
7. Were costs and consequences adjusted for differential timing?	Yes
8. Was an incremental analysis performed?	Yes
9. Was allowance made for uncertainty?	Yes. The DES approach allows some parameter uncertainty to be taken into account during the base-case analysis, although key variables were held constant (utility gains from DDD, risk of pacemaker syndrome, unit costs and AF risk reduction). A further 100 simulations were carried out to generate probabilistic results
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes

Caro evaluation of dual-chamber pacing (Sculpher[40] framework for appraisal of decision-analytic models)

1. Structure	
Is there a clear statement of the decision problem, the context and the perspective?	Yes
Is a theory of the underlying disease detailed?	Yes. Conservative assumptions regarding the impact of dual-chamber pacing on mortality and heart failure are assumed
	The DES approach allows modelling of stroke to take account of age, gender, hypertension, prior history of diabetes and TIA or stroke
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	Yes. The implications of relaxing assumptions are explored through one-way and multiway sensitivity analyses
2. Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	The choice of DES approach is appropriate and allows flexibility in accommodating different patient characteristics. The argument against a Markovian approach is overstated
	The duration is restricted to 5 years on the basis of a lack of longer term data. This is reasonable, although the purpose of the model should be to explore the potential longer term consequences since they are likely to be important given the potential life expectancy of patients
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Disease progression is modelled appropriately for those consequences included in the model. Time to events is not reported
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	Not reported
Have any important disease states been omitted from the model?	There is a case for including mortality and heart failure, taking account of the uncertainty in their relative incidence. The model is therefore a conservative simplification
3. Options	
Is there a clear statement of the options being evaluated?	Yes
Do these appear to cover the range of logical and feasible options?	Yes
4. Time horizon	
Is the time horizon of the analysis stated?	Yes
If so, is this justified in terms of the underlying disease and the effect of interventions?	Yes, although a longer time horizon would be justified with appropriate caution
5. Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated?	Not reported
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	Not reported
6. Data identification	
Are the sources of parameter values in the model clearly stated?	Mostly. It is not completely clear how utilities are handled in the model. A constant difference of 0.02 is assumed between arms, with an identical declining rate of 0.01 applied to both arms. It is not clear, therefore, how the utility associated with discrete events is handled in the model, i.e. stroke, AF, complications
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	The evidence base used in the model is appropriate. There is some underestimation of costs of stroke, which biases against dual-chamber pacing, and the complications of anticoagulation are not considered, biasing against single-chamber pacing

continued

For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane Library)?	Search sources are not reported
Are ranges specified for parameters?	No
Is there evidence to suggest selective use of data?	Some restrictions have been placed on the analysis, although these are not unreasonable
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	No. The only parameter for which this applies is resource use associated with anticoagulation
Are the claims made about the model results tempered by the limitations of the data?	Yes
7. Data incorporation For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	In most cases
Has a stochastic analysis been undertaken?	Yes. Limited to 100 simulations, presumably for reasons of computational expense. The DES approach reflects some parameter uncertainty in sampling each individual's characteristics and allocating risks of events, although specific details are not included on which estimates are sampled from distributions (in particular whether risks are sampled or fixed)
If so, do the distributions in parameter values reflect second order uncertainty?	Yes
Have appropriate distributions been selected for each parameter?	No. Triangular distributions are used for the multiway sensitivity analyses. Characteristics of distributions used in the base case are not reported
Have interval rates been translated into transition probabilities using the appropriate formula?	Not relevant
If appropriate, has a half-cycle correction been applied to adjust the time-related estimate in the model?	Not relevant
8. Internal consistency Is there a statement about the tests of internal consistency that were undertaken?	No
9. External consistency Are any relevant studies and/or models identified by the analyst for purpose of comparison?	No. The predicted numbers of people suffering consequences after pacing can be compared to the crude numbers observed in the trials included in the present meta-analysis (a) Across all the trials, 2.4% of people suffered a stroke on dual-chamber pacing, compared with 2.7% on single chamber, a difference of 0.3%. The Caro model predicts a difference of 0.26%. The relative improvement is around 25%, compared with the (non-significant) OR of 0.81 from the present meta-analysis (b) The risk difference for chronic AF in the Caro model is 2.95%. In the trials (which were of less than 5 years' duration and did not all report chronic vs transient AF), the difference in AF risk was 1.5% including data from UKPACE and 1.7%. (c) The Caro model predicts a slight increase in complications requiring operative intervention (0.128%), which may be an underestimate. In CTOPP, pneumothorax, haemorrhage and lead dislodgement fall into this category. Lead dislodgement occurred with increased absolute risk of 2.8% in dual-chamber pacing. The impact of this on the results is considered in sensitivity analysis and is not significant

continued

Have any comparisons of the outputs of the model with independent external sources been reported?	No
If so, are the conclusions justified? Have discrepancies been investigated and explained?	In general, the conclusions follow from the results

