Dual versus Single Chamber Pacemaker Therapy for Atrioventricular Block and Sick Sinus Syndrome

A Birmingham Technology Assessment Group Report

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About Birmingham Technology Assessment Group

The Birmingham Technology Assessment Group produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities. Each review takes 3-6 months and aims to give a timely and accurate analysis of the available evidence, generating an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

About InterDEC

BTAG is part of a wider collaboration with three units in other Regions (the Trent Working Group on Acute Purchasing, the Scottish Health Purchasing Information Centre and the Wessex Institute for Health Research and Development) to share the work on reviewing the effectiveness and cost-effectiveness of clinical interventions. This group, "InterDEC", shares work, avoids duplication and improves the peer reviewing and quality control of these reports.

Contributions of Authors

Janine Dretzke (JD) was the main author. She was responsible for the day-to-day management of the report; undertook all searches; designed the protocol, designed and piloted data inclusion, data extraction and study quality proformas; undertook assessment of study eligibility, validity and extracted and collated data for them; liased with external experts and wrote and collated the report.

Rod Taylor (RT) was the project manger and took overall responsibility for the report. He advised on protocol development; undertook quality assessment of a subset of studies; wrote the section on the review of previous economic studies; assisted in the general writing of the report and provided general statistical advice.

Gregory Lip (GL) provided clinical guidance, assisted in the protocol development and commented on the draft report.

William Toff (WT) provided clinical guidance and commented on the draft report.

James Raftery (JR) provided health economics advice and commented on the draft report.

Anne Fry-Smith (AFS) advised on the search strategy and applied in- and exclusion criteria to a subsection of identified studies.

Conflicts of Interest

None.

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West Midlands Development and Evaluation Committee Recommendation:

The recommendation for the preferential use of dual chamber pacemakers over single chamber pacemakers for atrioventricular block and sick sinus syndrome is:

Borderline

Whilst 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 British Pacing and Electrophysiology Group[1] guidelines for atrioventricular block (see table 2).

Anticipated Expiry Date

- This report was completed in February 2002.
- The searches on clinical effectiveness were completed in June 2001, searches on cost-effectiveness in July 2001.
- Five large randomised controlled trials are currently ongoing in the UK, USA, Denmark and Canada, which will provide important new evidence (see table 5 of this report for details).
- On reporting of these results it is anticipated that this report require updating.

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Executive Summary

Background
Over the last 20 years, there has been an increase both in the overall implantation rate of pacemakers, and the implantation of dual chamber pacemakers compared to single chamber pacemakers for atrioventricular block and sick sinus syndrome.[2]

This systematic review was undertaken to address a regional policy question regarding the short- and long-term clinical and cost-effectiveness of dual versus single chamber pacemaker therapy. Dual chamber pacing systems are believed to have an advantage over single chamber models in that they more closely maintain normal cardiac physiology by preserving atrioventricular synchrony, however dual chamber models are up to twice the cost of single chamber models.[3]

The focus of this review was the comparison of dual and single (ventricular) pacing systems. The review has not investigated the potential benefits of single chamber atrial pacing compared to single chamber ventricular pacing, nor the potential differences in effectiveness between rate-adaptive and non rate-adaptive pacemakers. In order to inform the choice of type of pacemaker for a given indication, the results of this review need to be considered in conjunction with these other pacing issues.

Evidence of effectiveness
The quality of the clinical effectiveness evidence was poor, and therefore the findings of this review are potentially subject to bias and overestimation of effect size. There was heterogeneity between studies in terms of population characteristics, outcomes measured and type of randomisation (mode or device), and the potential biases associated with this need to be taken into account. Nevertheless, a consistent benefit across studies of dual chamber pacing compared to single chamber pacing was observed for both primary and secondary outcomes. This included a statistically significant reduction in pooled mortality, pacemaker symptoms and exercise capacity. The effectiveness according to condition (sick sinus syndrome or atrioventricular block) could not be thoroughly investigated as the majority of patient data was represented in an aggregated form.

The clinical effectiveness findings support the current British Pacing and Electrophysiology Group guidelines [1] that recommend dual chamber (over single chamber) pacing for AV block.

Economic analysis
This review was unable to identify any studies formally assessing the cost-effectiveness of dual compared to single chamber pacing. The results of the four costing studies of dual versus single pacing were inconclusive. Two studies reported an overall reduction in the incremental health service costs (including downstream costs such as complications and follow up clinics) with dual chamber pacing relative to single chamber pacing while two studies reported an increase in overall incremental health service costs.

Implication for future research
The five large randomised controlled trials being carried out in the UK, USA, Canada and Denmark, which are either due to report shortly or are ongoing, will provide important new evidence. The results of this report will have to be updated once results have been fully reported.

1 Introduction

Cardiac pacemakers are used effectively to replace or control the heart's intrinsic electrical activity. Compared with early pacemaker models, which paced at a fixed rate and could not be inhibited or synchronised with the underlying heart rhythm, modern pacemaker systems have become more sophisticated in terms of programmable modes and rate responsiveness, and they are better able to mimic the physiological pattern of cardiac activation.

Both dual chamber and atrial based pacing (see section 2.2) are believed to have an advantage over single chamber ventricular pacing in that they more closely resemble normal cardiac physiology by maintaining atrioventricular synchrony and dominance of the sinus node, when intact.[4,5] This in turn is thought to reduce the incidence of 'pacemaker syndrome' (a series of symptoms associated with the loss of AV synchrony such as breathlessness, syncope, chest pain and fatigue), atrial fibrillation, stroke, thromboembolic events and heart failure, thereby improving patient survival and/or quality of life. [6,4,7]

However, more complex models of pacemaker, such as dual chamber rate-responsive devices, are up to twice the cost of simple models, such as single chamber non-rate-responsive devices. [3] This is due to more expensive hardware (generator and additional lead), longer time needed for implantation and potentially additional follow-up due to increased complications or reprogramming requirements. [1,6]

An ageing UK population and an increasing survival rate amongst recipients of paediatric congenital heart surgery are likely to increase the pacemaker implantation rate, which is currently below the European average.[2] Pacemaker therapy is also being used for a variety of new indications, such as atrial fibrillation and heart failure. In addition to an overall increase in the number of new implants there has been a clear trend over the last 20 years to increased use of more complex rate-responsive and/or dual chamber systems.[2]

This systematic review was undertaken to address a regional policy question regarding the short- and long-term clinical and cost-effectiveness of dual versus single chamber (ventricular) pacemaker therapy. Although of clinical relevance, the review did not investigate the evidence regarding the potential clinical benefit and cost-effectiveness of single chamber atrial pacing compared to ventricular pacing. Neither did the review aim to assess the suitability of a given pacemaker model for specific indications.

A number of reviews exist on the topic but none include both a systematic search of different data sources and a review of economic studies. [4,5,8]

2 Background

2.1 Indications for pacing

Cardiac bradyarrhythmia (slow heart rhythm) results from disturbance of the generation or conduction of cardiac electrical activity and can be corrected by implantation of an artificial pacemaker. Sick sinus syndrome (SSS), where the disturbance occurs at the sinus node, and atrioventricular block (AV block), where the disturbance occurs at the AV node, accounted for around 70% of UK pacemaker implants in 1999.[2]

Sick sinus syndrome
SSS refers to a spectrum of cardiac arrhythmias that includes sinus arrest, sinoatrial block, sinus bradycardia or alternating paroxysmal atrial tachyarrhythmias with bradycardia (tachy-brady syndrome). In sinus arrest, the sinus node fails to initiate an impulse, whilst in sinoatrial block, an impulse from the sinus node is generated but fails to activate the atria.[9] Patients can develop symptoms such as syncope, lightheadedness or dyspnoea during episodes of bradycardia, while patients with the tachy-brady syndrome may develop atrial fibrillation.[10] Documented symptomatic bradycardia is generally considered to be an indication for pacing.[7, 11] Chronotropic incompetence is a type of sinus node dysfunction, where there is an inadequate sinus response to exercise or stress.[6]

Atrioventricular block
AV block refers to an abnormality in AV conduction and is classified as first, second (type I or II) or third degree (complete) block. Complete heart block is defined as the absence of all atrioventricular conduction. Patients may be asymptomatic or experience symptoms due to bradycardia (slow heart rate) and/or ventricular arrhythmias. Pacemaker therapy is generally recommended for patients with symptomatic bradycardia and also on prognostic grounds for high-grade AV block.[6, 9]

Other indications
Other indications for pacing include combined SSS with AV block, neurocardiogenic syncope and pause-dependent ventricular or supraventricular tachycardia.[6,10] In recent years, pacemaker therapy has also been advocated for conditions such as hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, the long QT syndrome and after cardiac transplantation.[6]

2.2 Pacing systems and modes

Permanent pacing systems consist of an implantable pulse generator containing a battery and electronic circuitry, together with one (single chamber pacemaker) or two (dual chamber pacemaker) leads. The leads both conduct intrinsic atrial or ventricular signals to the sensing circuitry and deliver the pulse generator charge to the myocardium.[12]

Single chamber pacemakers sense/pace either in the atrium or the ventricle, while dual chamber pacemakers can sense/pace in both chambers. The atrial or ventricular output can either be inhibited or triggered in response to a sensed signal. Rate responsive pacemakers have one or more sensors that detect physical activity and adjust the pacing rate accordingly, which is necessary in patients with chronotropic incompetence.[13,1]

Parameters governing pacemaker operation such as pacing mode, output (voltage and pulse duration), sensitivity to intrinsic depolarisation (atrial, ventricular or both), rate (lower and upper rate limits and sensor based lower and upper rate limits), refractory period and rate adaptation can be reprogrammed non-invasively according to the recipient's requirements.[11,7] A dual chamber device, for example, can be programmed to a single chamber operating mode.

The North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) developed the NBG (NASPE BPEG Generic Code) code to describe different pacing modes.[14] The first letter signifies the chamber being paced (A=atrium, V=ventricle, D=both), the second, the chamber being sensed (A=atrium, V=ventricle, D=both) and the third, the response to a sensed signal (I=inhibited, T=triggered, D=both). The fourth letter (R) indicates whether the device has rate responsive capability and the fifth (rarely used) letter indicates the presence of antitachycardia pacing capabilities.[1,11] Table 1 describes the commonly used pacing modes:

Table 1: Pacing modes (NBG code) [1,11]

Chamber paced	*Chamber sensed*	*Mode of response to sensing*	*Rate adaptive behaviour*	*Description*
A	A	I	-	Atrial pacing on demand; output inhibited by sensed atrial signals.
A	A	I	R	Atrial pacing on demand; output inhibited by sensed atrial signals; atrial pacing rates can decrease and increase in response to sensor input, up to the programmed sensor-based upper limit of the rate.
V	V	I	-	Ventricular pacing on demand; output inhibited by sensed ventricular signals.
V	V	I	R	Ventricular pacing on demand; output inhibited by sensed ventricular signals; ventricular pacing rates can decrease and increase in response to sensor input, up to the programmed sensor-based upper limit of the rate.
V	D	D	-	Paces the ventricle; senses in both the atrium and the ventricle; synchronises with atrial activity and paces the ventricle after a pre-set atrioventricular interval up to the programmed upper limit of the rate.
D	D	I	-	Paces and senses in both the atrium and the ventricle; the only response to a sensed P or R wave is inhibition. No tracking of intrinsic atrial activity.
D	D	I	R	Paces and senses in both the atrium and the ventricle; the only response to a P or R wave is inhibition; atrial and ventricular pacing rates increase and decrease independently in response to sensor input; atrioventricular synchrony may not be achieved.
D	D	D	-	Paces and senses in both the atrium and the ventricle; paces the ventricle in response to sensed atrial activity up to the programmed upper limit of the rate.
D	D	D	R	Atrial and ventricular pacing rates can increase and decrease in response to sensor input up to the programmed sensor-based upper limit of the rate.

A=Atrial; V=Ventricular; I=Inhibited; R=Rate-adaptive; D=Dual

The choice of mode depends on the patient's underlying indication for pacing. A patient with SSS may only require atrial stimulation, as AV conduction can occur naturally, whilst a patient with AV block will require some form of ventricular stimulation.

The BPEG 1991 guidelines[1] stipulate that patients with intact AV conduction should be paced in the atrium only, whilst the ventricle should be paced if there is actual or threatened AV block. A contraindication to dual chamber pacing is AV block with chronic atrial fibrillation.

Table 2 shows the BPEG recommended pacing modes for various indications.

Table 2: BPEG recommended pacing modes [1]

Diagnosis	Optimal	Alternative	Inappropriate
Sinus Node Disease (SND)	AAIR	AAI	VVI, VDD
Atrioventricular Block (AVB)	DDD	VDD	AAI, DDI
SND and AVB	DDDR, DDIR	DDD, DDI	AAI, VVI
Chronic Atrial Fibrillation (AF) with AVB	VVIR	VVI	AAI, DDD, VDD
Carotid Sinus Syndrome (CSS)	DDI	DDD, VVI (hysteresis recommended)	AAI, VDD
Malignant Vasovagal Syndrome (MVVS)	DDI	DDD	AAI, VVI, VDD

The selection of mode according to the BPEG guidelines reflects the assumption that maintenance of AV synchrony where possible is most favourable.

Pacing and AV synchrony

The normal sequence of atrial depolarisation and contraction followed by ventricular depolarisation and contraction is termed atrioventricular (AV) synchrony. Maintenance of this sequence results in optimal ventricular filling and cardiac output.[4]

Asynchronous atrial and ventricular activity or retrograde atrial activation is thought to occur more frequently with VVI or VVIR pacing modes ('non-physiological' modes) and to be prevented by single chamber atrial or dual chamber pacing ('physiological' modes), as these modes allow dominance of the sinus node and more closely mimic normal cardiac physiology. [15,11,13,4,16,5]

'Pacemaker syndrome' refers to a spectrum of symptoms such as (pre-)syncope, dyspnoea, chest pain, palpitations and lethargy associated with this loss of AV synchrony.[16,17]

The incidence of reported pacemaker syndrome in VVI(R) pacemaker recipients varies widely in the literature, with estimates ranging from 7-10 % up to 83%.[15,11] One reason for this variation is the fact that there is no standard definition for pacemaker syndrome. Another is that the typical symptoms are common in cardiac patients with or without pacemakers.[4] Symptoms may also be a sign of pacemaker malfunction.[17]

In addition to avoiding pacemaker syndrome, it has also been suggested that dual chamber pacemakers reduce the risk of atrial fibrillation, stroke and death, and enhance exercise capacity and quality of life compared to single chamber pacemakers.[4,6]

2.3 Current service provision

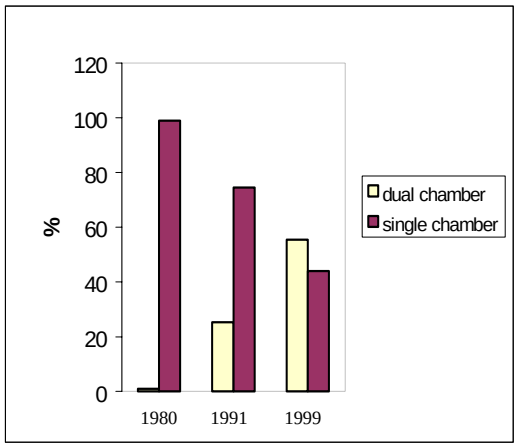
There is good evidence in the UK that the BPEG[1] guidelines are still not adhered to as outlined below.