Sutton and Bourgeois (1996)[98]

Authors:	Sutton and Bourgeois	**Inclusion criteria:**
Date:	1996	Age ≥ 65 years
Type of study:	cost–benefit analysis	Patients with physically active life selected for implantation of dual-chamber pacemakers in stable sinus rhythm 24–48 hours after admission
Country:	UK	
No. of centres:		
Protocol presented in separate publication? No		**Exclusion criteria:**
Recruitment period: NA		Not stated
Follow-up period:		
Average follow-up:		
Intervention:	DDD	**Primary and secondary outcomes:** **Outcome measurement:**
Comparison:	VVI	
Pacing indications:	complete heart block	
No. of patients:	18	
Diagnostic criteria:		Definition retrograde activation
		Definition of pacemaker syndrome: Hospitalisation for heart failure
Characteristics of programming provided?		Patients receive same device?
		Lower rate: upper rate:
		Other programming features:

Results: population states

	SSS/VVI	SSS/DDD	AVB/VVI	AVB/DDD
Incidence at first year of:				
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%	2%
Pacemaker syndrome	2%	0%	2%	0%
Mortality	6%	3%	7%	5%
Incidence at following years of:				
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%
Patient's survival at:				
Year 1	94%	97%	93%	95%
Year 2	88%	94%	87%	90%
Year 3	83%	91%	81%	86%
Year 5	74%	86%	70%	79%
Year 7	67%	81%	61%	71%
Year 10	57% (43% have a DDD result of upgrade)	71%	51% (42% have a DDD result of upgrade)	61%
Patient with heart failure at (% of survivors):				
Year 1	6%	2%	6%	2%
Year 5	30%	10%	30%	11%
Year 10	52%	21%	53%	21%
Disability at (% of survivors):				
Year 1	1%	0%	0%	0%
Year 5	10%	2%	5%	1%
Year 10	36%	8%	22%	3%

Results: costs

	SSS/VVI	SSS/DDD	AVB/VVI	AVB/DDD
Cumulative cost at (in arbitrary units, excluding cost of routine replacement at year 6 (300):				
Year 1	283	357	273	355
Year 2	372	384	338	375
Year 3	494	422	423	402
Year 5	870	548	662	484
Year 7	1413	726	976	591
Year 10	2453	1118	1642	783
Cost of disability and heart failure:				
Disability units	1334 (55%)	422 (38%)	680 (41%)	123 (16%)
Heart failure units	693 (28%)	239 (21%)	510 (31%)	169 (22%)

Sutton and Bourgeois[98] (Sculpher[40] framework for economic evaluations)

Sutton and Bourgeois		
1. Structure of the model		
Is there a clear statement on the decision problem, context and perspective?	Not very clear	
Theory of underlying disease?	Indirectly but not explained nor referenced	
Assumptions in the model clearly specified? Justified? Relaxed?	1. Mortality of patients is equal whether heart failure complications occur or not 2. Probabilities of first year are different to probabilities of subsequent years 3. ITT (cost of upgrade is added to the ventricular arm) 4. DDD and AAI are assumed to be the same pacing system, thus data were pooled together. This is inappropriate (since AAI is not recommended in AVB and ventricular is not recommended in SSN)	
2. Disease states		
Model type appropriate for the time dimension of the disease?		No
Justification of the choice of states provided		No
Empirical evidence of the suitability of the states?		No
Any important states omitted?		?
3. Options and strategies		
Is there a clear statement of the options being evaluated?		Yes/indirectly
Cover full range of logical and feasible options		?
4. Time horizon		
Exhaustive in time and coverage of option through time		Model run for 10 years
Justification based on disease and effect of interventions		? No
5. Cycle length		
Used if relevant?		?
Justified? Related to disease?		
6. Data identification		
Sources of parameter values	Literature survey for outcomes (upgrade from VVI to DDD, AF, stroke, disability as result of stroke, heart failure, pacemaker syndrome, mortality). Pacemaker-mediated tachycardia omitted since it does not contribute to costs and morbidity Upgraded were considered equal to total incidence of pacemaker syndrome plus half the incidence of heart failure Costs: an arbitrary currency unit was used; year base: 1991 Pacemakers, survey of six manufacturers (UK market charges) cost of VVI = 100, cost of DDD = 166 Procedures, hospitalisation, medications: one-site charges for implantation (Westminster Hospital). Single chamber: 45-minute implantation, dual-chamber 60-minute implantation, plus two nights as hospital inpatient. Follow-up costs: charges derived from the same site Cost of AF therapy and outpatient therapy as above. Stroke: costed based on seven nights' inpatient stay plus long-term care costs of permanent disability (local figures, no more details). Heart failure: medical treatment with furosemide and ACE at standard UK prices and average daily doses, cost of complications for HF assumed equal to 1 week inpatient stay Upgrading costs: cost of new generator plus additional pacing lead plus 60-minute use of operation room, one night's stay and disposal of explanted generator	

continued

	Is reasonable empirical justification from early iterations of the model given that these data are obtained from all low-cost data sources (i.e. secondary data)?	No
	Are ranges specified for parameters?	Sensitivity: yes
	Evidence to suggest selective use of data?	No, only non-randomised trials were used though (RCTs were not available). Pacemaker syndrome was not calculated considering cross-over trials
	If parameters are valued based on elicitation of expert opinion methods, have methods been adequately described (inclusion criteria, sample size, elicitation methods)?	No
	Are the claims made by model 'tempered' by limitations in the data?	No
7.	Data incorporation For each parameter, is there a clear justification on how data have been incorporated into the model?	Yes
	Has a stochastic analysis been undertaken? If so, do the distributions in parameters reflect second order uncertainty? Have appropriate distributions been selected for each parameter?	No
	Have interval rates been translated into transition probability using the appropriate formula?	?
	Has a half-time related estimate been applied?	No
8.	Internal consistency Does it work? Is there a statement about internal consistency?	Not clear

Mahoney[94] (Sculpher[40] framework)

1.	Structure Is there a clear statement of the decision problem, the context and the perspective?	
	Is a theory of the underlying disease detailed?	No. The study refers to progression to adverse outcomes (AF, CHF, thromboembolism, stroke and mortality) as main events considered without further description. Pacemaker syndrome is considered with no additional explanation for the method used
	Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	No, the model used is not described
2.	Disease states Is the chosen model type appropriate for the time dimension of the disease process?	Not stated
	Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Not stated
	Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	Not stated
	Have any important disease states been omitted from the model?	All relevant states have been considered
3.	Options Is there a clear statement of the options being evaluated?	Yes, the study aimed to determine the long-term costs for individuals paced in DDD, AAI or VVI modes
	Do these appear to cover the range of logical and feasible options?	Yes
4.	Time horizon Is the time horizon of the analysis stated?	No
	If so, is this justified in terms of the underlying disease and the effect of interventions?	N/A
5.	Cycle length (if relevant) If relevant, is the cycle length used in the model stated?	No
	Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	No

continued

6. Data identification		
Are the sources of parameter values in the model clearly stated?	Effectiveness data sources were not described. Cost data were derived from DRG payments for urban areas without further details	
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?		No
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane Library)?		No
Are ranges specified for parameters?		No
Is there evidence to suggest selective use of data?	It is not possible to draw conclusions since data are not reported	
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?		NA
Are the claims made about the model results tempered by the limitations of the data?	Yes. The model concludes that the cost of atrial-based pacing is higher at implant but becomes lower by 24–27% with DDD and by 34–35% with AAI when subsequent events are considered	
7. Data incorporation		
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?		No
Has a stochastic analysis been undertaken?		No
If so, do the distributions in parameter values reflect second order uncertainty?		NA
Have appropriate distributions been selected for each parameter?		NA
Have interval rates been translated into transition probabilities using the appropriate formula?		NA
If appropriate, has a half-cycle correction been applied to adjust the time-related estimate in the model?		Not stated
8. Internal consistency		
Is there a statement about the tests of internal consistency that were undertaken?		No
9. External consistency		
Are any relevant studies and/or models identified by the analyst for purpose of comparison?		No
Have any comparisons of the outputs of the model with independent external sources been reported?		No
If so, are the conclusions justified? Have discrepancies been investigated and explained?		Not stated

Health Technology Assessment Programme

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We look forward to hearing from you.

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