In 1999, there were 17,160 new pacemaker implants in the UK, which is a rate of 297.4 per 1,000,000 population. The mean age at first implant in 1999 was 74.53 years, with the majority of recipients (87.7%) aged over 60 years.[2]

Although the annual implantation rate has been increasing during the past decade, there has been little growth over the last four years in the UK and the implant rate is behind (29% less than) that of other comparable European countries. Reasons for this could include block at the primary care stage, lack of specialist resources, an increasing burden of following up larger patient numbers, a financial compromise between numbers of new implants and complexity of implanted pacemakers or a reduction in pacing budgets due to an increasing number of ICD (Implantable Cardioverter-Defibrillator) implants.[2]

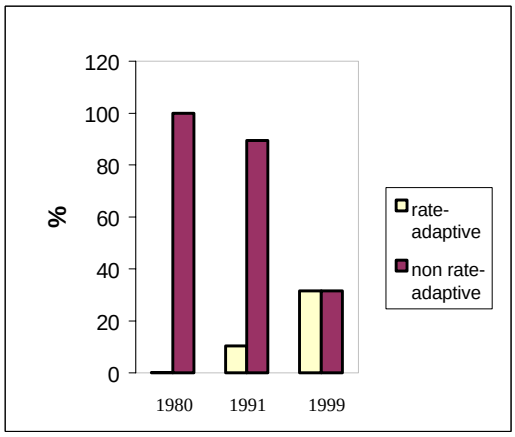
There has, however, been a clear trend towards an increase in the use of rate responsive and/or dual chamber pacemakers, accompanied by a decrease in single chamber ventricular and non-rate responsive pacemakers. This is shown in Figures 1-4 (data from National Pacemaker Database[2]):

Figure 1: Trends in single and dual chamber pacing in complete heart block



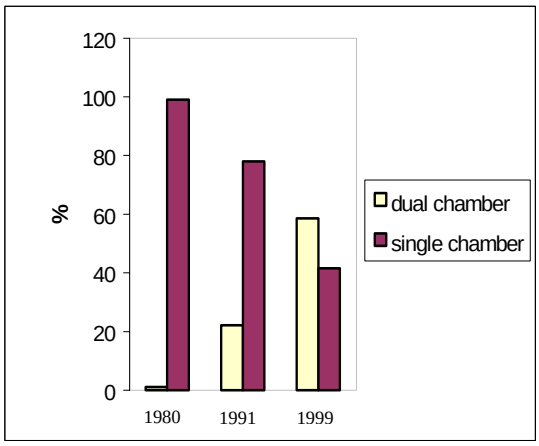
Dual = DDD, DDDR, VDD, VDDR
Single = VVI, VVIR

Figure 2: Trends in rate-adaptive and non rate-adaptive pacing in complete heart block



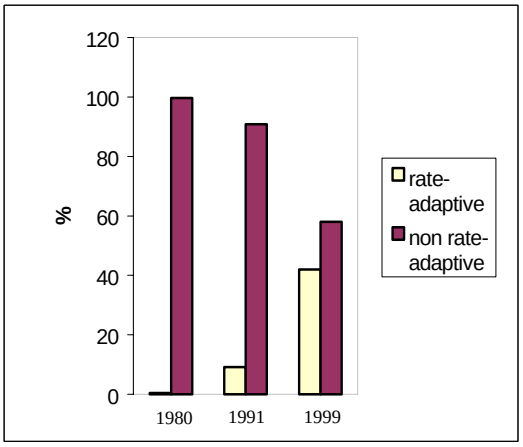
Rate-adaptive = DDDR, VDDR, VVIR
Non rate-adaptive = DDD, VDD, VVI

Figure 3: Trends in single and dual chamber pacing in sick sinus syndrome



Dual = DDD, DDDR, VDD, VDDR
Single = AAI, AAIR, VVI, VVIR

Figure 4: Trends in rate-adaptive and non rate-adaptive pacing in sick sinus syndrome



Rate-adaptive = AAIR, DDDR, VDDR, VVIR
Non rate-adaptive = AAI, DDD, VDD, VVI

Despite these trends, the distribution still does not reflect the BPEG guidelines, which recommend dual chamber or single chamber rate-responsive pacemakers as optimal therapy. This may be due to both the higher cost of more complex models and the lack of reliable comparative trial data, which might make physicians reluctant to adopt the more expensive technology. It is likely that the annual rate of new pacemaker implants will increase in the future. Reasons for this include an ageing population and an increased number of patients surviving congenital heart surgery. In addition, advances in pacemaker technology may increase the scope for pacing therapy for new and emerging indications. There is therefore a need to establish what evidence is available in terms of cost-effectiveness of more complex models.

3 Question addressed by review

This report aims to systematically review the available evidence regarding both short-term and long-term clinical effectiveness and cost-effectiveness of dual chamber pacemakers compared to single chamber ventricular pacemakers in adults with sick sinus syndrome, atrioventricular block or both, in terms of morbidity and mortality (primary outcomes) and quality of life, exercise capacity and complication rates (secondary outcomes).

The review will not investigate the evidence regarding the potential clinical benefit and cost-effectiveness of atrial based pacing compared to ventricular pacing. Neither does the review aim to assess which pacemaker model is the most suitable for a given indication.

There are a number of existing reviews but none that include both a systematic search of different data sources and a review of economic studies. [4,8,5]

4 Methods for review of clinical effectiveness

4.1 Search strategy

Scoping search
A scoping search (see appendix 1) was performed to identify appropriate literature concerning the background for the report, to ensure that no previous systematic reviews exist on the topic and to develop both the inclusion-and exclusion criteria and the data extraction proforma for the review.

Primary completed and ongoing research:
A formal search strategy for identifying randomised controlled trials using a validated search filter was developed with AFS. Electronic searches of MEDLINE, EMBASE, Science Citation Index and the Cochrane Library Controlled Clinical Trials Register were undertaken between 30/5/01 and 5/6/01 (see appendix 1). Searching was carried out as far back as 1980 as it was in the early 1980s that dual chamber pacemakers started to be increasingly implanted. No language restrictions were applied.

Ongoing research:
In order to identify ongoing research, the following data sources were searched: Cochrane Library Controlled Clinical Trials Register, National Research Registry, MRC funded projects, UK department of health research, British Heart Foundation, clinicaltrials.gov/ct/gui/c/b, www.controlled-trials.com, www.CentreWatch.com.

Personal contacts
Clinical experts (WT, GL) advised on published and ongoing trials, and the co-ordinators of all identified ongoing trials were contacted by letter for further information (see table 5).

Pacemaker related web sites
Professional associations' sites, such as the UK Pacing Society and the American Heart Association, patient group sites and manufacturers' sites were searched using '*pacemaker(s)*' and '*pacing*' as search terms.

Reference lists
Reference lists from reviews identified in the preliminary scoping search and included primary studies were searched for additional relevant primary studies.

4.2 Inclusion and exclusion criteria

All studies identified through the above search strategy were assessed by JD, and decisions on inclusion or exclusion made on the basis of the criteria listed below. A random sample of identified studies (10% of those studies remaining after initial exclusion criteria were applied) were independently assessed by AFS against the inclusion and exclusion criteria. A weighted Kappa score was calculated to determine the level of agreement (K=0.66, which indicated a good level of agreement[18]). Disagreements were resolved by a third party (RT). Only studies that met the following criteria were included:

Study design
Randomized controlled trials (RCTs) of either parallel or crossover design, comparing single with dual chamber pacemaker therapy.

Study duration
Only studies in which patients were paced for a minimum duration of 48 hours or more in one pacing mode were included in order to rule out any immediate complications after implantation or reprogramming.

Intervention
Permanent rate-adaptive or non rate-adaptive pacemakers capable of sensing and pacing in both the atrium and ventricle, i.e. dual chamber pacemakers (e.g. DDD, DDDR, DDI, DDIR, VDD or VVDR).

Comparator
Permanent rate-adaptive or non rate-adaptive pacemakers capable of sensing and pacing in either the ventricle or the atrium, i.e. single chamber pacemakers (VVI, VVIR, AAI, AAIR). Studies that compared more than one type of dual or single chamber pacemaker were included providing a single pacing mode was compared to a dual pacing mode as part of the study.

Study population
Patients aged 18 or over, where the majority of the population had sick sinus syndrome, atrioventricular block or both. There were no restrictions regarding the numbers of patients in a study.

Outcomes
The outcomes were chosen to reflect both costs and benefits to the patients (in terms of survival, symptoms, exercise capacity and quality of life) as well as costs to the health care provider (in terms of resources required for a patient over time). The chosen outcomes reflect assumptions made in the literature regarding potential benefits of dual chamber systems. Included outcomes were:

Primary outcomes:

- Cardiovascular mortality

- Morbidity: symptoms of pacemaker syndrome (as defined by the author of the trial), onset of atrial fibrillation, stroke or other thromboembolic events, heart failure

Secondary outcomes:

- Patient related quality of life (assessment to include: measurement of psychological/mental functioning; social functioning; physical status including ability to undertake everyday activities; symptoms caused by disease or treatment)

- Exercise assessment (a measurement of exercise duration or walking distance)

- Complication rate (including device complications severe enough to warrant an additional visit to hospital, surgical procedure or re-implantation of the pacemaker)

4.3 Quality assessment strategy

Quality assessment was performed to identify threats to the validity of the studies and to enable sensitivity analyses to be undertaken if appropriate. It has been reported that poor quality of controlled trials can introduce biases that result in substantial overestimates of the treatment effect size.[19]

A quality assessment checklist based on the Jadad scale[20](see data extraction form, appendix 2) was used for the quality assessment of both parallel and crossover studies, and a score calculated. Items assessed included method of randomisation, concealment, blinding, completeness and intention to treat analysis. It was also investigated whether outcomes were assessed both at the outset and end of each trial period. A number of assumptions were made when using the quality checklist (see appendix 3 for details). In addition to the Jadad criteria a number of other aspects of quality were assessed:

Parallel studies:
Additional quality items assessed were mode or device randomisation, comparability of study arms at the beginning of a trial, comparability of treatment of both study arms throughout the trial and adequacy of statistical power.

Randomisation by device (i.e. hardware) or mode (i.e. software) may have an influence on treatment effect. Whilst device randomisation reflects everyday practice, as patients receive the most appropriate device according to their condition, mode randomisation is more artificial in that patients randomised to a single chamber mode have a dual chamber device with an additional, unused lead implanted, which is then programmed to a single mode. In addition, any potential differences in complication rate or type between a single and a dual device would not manifest themselves in a trial using mode randomisation.

There is an argument that mode randomisation can lead to bias, as the decision to upgrade from a single to a dual mode may be influenced by the ease with which this can be achieved. There is a potential for overestimating the incidence of pacemaker syndrome and changing the mode of a too high proportion of pacemakers. In contrast, the incidence of pacemaker syndrome may be underestimated in the case of device randomisation, as comparatively minor symptoms may not be thought worth the risk of reimplantation.[21]

Crossover studies:
Additional items, which are particularly relevant for assessing the quality of a crossover study, are washout periods, period effect tests and unscheduled crossover rates. A washout period was considered to be present if there was a period of time between the 2 treatments, which was not included in the outcome assessment. Washout periods and period effect tests are important as the treatment in the first crossover period can influence the effect of the treatment (and therefore the outcomes) in the second crossover period and vice versa.[22] Equally, any treatment before the start of the study may influence the effect of subsequent treatment. The validity of assessment tools was also investigated.

All the quality items listed above were considered to be essential to the validity of the study. A study was judged to be of 'inadequate quality' if there was evidence of failure to meet two or more quality criteria. Studies were ranked according to study quality in order to assess the feasibility of carrying out sensitivity analyses of the impact of quality on the clinical effectiveness results.

4.4 Data extraction strategy

A data extraction proforma (appendix 2) was used to extract data on study characteristics, study quality and results. The proforma was piloted on a sample of primary studies and modified before use. Data from all included studies was extracted by JD. Quality data from a 10% sample of included studies was extracted independently by RT. Where data was only available in abstract form, or where it was not evident from the full publication whether the inclusion criteria applied, the authors were contacted.

4.5 Data synthesis

Results were collated in summary tables according to design (parallel or crossover) and outcomes, and the direction of effect described. A vote counting approach was used initially to show the direction of effect for all studies, as not all study results could be pooled due to lack of appropriate

data. Where appropriate data was available, meta-analysis was carried out using Review Manager software version 4.0.4. As there was no statistical evidence of heterogeneity, fixed effects pooling was used. Odds ratios (95% CI) were calculated for binary data and standardised mean differences (95% CI) were calculated for continuous data. Where possible, funnel plots were generated to assess publication bias. Results for patients with sick sinus syndrome and atrioventricular block are presented separately where possible.

5 Clinical effectiveness results

5.1 Quantity and quality of identified studies

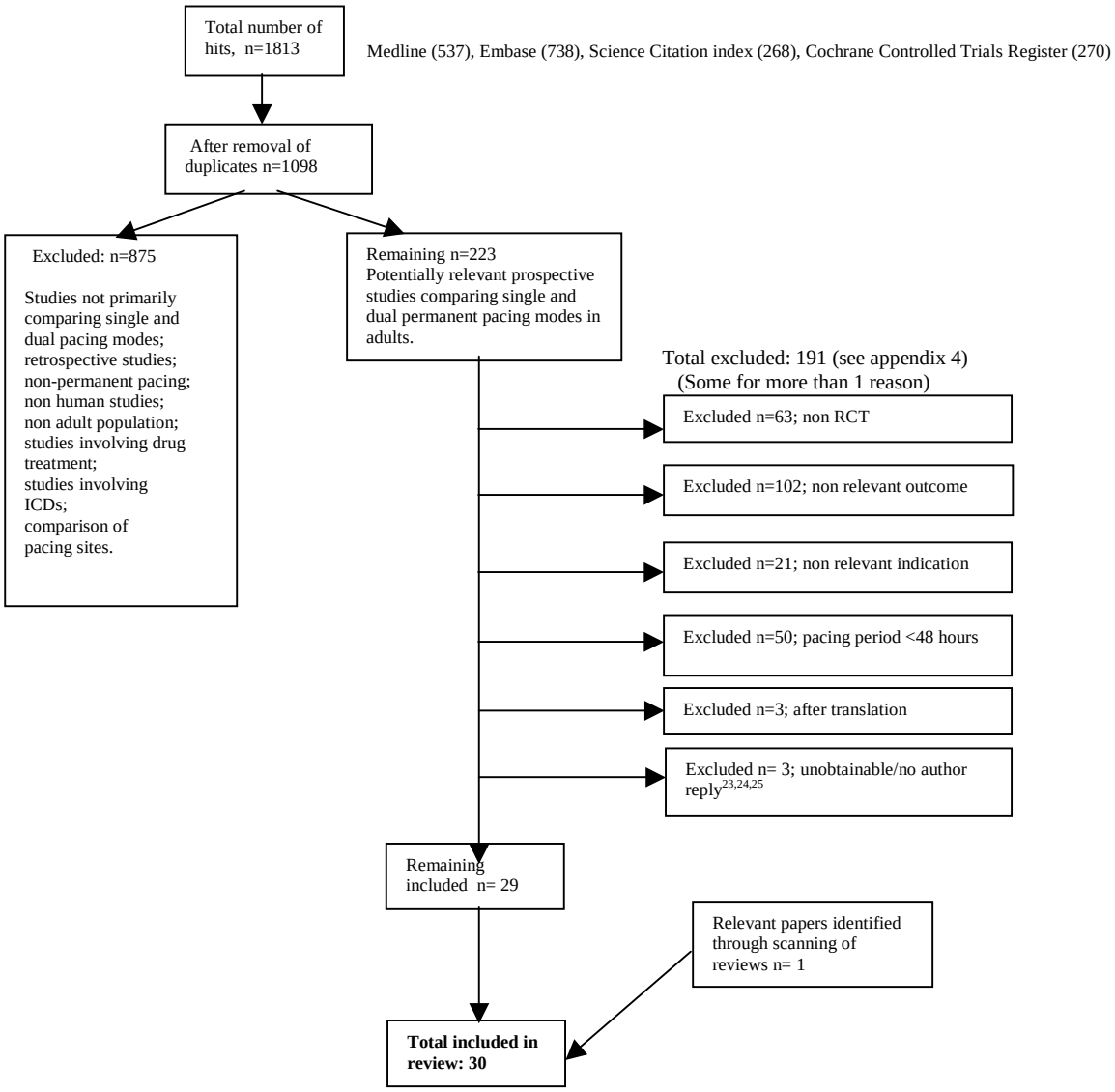
5.1.1 Quantity of identified studies

A total of 30 clinical effectiveness studies met the inclusion and exclusion criteria. The flowchart (Figure 5) shows how these were obtained. 875 studies were excluded at an early stage, as they were very clearly not applicable. The remaining 223 studies all related to a comparison between dual and single modes, but were excluded for one or more of the following reasons: study design other than RCT; patients with a condition other than atrioventricular block or sick sinus syndrome; patients in one pacing mode for less than 48 hours; outcome other than mortality or morbidity, quality of life, exercise capacity or complication rate assessed. Of these 223 studies, 29 were included, and 191 were excluded. Three studies were identified for potential inclusion, but sufficient details could not be obtained from the authors to make a decision to include or exclude them at the time of writing (at 13/09/01). All excluded/unobtainable studies are listed in appendix 4. One additional study, which was not identified by the search, was obtained through checking of citation lists

Of the 30 included RCTs, 4 were of parallel design and 26 were crossover RCTs. In addition, 5 ongoing or planned trials were identified.

The large number of citations identified, compared to the small number of subsequently included studies can be explained by the fact that there is a large volume of publications relating to pacemakers, many of which feature keywords which were necessarily included in the search strategy. In addition, a wide search filter was used to ensure that all randomised controlled trials were captured.

Figure 5: Search strategy for primary studies



5.1.2 General study characteristics

Tables 3-5 summarise the general study characteristics in terms of author, year, country, study design (parallel or crossover), population characteristics, intervention and comparator, pacing mode, length of study and outcomes investigated.

Parallel studies
Three fully published parallel RCTs and 1 parallel RCT published in abstract form only were identified, details of which are shown in table 3. Further details on the trial published in abstract form could not be obtained. There was heterogeneity between trials in terms of randomisation by mode or device, outcomes investigated, mode of pacemaker and population.

Both the trial by Connolly et al. (2000)[26]and Mattioli et al. (1998)[27]compare single chamber ventricular pacemakers with 'physiological' pacemakers (any mode that includes atrial sensing and/or pacing, i.e. dual or single chamber atrial pacing), whilst the trial by Lamas et al. (1998)[28]and Wharton et al. (1998)[29] compare only one dual mode with a single (ventricular) mode. 2 of the 4 trials use device randomisation, 2 use mode randomisation.

The mean ages of the populations in the fully published reports vary between 73 and 79, the median age of the population in the trial reported by abstract is 72. Table 6 lists proportions of patients with AV block or SSS, cardiovascular co-morbidity and cardiovascular drugs used. Populations are patients with SSS or AV block in 2 trials, patients with SSS or AV block or both in 1, and patients with SSS (with tachy-brady syndrome) in the trial by Wharton et al. (1998)[29]. The three fully published studies include patients with hypertension and ischaemic heart disease, the study by Connolly et al. (2000)[26] includes patients with arrhythmias and the study by Lamas et al. (1998)[28] includes patients with arrhythmias and heart failure. The three fully published studies report use of anti-platelets, the study by Connolly et al. (2000)[26] also lists anti-arrhythmic drugs and the study by Lamas et al. (1998)[28] reports varied drug use (beta-blockers, calcium antagonists, ACE inhibitors, diuretics, cardiac glycosides and anti-platelets). There is some variation in exclusion criteria for the three fully published trials, however all exclude patients with chronic atrial fibrillation. It is expected that these differences in populations may have an effect on the treatment, and the comparability of treatment effects between studies.

The outcomes assessed are pacemaker syndrome (in 2 studies), atrial fibrillation (in 4 studies), stroke (in 4 studies), heart failure (in 3 studies), mortality (in 3 studies), quality of life (in 2 studies) and complication rate (in 1 study). The mean length of follow up in the 4 trials ranged from 18.3 to 36 months.

Crossover studies
26 crossover trials were identified, details of which are shown in table 4. Patient numbers are smaller compared to the parallel studies (between 8 and 44 patients), although with patients acting as their own controls the numbers are effectively doubled. The study durations are shorter (between 7 days and 3 months for each crossover period), and the outcomes investigated are subsequently restricted to more short term ones (symptoms of pacemaker syndrome assessed by questionnaires and/or exercise tests). 25/26 studies investigate symptoms of pacemaker syndrome, whilst 14/25 investigate exercise capacity (duration or walking distance).

There is some variation in the modes compared (e.g. VVI vs DDD, VVI vs VDD, VVIR vs DDDR etc), and the number of modes compared (19 studies compare 2 modes, 6 studies compare 3 modes and 1 study compares 4 modes). Studies compare both non-rate-adaptive modes, rate adaptive modes or a combination of both. All comparators are ventricular pacemakers (VVI, VVIR), only 1 trial (Lau et al. (1))[30] compares dual chamber pacemakers to both ventricular and single chamber atrial pacemakers.

The mean age of patients (shown in table 4) ranges from 52 to 81. Overall there are slightly more men than women. Table 7 shows patients details regarding main pacing indication (AV block or SSS), cardiovascular co-morbidity and cardiovascular drugs used. There is heterogeneity both in the reporting of details and patient characteristics. All studies (19/25) that reported patient co-morbidity included patients with hypertension and/or ischaemic heart disease, which would be expected in an older pacemaker population. 11 study populations included patients with either dilated cardiomyopathy, heart failure, additional arrhythmias or a combination of these disorders. 6 studies excluded patients with chronic atrial fibrillation or flutter, 3 studies excluded patients on the basis of specific drug use and 2 excluded patients with congestive heart failure. 3 studies excluded patients on basis of chronotropic incompetence, whilst 5 studies stated that some or all of their patients were chronotropically incompetent. The whole population in the study by Kenny et al. (1986)[31] had angina pectoris, whilst the entire population in the study by Kamalvand et al. (1997)[32] had a history of atrial tachyarrhythmias. As with the parallel studies, it is expected that these differences in populations may have an effect on the treatment and the comparability of treatment effects between studies.

The 2 publications by Linde-Edelstam et al. (1992 (1) & (2))[33,34] appear to relate to the same trial as the study populations are identical, however different outcomes are investigated, and the studies have therefore been listed separately.

Comparison between parallel and crossover studies

It can be seen from table 3 and 4 that the mean age of the patients taking part in crossover studies (mean age 67.0) is lower than the mean age of those taking part in the parallel studies (mean age 73.7). It could be argued that younger patients, particularly those selected on the basis of their ability to take part in studies assessing exercise capacity, may be fitter or healthier than the general pacemaker population and therefore not representative. It should also be noted that the exercise tests undertaken may not necessarily be representative of the type of activities undertaken as part of daily life, and an improvement in an exercise test may not be generalisable in terms of ability to function in everyday life. Direct comparisons between crossover and parallel study results should be undertaken cautiously.

Ongoing and planned studies

Five ongoing or planned trials were identified, details of which are listed in table 5. All trial co-ordinators were contacted for additional information and responses are detailed in the table. All are parallel RCTs due to run for several years with patient numbers between 235 (1 study) and 2000 or above (4 studies). Outcomes vary between studies but include mortality, quality of life, atrial fibrillation, pacemaker syndrome and cost-effectiveness. Patient populations include those with AV block, SSS or both. No interim results were obtainable at the time of completion of this report, but results for some of the trials should be available at the end of 2001 or in 2002.

Table 3: General study characteristics: parallel studies

Author, Year	Country	Population			Intervention	Comparator	Mode or device randomisation	Length of study	Outcomes						
		Indication	Size (m/f)	Age					PMS	AF	S	HF	M	QOL	CR
Connolly et al., 2000[26]	Canada	SSS or AV block or both	2568 (ventricular group: 60.2%/39.8%; physiological group: 57%/43%)	73 +/-10	'Physiological' pacemaker (dual or atrial, some rate-adaptive) n=1094	Ventricular pacemakers, some rate-adaptive n= 1474	Device	36 months average (range 24-60 months)		✓	✓	✓	✓		✓
Lamas et al., 1998[28]	USA	SSS or AV block	407 (60%/40%)	76 +/- 7	DDDR n=203	VVIR n=204	Mode	18.3 months average (range 7.2-33.2 months)	✓	✓	✓	✓	✓	✓	
Mattioli et al., 1998[27]	Italy	SSS or AV block	210 (113/97)	79 +/- 9	'Physiological' pacemaker (DDD, VDD, AAI) n=105	VVI, VVIR n=105	Device	24 months		✓	✓				
Wharton et al. 1998[29]*	USA	SSS (with tachy-brady syndrome)	198 (109/89)	Median 72	DDDR n=100	VVIR n=98	Mode	23.7 months median	✓	✓	✓	✓	✓	✓	

PMS: symptoms of pacemaker syndrome; AF: onset of chronic atrial fibrillation; S: stroke or other thromboembolic event; HF: development of heart failure; M: all cause mortality; QOL: quality of life; CR: complication rate
*Based on abstract only (no author reply received at time of completing the report)

Table 4: General study characteristics: crossover studies

Author, Year	Country	Population			Intervention	Comparator	Length of study	Outcomes investigated			
		Indication	Size (m/f)	Age				Symptoms of pacemaker syndrome	Quality of life	Walking distance	Exercise duration
Avery et al., 1994[35]	UK	AV block	13 (7/6)	Mean 79.4	DDD	VVI	1 month	✓		✓	
Boon et al., 1987[36]	UK	AV block or SSS	15 (13/2)	Mean 69 (range 54-81)	DDD	VVI	4 weeks	✓			
Capucci et al., 1993[37]	Italy	AV block or SSS or both	14 (12/2)	Mean 66.5 (+/- 5)	DDD, DDDR	VVI	1 month	✓			✓
Channon et al., 1994[38]	UK	AV block	16 (8/8)	Mean 81.25 (range 77-88)	DDD	VVI	7 days	✓		✓	
Davis et al., 1985[39]	Australia	AV block	14 (10/4)	Mean 65 (range 23-84)	VDD	VVI	3 weeks	✓			✓
Deharo et al., 1996[40]	France	AV block	18 (14/4)	Mean 70 (+/- 6.5)	DDD	VVIR	1 month	✓			✓
Hargreaves et al., 1995[41]	UK	AV block	20 (14/6)	Mean 80.5 (+/-1)	DDD	VVIR	2 weeks	✓		✓	
Heldman et al., 1990[15]	USA	AV block or SSS or both	40 (23/17)	Mean 68 (+/- 10, range 47-86)	DDD, DDI	VVI	1 week	✓			
Kamalvand et al., 1997[32]	UK	AV block or SSS or both	48 (28/20)	Mean 64 (+/- 13)	DDDR, DDDR with mode switching	VVIR	4 weeks	✓			✓
Kenny et al., 1986[31]	UK	AV block or SSS or both	10 (4/6)	Mean 69.7 (+/- 10.4, range 52-83)	DDD (100), DDD (150)	VVI	1 month	✓			

Table 4 contd.

Author, Year	Country	Population			Intervention	Comparator	Length of study	Outcomes investigated			
		Indication	Size (m/f)	Age				Symptoms of pacemaker syndrome	Quality of life	Walking distance	Exercise duration
Kristensson et al., 1985[42]	Sweden	AV block	44 (22/22)	Mean 68 (+/- 13, range 18-84)	VDD	VVI	3 weeks	✓			
Lau et al., 1994 (1)[30]	Hong Kong	SSS	15	Mean 66 (+/- 2)	DDDR	AAIR, VVIR	4 weeks	✓	✓		
Lau et al., 1994 (2) [43]	Hong Kong	AV block or SSS	33	Mean 66 (+/- 1)	DDD, DDDR	VVIR	8 weeks	✓	✓		
Linde-Edelstam et al., 1992 (1) [33]*	Sweden	AV block	17 (13/4)	Mean 64 (+/- 11)	DDD	VVIR	2 months	✓	✓		
Linde-Edelstam et al., 1992 (2) [34]*	Sweden	AV block	17 (13/4)	Mean 64 (+/- 11)	DDD	VVIR	2 months				✓
Lukl et al., 1994[44]	Czech Republic	AV block or SSS	21	Mean 68 (+/- 8)	DDD	VVIR	2 weeks	✓	✓		
Menozzi et al., 1990[45]	Italy	AV block	14 (4/10)	Mean 72 (+/- 6)	DDD	VVIR	6 weeks	✓			
Mitsuoka et al., 1988[46]	UK	AV block or SSS	16 (14/2)	AV block group: 64.1 (+/- 12.2) SSS group: 63.3 (+/- 13.1)	DDD	VVI	1 month	✓			
Oldroyd et al., 1991[47]	UK	AV block	10 (7/3)	Mean 56 (23-74)	DDD	VVIR	1 month	✓			✓
Perrins et al., 1983[48]	UK	AV block	13 (9/4)	Mean 65 (32-87)	VDD	VVI	1 month	✓			
Rediker et al., 1988[49]	USA	AV block or SSS	19 (15/4)	Mean 69.5 (35-83)	DDD	VVI	6 weeks	✓			✓
Saner & Fricker, 1996[50]	Switzerland	AV block or SSS	12 (7/5)	Mean 68 (36-80)	DDD	VVIR	6 weeks	✓			✓

Table 4 contd

Author, Year	Country	Population			Intervention	Comparator	Length of study	Outcomes investigated			
		Indication	Size (m/f)	Age				Symptoms of pacemaker syndrome	Quality of life	Walking distance	Exercise duration
Sulke et al., 1994[51]	UK	AV block or AV block with SSS	10 (6/4)	53 (+/- 9.4, range 42-67)	DDDR	VVIR	4 weeks	✓			
Sulke et al., 1992[52]	UK	AV block or AV block with SSS	16 (11/5)	Mean 66.6 (41-84)	DDD	VVI	4 weeks	✓			✓
Sulke et al., 1991[53]	UK	AV block or AV block with SSS	22 (9/13)	Mean 51.9 (18-81)	DDD, DDIR, DDDR	VVI	4 weeks	✓			✓
Yee et al., 1984[54]	Canada	AV block	8 (4/4)	Mean 58.9 (+/- 18.4)	VDD	VVI	3 months	✓			✓

*Both publications by Linde-Edelstam et al. use the same study population, with each publication looking at different outcomes.

Table 5: General study characteristics: planned and ongoing trials

Name of Trial (Country)	Design	Population	Intervention	Comparator	Mode or device randomisation?	Length of Study	Outcome(s)	Stage of trial/expected completion date	Comments
UK PACE (UK)[55,56]	Parallel RCT	2000 patients >/= 70 years with AV block	DDD (50%)	VVI (25%), VVIR (25%)	Device	Minimum of 3 years	All cause mortality, quality of life, exercise capacity, cardiovascular events, cost-utility	September 2002	No interim data at time of report completion.
MOST (USA)[57]	Parallel RCT	2000 patients with SSS	DDDR	VVIR	Mode	Average 3 years	Primary: Stroke and all cause mortality Secondary: quality of life, cost-effectiveness, atrial fibrillation, development of pacemaker syndrome	Completion of trial likely end 2001.	No details obtained from author on unpublished data.
CTOPP (Canada) [26,58]	Parallel RCT	2568 patients with SSS, AV block or both	Physiological pacemakers	Ventricular pacemakers	Device	Follow-up extended from 3 to 6 years	Primary: mortality and stroke Secondary; atrial fibrillation, heart failure, complication rate	No details obtained for extension of follow up.	Published study included in this report. [26]
STOP-AF (UK)[59,60]	Parallel RCT	235 patients with SSS (mean age 73)	AAI(R), DDD(R)	VVI(R)	Mode	2 years planned but now extended	Primary: Permanent atrial fibrillation Secondary: death, intolerable pacemaker syndrome, worsening CCF (embolic events, mild pacemaker syndrome and symptomatic arrhythmias will also be noted)	Completion of trial likely end 2001.	No formal interim data at time of report completion.
DANPACE [61,62]	Parallel RCT	1900 patients with SSS	DDD	AAI	No information given	Mean 5.5 years	Primary: all cause-mortality No further details received.	Recruitment initiated 2 years ago, due to continue for 5-7 years. Final analysis scheduled after a mean follow-up time of 5.5 years for the total population.	Interim analyses scheduled to be performed by an international safety and ethical committee to determine whether study should continue. No data available at time of report completion.

Table 6: Patients' main indication for pacing, cardiovascular co-morbidity and drugs: parallel studies*

Study, Year	n/N AV Block	n/N SSS	n/N AV Block and SSS	Other /unknown	Hypertension/hypertensive heart disease	Ischaemic heart/coronary artery disease (including angina or previous MI)	Dilated cardiomyopathy	(Congestive) heart failure	Arrhythmias	Beta Blockers	Calcium Antagonists	ACE inhibitors	Diuretics	Nitrates	Anti-arrhythmic drugs	Cardiac Glycosides	Antiplatelets	Comment
Connolly et al., 2000 [26]																		Patients excluded if they had chronic atrial fibrillation, a pacemaker due to AV node ablation or if they were expected to die of a nonvascular cause in the next 2 years.
	52.2%	33.9%	8.1%	5.8%	35.2%	17.5%			20.9%						11.5%		34.9%	
Ventricular Group (n=1474)	50.8%	33.4%	8.5%	7.4%	35.2%	17.4%			21.4%						12.6%		33.7%	
Physiologic Group (n=1094)																		
Lamas et al., 1998 [28]																		Patients were excluded if they had clinically overt congestive heart failure, atrial fibrillation without documented sinus rhythm for 6 months, serious non-cardiac illness or inadequate atrial-capture or sensing thresholds.
Ventricular Group	201/ 407 (total)	175/ 407 (total)		31/ 407 (total)	51%	33%		28%	30%	16%	24%	27%	36%			23%	37%	
Dual Group					52%	33%		26%	27%	9%	26%	31%	34%			17%	41%	
Mattioli et al., 1998 [27]	100/ 210	110/ 210			101	99											101	Patients with history of cerebral events, (paroxysmal) atrial fibrillation, congenital heart disease, dilated cardiomyopathy, valvular heart disease and those treated with anti-arrhythmic drugs excluded.
Wharton et al., 1998 [29]		198/ 198																Information from abstract only. All patients with tachy-brady syndrome.

* Only those co-existing cardiovascular diseases and drugs listed, which fall into the above categories; details on non-cardiovascular diseases and drugs not listed. Patients can be listed in several categories; only drugs listed in the British National Formulary [63] were categorised.

Table 7: Patients' main indication for pacing, cardiovascular co-morbidity and drugs: crossover studies*

Study, Year	n/N AV Block	n/N SSS	n/N AV Block and SSS	Hypertension/ hypertensive heart disease	Ischaemic heart/ coronary artery disease (including angina or previous MI)	Dilated cardiomyopathy	(Congestive) heart failure	Arrhythmias	Beta Blockers	Calcium Antagonists	ACE inhibitors	Diuretics	Nitrates	Anti-arrhythmic drugs	Cardiac Glycosides	Antiplatelets	Comment
Avery et al., 1994 [35]	13/13																No patients had previous cardiac surgery or were receiving cardiac medication. No evidence of left ventricular impairment. No other chronic disability.
Boon et al., 1987 [36]	11/15	4/15															Patients excluded if presence of atrial fibrillation or angina on effort. No other details on co-morbidity or medication.
Capucci et al., 1993 [37]	4/14	5/14	5/14	4	1	2											Exclusion criteria: congestive heart failure, patients with possible drug influence on sinus automaticity, AV or infranodal conduction and those with possible electrolytic and metabolic abnormalities excluded. 7/14 patients chronotropically incompetent.
Channon et al., 1994 [38]	16/16			4	1				1	2	2	4				2	
Davis et al., 1985 [39]	13/13																Exclusion from study due to symptomatic left ventricular failure, if pacemaker was inhibited by normal cardiac rhythm, and due to pacemaker syndrome. No other details on co-morbidity or medication.
Deharo et al., 1996 [40]	18/18			2	3	1											Patients excluded due to: frequent atrial arrhythmias, chronotropic atrial insufficiency, exercise incompetence or contraindication, beta-blocker use. No patient had evidence of heart failure. Enrolled patients maintained on same drug regimen.
Hargreaves et al., 1995 [41]	20/20			6	1					2	2	3				2	Exclusion due to left ventricular dysfunction, evidence of retrograde AV conduction and chronotropic incompetence.
Heldman et al., 1990 [15]	14/40	21/40	5/40	2	9		3										4 patients with history of pacemaker syndrome. 1 patient had AV block associated with aortic replacement. No details on medication.
Kamalvand et al., 1997 [32]	25/48	23/48 SSS with or without AV block		11	16												All patients had history of atrial tachyarrhythmias. Use of class I and III anti-arrhythmic drugs discontinued before study. Other drugs (beta-blockers, digoxin, calcium channel antagonists) allowed (no details on patient numbers).
Kenny et al., 1986 [31]	6/10	2/10	2/10	3	10					3		3	10	2			All patients in study had angina pectoris, 3 of which had had previous MI.
Kristensson et al., 1985 [42]	44/44			11	11			5	5	4		16	3	1	18		
Lau et al., 1994 (1) [30]		15/15		2	2			4	1	1	1		2	1	3	1	
Lau et al., 1994 (2) [43]	15/33	18/33															All patients some degree of atrial chronotropic incompetence. No details on co-morbidity or medication.

Table 7 contd.

Study, Year, Ref	n/N AV Block	n/N SSS	n/N AV Block and SSS	Hypertension/hypertensive heart disease	Ischaemic heart/coronary artery disease (including angina or previous MI)	Dilated cardiomyopathy	(Congestive) heart failure	Arrhythmias	Beta Blockers	Calcium Antagonists	ACE inhibitors	Diuretics	Nitrates	Anti-arrhythmic drugs	Cardiac Glycosides	Antiplatelets	Further details
Linde-Edelstam et al., 1992 (1) & (2) [33,34]	17/17			6	2	1			1	1	1	7	2		1		Exclusion criteria: abnormal atrial chronotropic response.
Lukl et al., 1994 [44]	14/21	7/21		5	5	1											9/21 patients chronotropically incompetent. No details on medication.
Menozzi et al., 1990 [45]	14/14				9												Exclusion criteria: congestive heart failure, intermittent AV block, patients with acute or precipitating causes including drugs or acute myocardial infarction, presence of idiopathic or acquired left ventricular hypertrophy or retrograde AV conduction. No details on medication.
Mitsuoka et al., 1988 [46]	8/16	8/16		1	4				2	3							All patients with SSS (8) had evidence of chronotropic incompetence.
Oldroyd et al., 1991 [47]	10/10			2	2												Exclusion criteria: patients with recent myocardial infarction, appreciable angina or respiratory disease, chronic atrial flutter/fibrillation and exercise induced arrhythmias. 2 patients receiving medication - no details given.
Perrins et al., 1983 [48]	13/13																Exclusion criteria: severe physical disability, coincidence of another disease with a short prognosis, chronic atrial fibrillation, presence of dominant sinus rhythm with rare episodes of bradycardia, carotid sinus syndrome, retrograde AV conduction, isolated SSS and very thin patients. No details on co-morbidity or medication.
Rediker et al., 1988 [49]	11/19	8/19		7	10		2										No details on medication.
Saner & Fricker, 1996 [50]	5/12	7/12			3												Exclusion criteria: significant concomitant valvular heart disease. No details on co-morbidity (other than previous MI in 3 patients) or medication.
Sulke et al., 1994 [51]	7/10		3/10														No details on co-morbidity or medication.
Sulke et al., 1992 [52]	12/16		4/16		2	1		2									Exclusion criteria: chronic atrial fibrillation or flutter, patients unable to walk on treadmill, baseline score suggestive of pacemaker syndrome. No details on medication.
Sulke et al., 1991 [53]	14/22		8/22		7		3	1									No details on medication. All patients had chronotropic incompetence.
Yee et al., 1984 [54]	8/8			1	3		2										Exclusion criteria: documented atrial flutter, fibrillation or a slow fixed sinoatrial rate. No details on medication.

* Only those co-existing cardiovascular diseases and drugs listed, which fall into the above categories; details on non-cardiovascular diseases and drugs not listed. Patients can be listed in several categories; only drugs listed in the British National Formulary [63] were categorised.

5.1.3 Quality assessment and threats to validity

Parallel studies
Table 8 shows the results of the quality assessment for the parallel studies.

Table 8: Quality of parallel studies

Study, Year	Was trial described as randomised?	Randomisation method stated	Adequate concealment described	Was trial described as double-blind	Statement regarding blinding of participants	Statement regarding blinding of outcome assessors	Withdrawals stated	Statement regarding intention to treat analysis	Jadad score (0-5)	Unscheduled crossover from a single mode (n/N)	Unscheduled crossover from a dual mode (n/N)	Were study arms comparable at entry?	Were both study arms treated identically?	Mode (M) or device (D) randomisation?	Were patient s paced before start of study?
Connolly et al., 2000[26]	✓	X	X	X	X	X	X	✓	1	2.1%, 2.7% and 4.3%*	10.8%, 12.8% and 17.1%*	✓	CT	D	X
Lamas et al., 1998[28]	✓	X	✓	X	X	✓	X	✓	1	53/ 204	4/ 203	✓	CT	M	X
Mattioli et al., 1998[27]	✓	X	X	X	X	✓	✓	✓	2	Crossovers occurred, but numbers not stated.		CT	CT	D	X
Wharton et al., 1998[29]	✓	X	X	X	X	X	X	✓	1	44%	9%	CT	CT	M	X

*at 1,3 and 5 years
X: criteria not met
✓: criteria met
CT: can't tell

The quality of a study was considered to be 'inadequate' if there was evidence of two or more major threats to validity. This was the case for all four parallel studies, which was also reflected by the low score on the quality assessment scale (1/5 or 2/5). It should be noted that the quality assessment of the study by Wharton et al. (1998)[29] was based on the abstract only.

None of the studies reported on the method of randomisation, and allocation concealment was reported for one study only (Lamas et al., 1998).[28] One trial (Lamas et al., 1998)[28] was described as single blind, there were no statements regarding blinding in the other studies. There were no statements regarding patient blinding specifically, although two studies describe blinding at the outcome assessments.

Three of the four studies give numbers for unscheduled crossovers, i.e. early crossover to the other mode due to intolerable symptoms, however only one study (Mattioli et al., 1998)[27] was explicit about withdrawals. For the remaining studies it could not be assessed whether the numbers of withdrawals or crossovers were high enough to pose a threat to validity.

There was a statement regarding intention to treat analysis in all 4 studies. In the study by Mattioli et al. (1998)[27] it was stated that pacemaker reprogramming during follow-up was not considered when performing the statistical analysis, which was taken to be sufficient evidence of intention to treat. The study by Lamas et al. (1998)[28] contained a statement regarding intention to treat, although outcome assessment was carried out early in the case of an unscheduled crossover, and the score carried forward for subsequent analysis. As the unscheduled crossovers both in the study by Lamas et al. (1998)[28] and Connolly et al. (2000)[26] were high, this may have had an influence on the final analysis of treatment effect despite the intention to treat analysis.

Two of the four studies, Lamas et al. (1998)[28] and Connolly et al. (2000)[26], stated that patient numbers had been calculated to provide adequate statistical power. The other two studies reported no power calculation.

As the quality assessment was based solely on the published report, a low quality score may be a reflection on inadequate reporting by the authors. The use of an alternative quality scale may also have resulted in a different score. However, based on this quality assessment, there is a threat to the validity of the results of all four parallel studies.

As there is no clear distinction between studies in terms of adequate/inadequate study quality, subsequent sensitivity analyses of effectiveness results were not carried out.

Crossover studies

The results for selected quality assessment items are shown in table 9 below (full quality assessment results are listed in appendix 5). The studies were ranked according to study quality (highest quality at the top). No weighting was given to different quality items.

Again, the quality of a study was considered to be 'inadequate' if there was evidence of two or more major threats to validity. All crossover studies were deemed by this criterion to be inadequate. However, twelve studies scored 4/5 on the modified Jadad scale and 14 studies scored 2/5. This is partly a reflection of the scoring system, which in some instances requires the fulfilment of two criteria in order to receive one additional point and so does not show more subtle differences between the studies. It also shows that quality assessment based on the Jadad scale is not an ideal assessment tool for crossover studies, as poor quality studies scored up to 4/5.
No crossover studies reported concealment of allocation and no study included an outcome assessment both at the beginning and end of each crossover period, although some reported baseline results. No studies carried out a period effect test with the exception of the study by Hargreaves et al. (1995).[41]

The washout periods for symptom assessment were considered to be inadequate for 24/25 studies. Only the study by Kristensson et al. (1985)[42] stated that the questionnaire referred only to the last week of a three week crossover period, resulting in two weeks of washout period. The questionnaires of all other studies related to the whole of the preceding crossover period, and in some instances a daily diary was kept from day 1 of each crossover period. In addition, a number of patient populations were paced before the start of the study, either in one of the study pacing modes or an alternative mode. It can therefore not be ruled out that treatment before or during the crossover periods of the studies had an influence on effect size.

Losses to follow-up were considered to be a threat to validity if they were >/= 20%. This was the case for 2 studies, Avery et al. (1994)[35] with 23% loss, and Lau et al. (1) (1994)[30] with 20% loss.

All studies had small patient numbers and none showed that there were sufficient numbers to provide adequate statistical power. All crossover studies used mode randomisation.

Generally, the tools used for assessment of symptom incidence and severity were not validated and had been designed specifically for the individual studies or adapted from similar studies. There was little consistency across studies in terms of assessment tools.

As with the parallel studies, poor quality may be a reflection on poor reporting by the authors, and a different quality assessment scale may have resulted in a different quality sore.

As there is no clear distinction between studies in terms of adequate/inadequate study quality, sensitivity analyses of effectiveness results were not carried out.

Table 9: Quality of crossover studies

	Modified Jadad Score (0-5)	Randomisation method stated	Trial described as double-blind	Statement regarding blinding of participants	Statement regarding blinding at outcome assessment	Intention to treat analysis performed	Number of withdrawals	Period effect test carried out	Outcome assessment at baseline and end of each crossover period	Adequate washout period for symptom assessment
Lukl et al., 1994[44]	4	X	✓	✓	✓	✓	0/21	X	X	X
Perrins et al., 1983[48]	4	X	✓	✓	✓	✓	0/13	X	X	X
Sulke et al., 1992[52]	4	✓	✓	✓	✓	CT	0/16	X	X	X
Sulke et al., 1991[53]	4	✓	✓	✓	✓	CT	0/22	X	X	X
Kristensson et al., 1985[42]	4	X	✓	✓	✓	CT	0/44	X	X	✓
Menozzi et al., 1990[45]	4	X	✓	✓	✓	CT	0/14	X	X	X
Mitsuoka et al., 1988[46]	4	X	✓	✓	✓	CT	0/8	X	X	X
Kenny et al., 1986[31]	4	X	✓	✓	✓	CT	0/10	X	X	X
Davis et al., 1985[39]	4	X	✓	✓	✓/X	CT	0/13	X	X	X
Linde-Edelstam et al., 1992 (2) [34]	4	X	✓	✓	✓	CT	2/17	X	X	N/A*
Channon et al., 1994[38]	4	X	✓	✓	✓	CT	2/16	X	X	X
Avery et al., 1994[35]	4	X	✓	✓	✓	X	3/13	X	X	X
Hargreaves et al., 1995[41]	2	X	✓	X	X	✓	0/20	✓	X	X
Kamalvand et al., 1997[32]	2	✓	✓	X	✓/X	X	5/48		X	X
Lau et al., 1992 (2) [43]	2	X	✓	X	✓	CT	0/33	X	X	X
Linde-Edelstam et al., 1992 (1)[33]	2	X	✓	✓	X	CT	0/17	X	X	X
Oldroyd et al., 1991[47]	2	X	✓	X	✓/X	CT	0/10	X	X	X
Capucci et al., 1993[37]	2	✓	X	X	✓/X	N	2/14	X	X	X
Deharo et al., 1996[40]	2	X	X	✓	X	CT	0/15	X	X	X
Heldman et al., 1990[15]	2	X	X	✓	X	CT	0/40	X	X	X
Lau et al., 1992 (1)[30]	2	X	✓	X	✓	X	3/15	X	X	X
Saner & Fricker, 1996[50]	2	✓	X	X	X	CT	0/12	X	X	X
Sulke et al, 1994[51]	2	X	✓	X	X	CT	0/10	X	X	X
Yee et al., 1984[54]	2	X	X	✓	X	CT	0/8	X	X	X
Rediker et al., 1993[49]	2	X	X	X	✓/X	X	0/19	X	X	X
Boon et al., 1987[36]	2	X	X	X	X	X	3/18	X	X	X

*study does not report on symptoms of pacemaker syndrome
X: criteria not met
✓: criteria met
CT: can't tell

5.2 Primary outcomes: morbidity and mortality

5.2.1 Primary outcomes parallel studies

Tables 10-14 show the incidence of pacemaker syndrome, atrial fibrillation, stroke, heart failure and mortality in dual/physiologic modes compared to single modes, whilst table 15 gives a summary of the direction of effect, both for individual studies and for pooled data. Results for death due to a cardiovascular cause were not reported separately, therefore data for all cause mortality has been extracted. The results for the study by Wharton et al. (1998)[29] are based on an abstract only.

Pacemaker syndrome:
Two studies investigated the incidence of pacemaker syndrome, Lamas et al.(1998)[28] and Wharton et al. (1998)[29]. Both found a high incidence of pacemaker syndrome in those patients paced in a ventricular mode. In the Lamas study, 53 out of 204 patients paced in the VVIR mode crossed over early to the DDDR mode due to pacemaker syndrome, 28% (27/98) of patients in the Wharton study crossed over early to the DDDR mode. It should be noted that crossovers (in both directions) are reported in the study by Connolly et al. (2000)[26], but the reason for these crossovers is not stated.

Crossover rate and type of randomisation (mode or device)
The crossover rates in both directions in the 2 studies using mode randomisation (Lamas et al. (1998)[28] and Wharton et al. (1998)[29] are higher overall than the crossover rate in the trial by Connolly et al. (2000)[26], which used device randomisation. The trials with mode randomisation have a higher crossover rate from single to dual pacing mode, whilst the study using device randomisation has a higher crossover rate from dual to single pacing mode. Crossovers occur in the study by Mattioli et al. (1998)[27] but are not quantified. The potential biases associated with mode or device randomisation (see section 4.3 quality assessment strategy) should be taken into account.

Atrial fibrillation:
All 4 studies assessed this outcome. 2 studies, Connolly et al. (2000)[26] and Mattioli et al. (1998)[27] found that the onset of chronic atrial fibrillation occurred more frequently in patients paced with ventricular pacemakers, whilst the other 2 studies found no statistically significant difference in incidence for either single or dual mode.

Stroke
All 4 studies assessed this outcome, although there were no details of results in the abstract by Wharton et al. (1998)[29]. 2 of the remaining 3 studies, Connolly et al. (2000)[26] and Lamas et al. (1998)[28] found no statistically significant difference in incidence for either single or dual mode. Mattioli et al. (1998)[27] found a significantly higher incidence in patients paced in a ventricular mode.

Heart failure
3 studies assessed this outcome, although there were no details of results in the abstract by Wharton et al. (1998)[29]. Lamas et al. (1998)[28] and Connolly et al. (2000)[26] found no statistically significant difference in incidence for either single or physiological modes.

Mortality
None of the studies investigated mortality due to a cardiovascular cause alone. 3 studies looked at all cause mortality, 2 of which, Connolly et al. (2000)[26] and Lamas et al. (1998)[28] found no significant difference in either mode, whilst Wharton et al. (1998)[29] found a higher incidence in patients paced in a ventricular mode.

Table 10: Pacemaker syndrome: parallel studies

Study	Outcome Measure	Single mode(s)	Dual mode(s)	Statistical significance	Direction of effect
		VVIR	**DDDR**		
Lamas et al., 1998[28]	n/N cases of pacemaker syndrome	53/204	0/203	p<0.0001*	Significantly higher incidence of pacemaker syndrome in VVIR mode compared to DDDR mode.
		VVIR	**DDDR**		
Wharton et al., 1998[29]	% of population with pacemaker syndrome	28% (27/98)	0% (0/100)	p<0.0001*	Significantly higher incidence of pacemaker syndrome in VVIR mode compared to DDDR mode.

*calculated by JD using Chi-square

Table 11: Atrial fibrillation: parallel studies

Study	Outcome Measure	Single mode(s)	Dual mode(s)	Statistical significance	Direction of effect
Connolly et al., 2000[26]	Annual rate (%)	**'Ventricular'[a]** 6.6 (97/1474)	**'Physiologic'[b]** 5.3 (58/1094)	Significant reduction in relative risk 18.0% [0.3 - 32.6%] p=0.05	Significantly higher incidence of atrial fibrillation in ventricular compared to physiologic modes.
Lamas et al., 1998[28]	n/N cases of atrial fibrillation (total population)	**VVIR** 38/204	**DDDR** 35/203	NS (p=0.8)	No significant difference in atrial fibrillation in VVIR compared to DDDR modes, or for SSS group compared to AV block group.
	SSS group	24/85	17/90	NS (p=0.06)	
	AV group	11/102	16/99	NS (p=0.26)	
Mattioli et al., 1998[27]	Freedom from atrial fibrillation (%)	**VVI, VVIR** Higher incidence of AF in total paced population in ventricular modes (no data available)	**DDD, VDD, AAI** Lower incidence of AF in total paced population in physiologic modes (no data available)	p<0.05	Higher incidence of atrial fibrillation in single ventricular modes compared to physiologic modes for total population and sick sinus group.
		Higher incidence of AF in SSS population in ventricular modes (7% at 12 months and 20% at 24 months, estimated from graph)	Lower incidence of AF in SSS population in physiologic modes (0% at 12 months and 3.5% at 24 months, estimated from graph)	p<0.05	No significant difference in incidence of AF in SSS group and AV block group.
Wharton et al., 1998[29]	Occurrence in population (%)	**VVIR** Recurrence of atrial tachyarrhythmia 43% (42/98)	**DDDR** Recurrence of atrial tachyarrhythmia 48% (48/100)	NS (p=0.09)	No significant difference in recurrence of atrial tachyarrhythmias in single compared to dual mode.

a=rate-adaptive and non-rate adaptive ventricular pacemakers (modes not specified)
b=physiologic (dual) and atrial (single chamber) devices (modes not specified)

Table 12: Stroke: parallel studies

Study	Outcome Measure	Single mode(s)	Dual mode(s)	Statistical significance	Direction of effect
		'Ventricular'[a]	**'Physiologic'[b]**		
Connolly et al., 2000 [26]	Annual rate of stroke (%)	1.1 (16/1474)	1.0 (11/1094)	NS*	No significant differences in stroke (or stroke and death combined) in ventricular compared to physiological modes.
		VVIR	**DDDR**		
Lamas et al., 1998 [28]	n/N cases of stroke in total population	5/204	3/203	NS*	No significant differences in stroke in VVIR compared to DDDR mode, or in SSS group compared to AV block group.
	SSS group	2/85	1/90	NS*	
	AV block group	3/102	1/99	NS*	
		VVI, VVIR	**DDD, VDD, AAI**		
Mattioli et al., 1998 [27]	n/N cases of stroke	19/105	10/105	p<0.05	Significantly higher incidence of stroke in ventricular compared to physiological modes. Higher incidence in SSS group (20/110) compared to AV block group (9/100), p<0.01. No results stated for sub-groups according to pacing mode.

a=rate-adaptive and non-rate adaptive ventricular pacemakers (modes not specified)
b=physiologic (dual) and atrial (single chamber) devices (modes not specified)
*calculated by JD using Chi-square

Table 13: Heart failure: parallel studies

Study	Outcome Measure	Single mode(s)	Dual mode(s)	Statistical significance	Direction of effect
		'Ventricular'[a]	**'Physiologic'[b]**		
Connolly et al., 2000 [26]	Annual rate (%)	3.5 (52/1474)	3.1 (34/1094)	Reduction in relative risk 7.9%; 95%CI -18.5-28.3%; p=0.52	No significant difference in heart failure in ventricular or physiological modes.
		VVIR	**DDDR**		
Lamas et al., 1998 [28]	n/N cases of heart failure in total population	17/204	9/203	NS*	No significant difference in heart failure in VVIR mode compared to DDDR mode.
	SSS group	7/85	6/90	NS*	
	AV block group	9/102	3/99	NS*	

a=rate-adaptive and non-rate adaptive ventricular pacemakers (modes not specified)
b=physiologic (dual) and atrial (single chamber) devices (modes not specified)
*calculated by JD using Chi-square

Table 14: Mortality: parallel studies

Study	Outcome Measure	Single mode(s)	Dual mode(s)	Statistical significance	Direction of effect
Connolly et al., 2000[26]	Annual rate of death from all causes (%)	'Ventricular'[a] 6.6 (97/1474)	'Physiologic'[b] 6.3 (69/1094)	Non significant reduction in relative risk 9.4% (95%CI -10.5 to 25.7%), p=0.3392	No significant difference in all cause mortality in ventricular compared to physiological modes.
	Annual rate of stroke or death due to cardiovascular causes combined (%)	5.5	4.9	Non significant reduction in relative risk 9.4% (95%CI -10.5 to 25.7%), p=0.33	No significant difference in stroke or death due to cardiovascular causes in ventricular compared to physiological modes.
Lamas et al., 1998[28]	n/N cases of death from all causes in total population	VVIR 34/204	DDDR 32/203	NS (p=0.95)	No significant difference in occurrence of death in VVIR and DDDR modes, or in SSS group compared to AV block group.
	SSS group	17/85	11/90	NS (p=0.09)	
	AV block group	15/102	17/99	NS (p=0.41)	
Wharton et al., 1998[29]	% mortality in paced population	VVIR 6.8 (6/98)	DDDR 3.2 (3/100)	p=0.007	Significantly lower mortality in DDDR compared to VVIR mode.

a=rate-adaptive and non-rate adaptive ventricular pacemakers (modes not specified)
b=physiologic (dual) and atrial (single chamber) devices (modes not specified)

5.2.1.1 Meta-analysis of primary outcome data: parallel studies

Incidence is reported as n/N cases in the studies by Lamas et al. (1998)[28] and Mattioli et al. (1998)[27], as % in the study by Wharton et al. (1998) and as annual rate (%) by Connolly et al. (2000)[26]. Where percentages were stated, patient numbers were calculated using the total number of patients. It should be noted that the pooled studies measured outcomes over different periods of follow-up that vary from 18.3 months to 36 months. The pooled estimates need to be interpreted in view of this (figures 6-10).

The odds ratio was calculated for mortality, atrial fibrillation, stroke and heart failure data, whilst for the pacemaker syndrome data the Peto odds ratio was calculated. As there was no statistical evidence of heterogeneity across studies for the outcomes reported, all pooling was undertaken using a fixed effects model.

A significant benefit of dual chamber pacing was evident for the occurrence of pacemaker syndrome symptoms (mean OR=0.1, 95% CI=0.06-0.16). For all other outcomes there is a non-significant trend towards a benefit from dual/physiologic pacing systems compared to single chamber ventricular pacing (atrial fibrillation: OR=0.9, 95% CI=0.70-1.15; stroke: OR=0.66, 95% CI=0.39-1.12; heart failure: OR=0.78, CI=0.53-1.14; mortality: OR=0.93, 95% CI=0.71-1.21). Although non significant all the pooled estimates were in the direction of a benefit of dual

compared to single chamber pacing. It was not possible to include all studies in the meta-analysis as their results were not reported in an appropriate format. Nevertheless, basing the results of a 'vote counting' synthesis across all studies (see Table 15) supported the findings of the meta-analysis.

A sensitivity analysis of the impact of study quality on results was not possible given the homogeneity of study quality.

Figure 6: Meta-analysis pacemaker syndrome: parallel studies

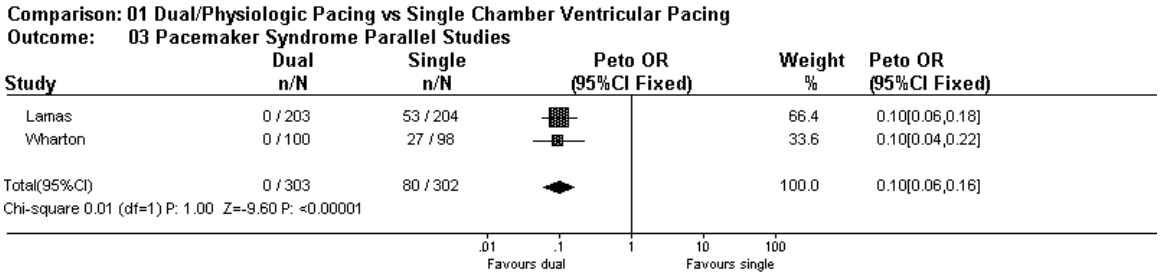


Figure 7: Meta-analysis atrial fibrillation: parallel studies

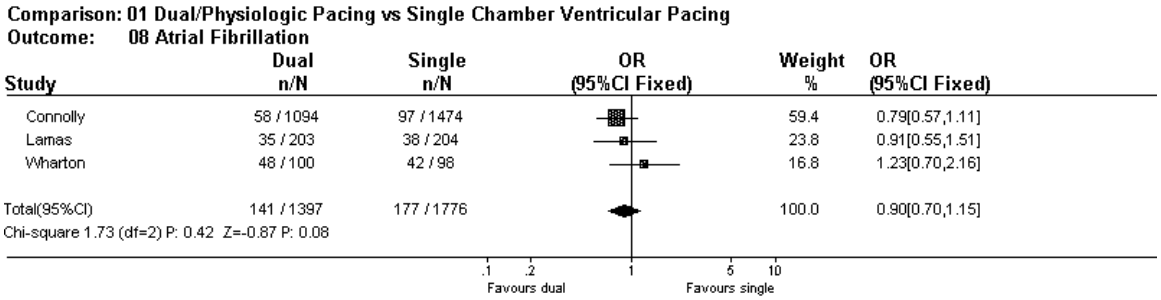


Figure 8: Meta-analysis stroke: parallel studies

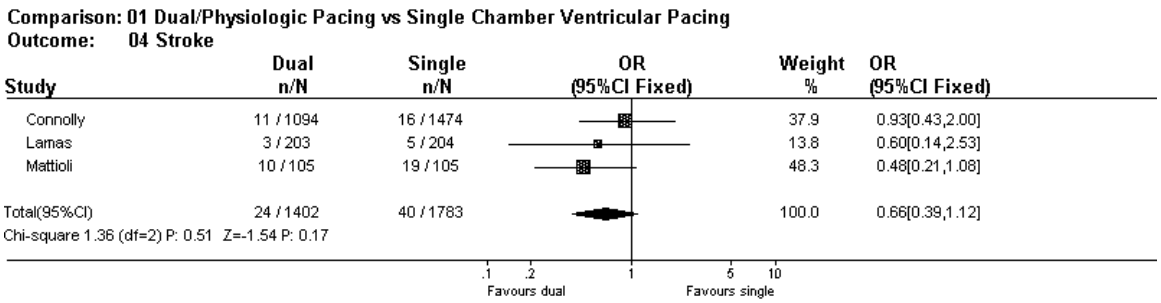


Figure 9: Meta-analysis heart failure: parallel studies

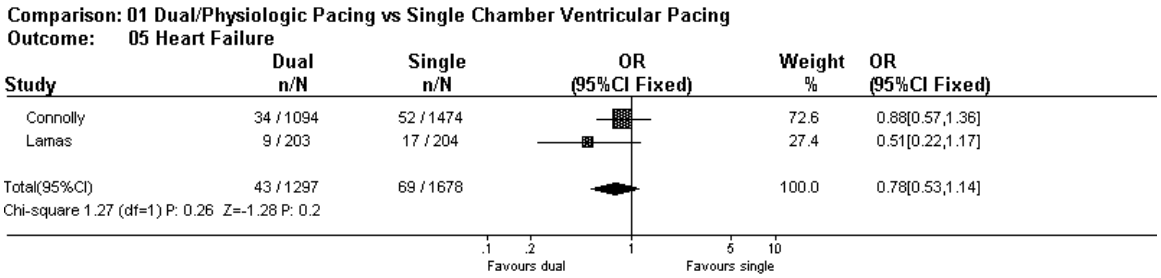


Figure 10: Meta-analysis mortality: parallel studies

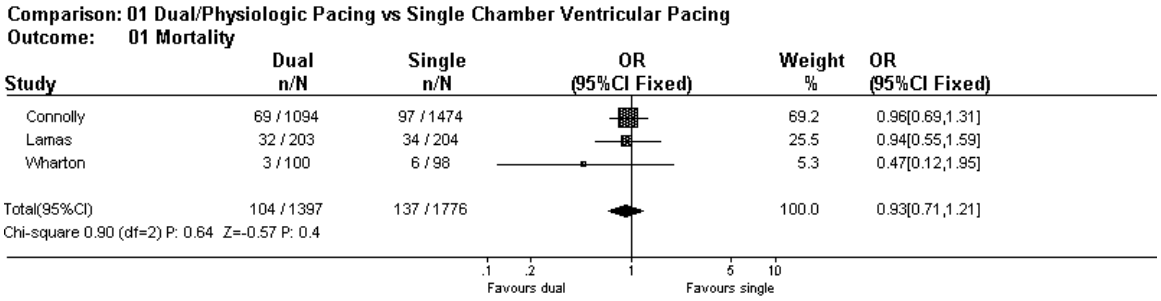


Table 15 summarises the direction of effect of both the 4 individual parallel studies and the pooled result:

Table 15: Summary of direction of effect: parallel studies

Outcomes	Statistically significantly lower incidence in a dual or physiologic mode	No statistically significant difference between modes.	Statistically significantly lower incidence in a ventricular mode	Comment
Pacemaker Syndrome				
Connolly et al., 2000[26]				Not measured.
Lamas et al., 1998[28]	✓			
Mattioli et al., 1998[27]				Not measured.
Wharton et al., 1998[29]*	✓			
Pooled Data:	Favours dual chamber pacing.			
Atrial Fibrillation				
Connolly et al., 2000[26]	✓			
Lamas et al., 1998[28]		✓		
Mattioli et al., 1998[27]	✓			
Wharton et al., 1998[29]*		✓		
Pooled Data:	Trend towards dual chamber pacing being more favourable, but not significant.			
Stroke				
Connolly et al., 2000[26]		✓		
Lamas et al., 1998[28]		✓		
Mattioli et al., 1998[27]	✓			
Wharton et al., 1998[29]*				No result details in abstract
Pooled Data:	Trend towards dual chamber pacing being more favourable, but not significant.			
Heart Failure				
Connolly et al., 2000[26]		✓		
Lamas et al., 1998[28]		✓		
Mattioli et al., 1998[27]				Not measured.
Wharton et al., 1998[29]*				No result details in abstract.
Pooled Data:	Trend towards dual chamber pacing being more favourable, but not significant.			
All cause mortality				
Connolly et al., 2000[26]		✓		
Lamas et al., 1998[28]		✓		
Mattioli et al., 1998[27]				Not measured.
Wharton et al., 1998[29]*	✓			
Pooled Data:	Trend towards dual chamber pacing being more favourable, but not significant.			

* abstract only available

5.2.1.2 Sub-group analyses (SSS and AV block populations) parallel studies

Atrial fibrillation:
The study by Lamas et al. (1998)[28] reported numbers of patients with atrial fibrillation according to pacing mode and indication (SSS or AV block). The incidence of AF was higher in a single mode for SSS (24/85 versus 17/90 in a dual mode) and higher in a dual mode for AV block (16/99 versus 11/102 in a single mode), however these differences were not significant. Mattioli et al. (1998)[27] found a significantly higher incidence of atrial fibrillation in a ventricular mode for the SSS group (7% at 12 months and 20% at 24 months versus 0% at 12 months and 3.5% at 24 months in a dual mode). Data for the AV block group was not stated.

Stroke/heart failure/mortality:
The only study that looked at these outcomes according to pacing mode and indication was the one by Lamas et al. (1998)[28]. There were no significant differences between SSS or AV block groups in either ventricular or dual modes (stroke: 2/85 in a single mode versus 1/90 in a dual mode for the SSS group, and 3/102 in a single mode versus 1/99 in a dual mode in the AV block group; heart failure: 7/85 in a single mode versus 6/90 in a dual mode for the SSS group, and 9/102 in a single mode versus 3/99 in a dual mode in the AV block group; mortality: 17/85 in a single mode versus 11/90 in a dual mode for the SSS group, and 15/102 in a single mode versus 17/99 in a dual mode in the AV block group).

Stroke or death due to a cardiovascular cause
The study by Connolly et al. (2000)[26] investigated this composite outcome. Hazard ratios (data not presented) showed that there was a trend for patients with SSS to benefit less from physiological pacing than those without, and a trend for those with AV block to benefit more from physiological pacing than those without. These trends were not statistically significant. The trial was not statistically powered for subgroup analysis.

5.2.2 Primary outcomes crossover studies

Symptoms of pacemaker syndrome
Due to the shorter duration of these studies (1 week-3 months) compared to the parallel ones (mean 18.3-36 months), the only outcome relating to morbidity was incidence and frequency of symptoms of pacemaker syndrome. There was heterogeneity between studies in terms of assessment tools, for example in terms of number and type of symptoms assessed and scoring scales.

Most studies reported results as mean symptom score with standard deviation (SD) or standard error (SE), either for total symptoms or for individual symptoms. Where the SE only was stated, the SD was calculated by JD. 2 studies did not state whether the measure of error given was the SD or SE, and, as there was no individual patient data, this could not be checked. In 7/25 studies the symptom score data was presented in graphical form only and means were estimated by JD. 3 authors report on mean episodes per week of particular symptoms, and 2 reported on number of patients with symptoms/specific score in each group.

Table 16 shows the direction of effect (fewer symptoms in a dual or single mode) for all crossover studies (see appendix 6 for full details of assessment tools and outcome measures).

The table shows that the direction of effect is divided between significantly fewer symptoms in a dual mode and no significant differences between dual or single modes. No studies showed that fewer symptoms occur in a single mode, except for the study by Kenny et al. (1986)[31], which shows a higher incidence for episodes per week of chest pain in DDI mode compared to VVI mode.

It should be noted that, as stated in section 5.1.2, patients taking part in the crossover studies may not be representative of the whole pacemaker population and that the trend towards effectiveness seen here may not be generalisable for the whole pacemaker population. In addition, as all crossover studies use mode randomisation, the potential biases associated with this, as outlined for the parallel studies in section 4.3 (quality assessment strategy), also apply.

Table 16: Direction of effect symptoms of pacemaker syndrome: crossover studies

Study	Population Size (n)	Significantly fewer symptoms in a dual mode	No significant difference in symptoms between modes	Significantly fewer symptoms in a single ventricular mode	Comment
Kamalvand et al., 1997[32]	48	✓for VVIR vs mode switching DDDR	✓for VVIR vs DDDR		
Kristensson et al., 1985[42]	44	✓for 4/9 symptoms	✓for 5/9 symptoms		
Heldman et al., 1990[15]	40	✓for 12/16 symptoms	✓for 4/16 symptoms		
Lau et al., 1994 (2)[43]	33	✓ for DDDR vs VVIR for 4/5 symptoms	✓ for DDD vs VVIR for 5/5 symptoms ✓ for DDDR vs VVIR for 1/5 symptoms		
Sulke et al., 1991[53]	22	✓			Mean score for VVIR versus mean dual mode score (DDD, DDDR, DDIR).
Lukl et al., 1994[44]	21	✓ for 6/11 symptoms	✓ for 5/11 symptoms		
Hargreaves et al., 1995[41]	20	✓for group mean and pacing order DDD/VVIR	✓ for pacing order VVIR/DDD		
Rediker et al., 1988[49]	19	✓for 3/5 symptoms			Results only stated for 3/5 symptoms.
Deharo et al., 1996[40]	18		✓		5/5 mean symptom scores.
Linde-Edelstam et al., 1992 (1)[33]	17	✓			4/4 mean symptom scores.
Channon et al., 1994[38]	16	✓			Mean symptom score and 3/7 individual symptom scores.
Mitsuoka et al., 1988[46]	16	✓ for 3/4 symptoms	✓ for 1/4 symptoms & attacks per week of 3 symptoms		
Sulke et al., 1992[52]	16	✓for DDD vs VVI	✓for VVI vs DDI		VVI compared to DDD and DDI.
Boon et al., 1987[36]	15	✓			Mean score for 4 symptoms.
Lau et al., 1994 (1)[30]	15	✓ for 1/6 symptoms (Both DDDR and AAIR better than VVIR)	✓ for 5/6 symptoms (all 3 modes)		VVIR compared to AAIR and DDDR.
Capucci et al., 1993[37]	14	✓for both DDD and DDDR compared to VVIR			VVIR compared to DDD and DDDR.
Davis et al., 1985[39]	14		✓		Results only stated for 6 out of 10 symptoms.
Menozzi et al., 1990[45]	14	✓ for 3/6 symptoms	✓for 3/6 symptoms		
Avery et al., 1994[35]	13	✓			Mean symptom score only stated.
Perrins et al., 1983[48]	13	✓ for weekly attack rates for 1/4 symptoms ✓ for 4/6 symptoms	✓ for weekly attack rates for 3/4 symptoms ✓for 2/6 symptoms		
Saner & Fricker, 1996[50]	12	✓			Mean symptom score only stated.
Kenny et al., 1986[31]	10	✓for episodes/week of dizziness (DDD 100 and DDD 150 better than VVI) ✓for episodes/week of chest pain (DDD100 better than VVI and DDD 150)	✓ for episodes/week for 1 symptom	✓ for episodes/week of chest pain (VVI better than DDD150)	VVI compared to DDD (100) and DDD (150)
Oldroyd et al., 1991[47]	10		✓		Mean scores for 3 symptoms.
Sulke et al., 1994[51]	10	✓			Mean symptom score only stated.
Yee et al., 1984[54]	8		✓		Mean symptom score only stated.

5.2.2.1 Meta-analysis of primary outcome data: crossover studies

In order to further investigate the direction of effect, results for mean total symptom score and most frequent individual symptoms were pooled in a meta-analysis using standardised mean differences and presented in Forest plots (Figures 11-16). Differences were standardised due to the scale of pacemaker symptom assessment varying across studies. Studies were only pooled if the mean (SD) was stated or could be calculated from available data. If more than 2 modes were compared then only one dual mode was used for comparison.

The Chi-square test for heterogeneity shows that overall there is no statistically significant heterogeneity between pooled study data ($p>0.05$) and therefore fixed effects pooling was used (Statistically significant heterogeneity was borderline, $p=0.05$, for total mean symptom scores, figure 11).

Total symptoms scores
There is a statistically significant reduction in total pacemaker symptoms in dual pacing compared to single mode of -0.74 standard deviation units (95%CI=-0.95-(-0.52) Only 1 small study (Yee et al., 1984)[54], which compared VVI to VDD, reported a non-significant higher mean symptom score in the dual mode compared to the single mode.

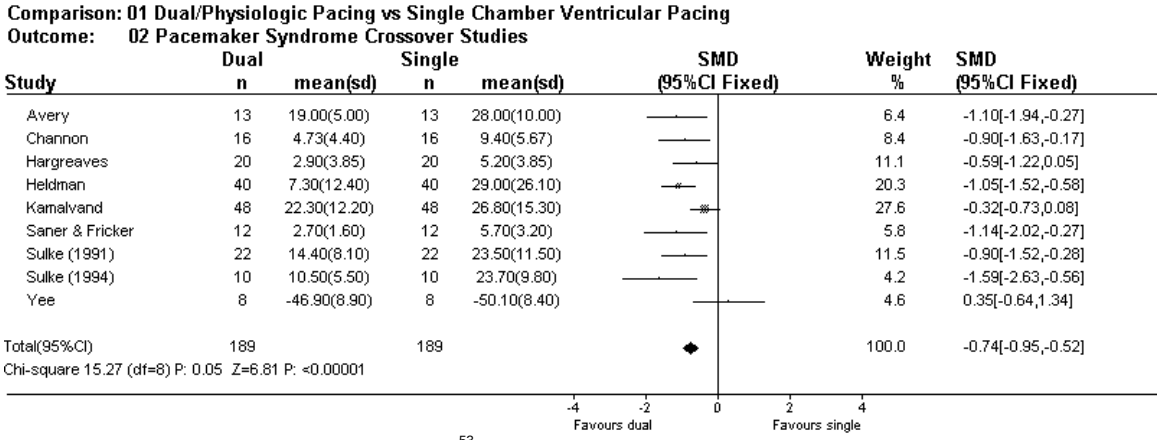
Individual symptom scores (dizziness, fatigue, chest pain, breathlessness, palpitation)
As with the total symptom score, there is a statistically significant reduction in individual symptoms with dual pacing, particularly with regard to dizziness (SMD=-0.89, 95% CI=-1.13-(-0.64)), fatigue (SMD=-0.77, 95% CI=-1.05-(-0.49)), breathlessness (SMD=-0.92, 95% CI=-1.18-(-0.66)) and palpitation (SMD=-0.69, 95%CI=-0.93-(-0.45), with the effect on chest pain being slightly less distinctive (SMD=-0.33, 95%CI=-0.60-(-0.05)).

None of the pooled standardised mean differences show a more favourable effect for single chamber pacing.

Sensitivity analyses of the effect of study quality on these findings was not appropriate due to the homogeneity of quality across studies.

Publication bias
A funnel plot (figure 17) was generated for total pacemaker symptom results, and the test for bias shown to be non-significant ($p=0.45$).

Figure 11: Meta-analysis total mean symptom score pacemaker syndrome: crossover studies* [scale in standard deviation units]



*The mean score given by Sulke et al., 1991[53] is comprised of the means for 3 dual modes against which 1 single mode was compared; The study by Kamalvand et al., 1997[32] compared VVIR with DDDR and mode switching DDDR-the mean score for DDDR was used here.

Figure 12: Meta-analysis mean score for dizziness: crossover studies [scale in standard deviation units]

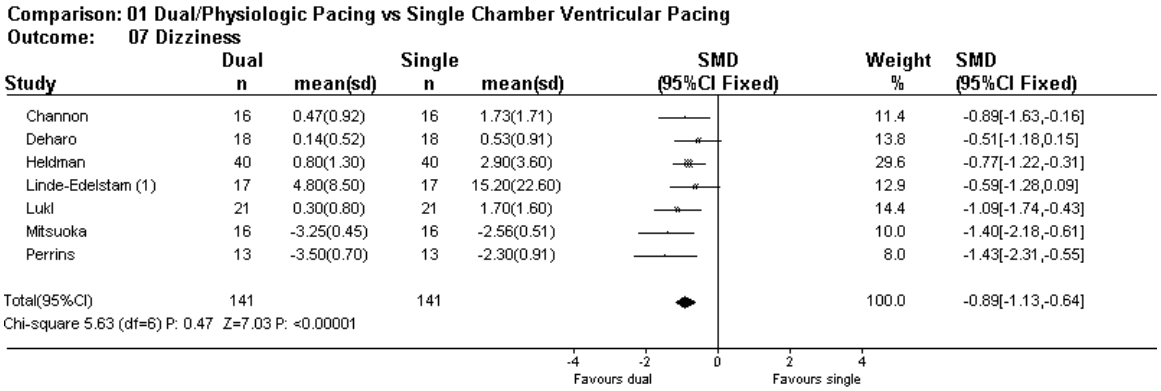
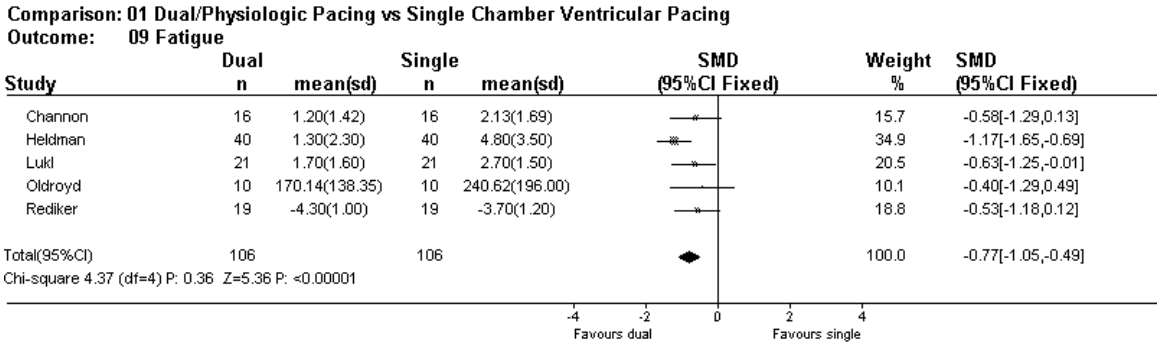


Figure 13: Meta-analysis mean score for fatigue: crossover studies* [scale in standard deviation units]



* mean and SD from the study by Oldroyd et al., 1991[47] were estimated by JD

Figure 14: Meta-analysis mean score for chest pain: crossover studies [scale in standard deviation units]

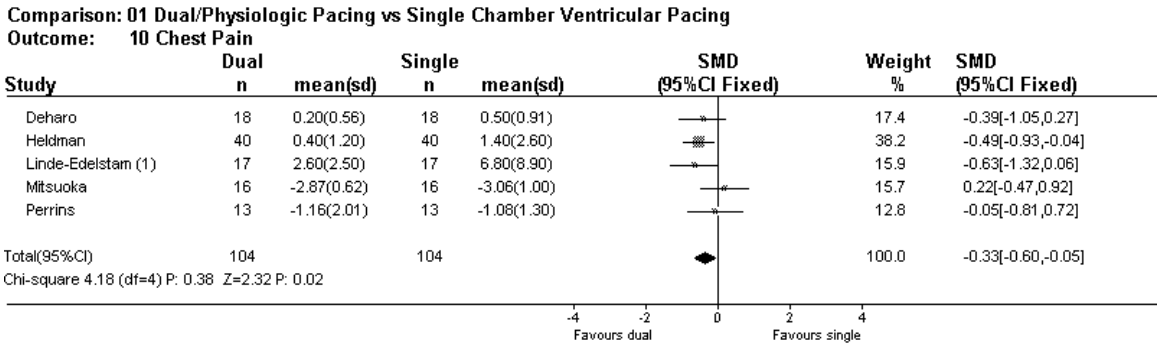


Figure 15: Meta-analysis mean score for breathlessness: crossover studies [scale in standard deviation units]

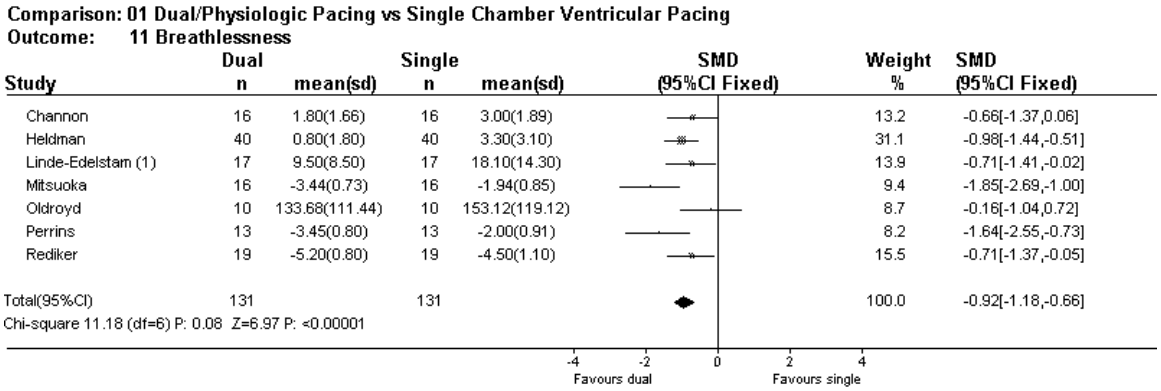


Figure 16: Meta-analysis mean score for palpitation: crossover studies [scale in standard deviation units]

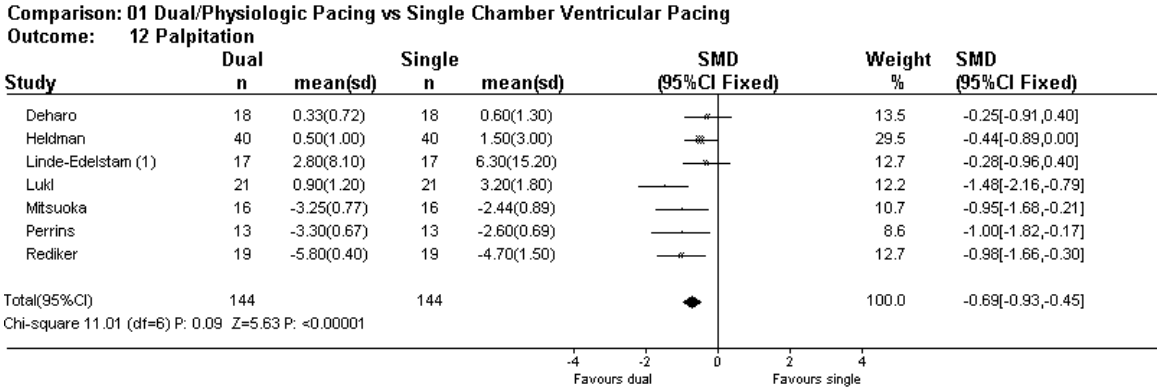
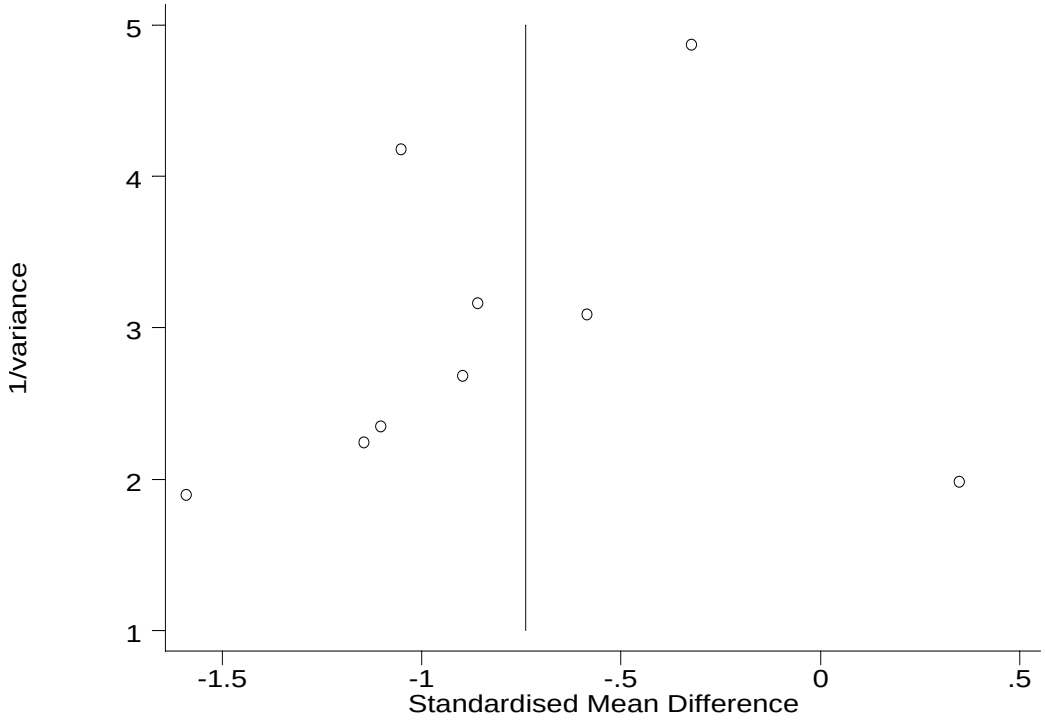


Figure 17: Funnel plot total pacemaker symptoms: crossover studies



5.2.2.2 Subgroup analyses (SSS and AV block populations) crossover studies

Comparison between studies
As there were 12 crossover studies with an AV block population only, but only 1 study with a SSS population only, there was insufficient information to compare studies according to population indication.

Comparison within studies
There were 2 studies, which presented results according to both pacing mode and indication (SSS or AV block). The results are shown below in table 17. The study by Mitsuoka et al. (1988)[46] shows there are some differences in significance of effect of the two modes between the 2 patient groups. The study is however very small (8 patients in each group) and conclusions as to the effect of pacing modes in different patient groups cannot be drawn due to lack of statistical power.

Table 17: Subgroup analyses primary outcome: crossover studies

Study/Outcome	SSS Group		Statistical Significance	AV Block Group		Statistical Significance
	Dual mode	Single mode		Dual mode	Single mode	
Mitsuoka et al., 1988[46]						
Mean symptom scores (SD): (higher score = improvement)						
Shortness of breath	3.37 (0.74)	2.0 (1.06)	NS	3.5 (0.75)	1.87 (0.64)	p<0.05
General well-being	3.25 (0.7)	2.0 (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 (1.30)	NS
Attacks per week:						
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
Heldman et al., 1990[15]	No results stated.	38% no or mild symptoms.		No results stated.	36% no or mild symptoms.	No significant difference between symptoms in the AV block or SSS group in a single mode.
Symptom questionnaire, 16 questions scored 0-10 (0=no symptoms)		62% moderate or severe symptoms.			64% moderate or severe symptoms.	
% patients with symptoms						

5.3 Secondary outcomes: quality of life, exercise capacity (duration and walking distance), complication rate

5.3.1 Secondary outcomes parallel studies

Quality of life

One study (Lamas et al., 1998)[28] assessed quality of life using the SF-36 index. No statistically significant difference between quality of life between single and dual mode was observed with the exception of mental health at 9 months and cardiovascular functional status at 18 months (benefit from dual chamber pacing). (See appendix 7 for full details of the assessment tools used)

The study by Wharton et al. (1998)[29]also assessed quality of life but the results are not stated in the abstract.

Exercise capacity

Exercise capacity outcome is not reported by any identified parallel studies.

Complication rate
No studies were identified that assessed long-term complications in the two pacing modes over the whole length of the trial period. One parallel study (Connolly et al., 2000)[26] investigated peri-operative complications as an outcome and found a higher incidence during dual chamber pacemaker implantation. Table 18 lists the results.

Table 18: Peri-operative complication rate

Study	Outcome Measure	Single mode(s)	Dual mode(s)	Statistical significance
Connolly et al., 2000[26]	Incidence of perioperative complications (%)	'Ventricular'[a]	'Physiologic'[b]	
	Any	3.8	9.0	p<0.001
	Pneumothorax	1.4	1.8	p=0.42
	Haemorrhage	0.4	0.2	p=0.32
	Inadequate pacing	0.3	1.3	p=0.002
	Inadequate sensing	0.5	2.2	p<0.001
	Device malfunction	0.1	0.2	p=0.40
	Lead dislodgement	1.4	4.2	p<0.001

5.3.2 Secondary outcomes crossover studies

Quality of life
4 crossover studies investigated quality of life. (See appendix 7 for full details of the assessment tools used) All studies used a variety of assessment tools for different aspects of quality of life, and found either no significant difference between quality of life in a single or dual mode, or a significantly higher quality of life in a dual mode. No study shows an increase in quality of life for patients paced with in a single mode regardless of which assessment tool was used.

Table 19 summarises the direction of effect for both the parallel study and the crossover studies.

Pooling of study data was deemed inappropriate given the large variation between both assessment tools used and items scored.

Sensitivity analysis of the impact of study quality on findings was not appropriate due to the homogeneity of quality across studies.

Table 19: Quality of life: parallel and crossover studies

Study	Population size	Statistically significant improvement in quality of life in a dual mode	No significant difference in quality of life in either a dual or single mode	Comment See Appendix 7 for full description of assessment tools and scores.
Lamas et al., 1988[28]	n=407	-Mental health at 9 months -Cardiovascular functional status at 18 months.	-9/9 items at 3 months -8/9 items at 9 months -8/9 items at 18 months	8 items assessed using SF-36: physical and social function, physical and emotional role, energy, pain, health perception, mental health at 3, 9 and 18 months. Cardiovascular functional status assessed using Specific Activities Scale.
Lau et al., 1994 (2)[43] **VVIR vs DDDR**	n=33	-4/5 items (physical malaise) -3/4 items (quality of life) -total sum for quality of life -4/5 items (illness perception)	-1/5 items (physical malaise) -1/4 items (quality of life) -1/5 items (illness perception)	DDDR, DDD and VVIR modes compared. 3 sets of items assessed (physical malaise, quality of life and illness perception). Not all items listed in results.
Lau et al., 1994 (2)[43] **VVIR vs DDD**		-1/4 items quality of life -total sum for quality of life -1/5 items (illness perception)	-5/5 items (physical malaise) -3/4 items (quality of life) -4/5 items (illness perception)	
Lukl et al., 1994[44]	n=21	-12/19 items	-7/19 items	19 questions on quality of life questionnaire.
Linde-Edelstam et al., 1992 (1)[33]	n=17	-4/4 items (cardiovascular symptomatology) -1/3 items (cognitive functioning)	-2/2 items (sleep disturbance) -2/3 items (cognitive functioning) -2/2 items (physical and social functioning) -1/1 item (depressive score) -3/3 items (mood states) -2/2 items (self-perceived health status)	7 sets of items assessed (cardiovascular symptomatology, sleep disturbance, cognitive functioning, physical and social functioning, depressive feelings, mood states, self-perceived health status)
Lau et al., 1994 (1)[30] **VVIR vs DDDR**	n=15	-1/1 item (general well-being) -1/6 items (incidence and frequency of symptoms) -1/11 items (psychologist's assessment)	-5/6 items (incidence and frequency of symptoms) -1/1 item (cardiovascular functional status) -10/11 items (psychologist's assessment)	DDDR, AAIR and VVIR modes compared. 4 sets of items assessed (general well-being, incidence and frequency of symptoms, cardiovascular functional status, psychologist's assessment)
Lau et al., 1994 (1)[30] **AAIR vs DDDR**			1/1 item (general well-being) -6/6 items (incidence and frequency of symptoms) -1/1 item (cardiovascular functional status) -11/11 items (psychologist's assessment)	

Exercise capacity

Table 20 shows a summary of the direction of effect for the outcomes exercise duration or walking distance (full details on exercise assessment tools and outcome measures in appendix 8).

Table 20: Direction of effect exercise capacity: crossover studies

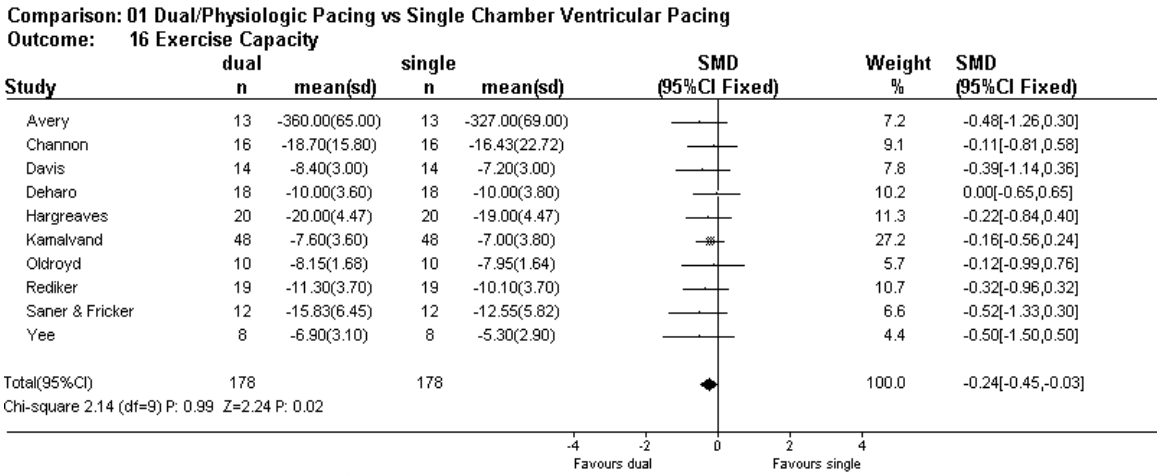
Study	Population Size (n)	Statistically significant greater exercise duration/distance walked in a dual mode	No statistically significant difference	Statistically significant greater exercise duration/distance walked in a single mode	Comment
Kamalvand et al., 1997[32]	48	✓for VVIR vs mode switching DDDR	✓for VVIR vs DDDR		
Sulke et al., 1991[53]	22	✓	✓		Significantly longer exercise time in DDDR mode compared to VVIR, DDD and DDIR; no significant difference between DDD, DDIR and VVIR modes.
Hargreaves et al., 1995[41]	20		✓		
Rediker et al., 1988[49]	19	✓			
Deharo et al., 1996[40]	18		✓		
Linde-Edelstam et al., 1992 (2)[34]	17		✓		
Channon et al., 1994[38]	16	✓			
Sulke et al., 1992[52]	16		✓		
Capucci et al., 1993[37]	14	✓	✓		Significantly longer exercise time in DDDR mode compared to VVIR; no significant difference between DDD and VVIR modes.
Davis et al., 1985[39]	14	✓			
Avery et al., 1994[35]	13	✓			
Saner & Fricker, 1996[50]	12	✓			
Oldroyd et al., 1991[47]	10		✓		
Yee et al., 1984 [54]	8	✓			

The results show that the capacity for exercise is either significantly better in a dual mode or similar in both dual and single modes. No studies show significantly better exercise capacity in a single mode. There is some heterogeneity amongst studies in terms of exercise test (e.g. treadmill or bicycle test, test protocol) and mode compared (e.g. VVIR vs DDD, VVI vs DDD). All studies assess the same outcome (minutes exercised or lengths/metres walked) and all outcome measurements were symptom limited.

5.3.2.1 Meta-analysis of secondary outcome data: crossover studies

The results for exercise duration or distance walked were pooled using standardised mean differences and presented in a Forest Plot below (figure 18). Differences were standardised as different studies used different scales of exercise capacity. Studies were only pooled if the mean and standard deviation (SD) was stated or could be calculated from the available data. The test for heterogeneity shows there are no significant differences between pooled study data.

Figure 18: Meta-analysis exercise capacity: crossover studies* [in standard deviation units]



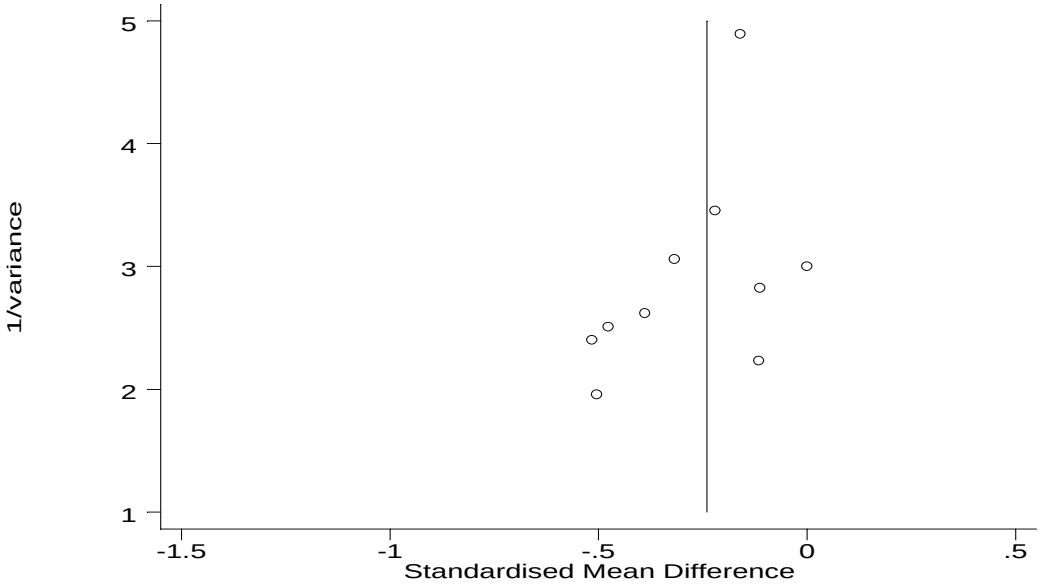
*The study by Kamalvand et al. (1997)[32] compares single to DDDR and mode switching DDDR-the result for DDDR was used here as none of the other studies used a mode switching mode as a comparator; results from the study by Sulke et al. (1991)[53] were not included as single mode is compared to 3 types of dual modes.

A statistically significant increase of 0.24 standard units (95% CI: 0.03 to 0.45) was observed with dual compared to single mode.

Publication bias

A funnel plot, figure 19 shown below, was generated for the exercise capacity data. The statistical test for bias was not significant (p=0.133).

Figure 19: Funnel plot exercise capacity data: crossover studies



5.3.2.2 Subgroup analysis (SSS and AV block populations) secondary outcomes

Parallel studies

Quality of life

The study by Lamas et al. (1998)[28] compared quality of life in a dual or single pacing mode in two patient subgroups (SSS and AV block). There was no significant difference for any of the SF-36 sub-scale scores in the AV block group. In the SSS group, there were significant differences favouring dual chamber pacing at 3 months in scores on the physical role, social function and emotional role sub-scales.

Crossover studies

Quality of life

Comparison between studies
One study had a SSS population (Lau et al., 1994 (1))[30], one an AV block population (Linde-Edelstam et al., 1992 (1))[33], and two studies had a mixed population with either SSS or AV block (Lau et al., 1994 (2)[43] and Lukl et al., (1994)[44], one of which (Lukl et al., 1994)[44] reported data separately for AV block and SSS patients. As all studies used different assessment scales, the results were not compared according to population sub-group.

Comparison within studies
The study by Lukl et al. (1994[44]) lists results for individual patients with SSS or AV block. 3/7 patients with SSS, and 8/14 patients with AV block had significantly better quality of life scores in a dual mode. These numbers are not statistically powered to show a difference between sub-groups.

Exercise capacity

9 studies assessing this outcome had populations with AV block, whilst 6 studies had populations with either AV block or SSS. As the data was presented in an aggregated form, i.e. not split according to indication, a comparison of effectiveness between the two sub-groups was not possible.

6 Conclusions clinical effectiveness

Quantity and quality of studies
4 parallel RCTs and 26 crossover RCTs were identified relating to the effectiveness of dual versus single chamber pacemakers. The parallel studies were of considerably longer duration (18.3-36 months) than the crossover studies (1 week to 3 months) with larger populations, and assessed more long-term outcomes. 5 large ongoing RCTs were identified.

There was heterogeneity both within and between parallel and crossover studies in terms of pacemaker modes compared, outcomes assessed, population characteristics and, particularly for the crossover studies, assessment tools used. The type of randomisation (mode or device) may potentially bias results, whilst the design of the crossover studies may not result in effect estimates that are generalisable for the whole pacemaker population.

Both parallel and crossover studies were assessed to be of poor quality as all had 2 or more threats to validity. However, the quality of reporting of aspects was also poor.

Clinical effectiveness: morbidity and mortality:
Pooled data from the parallel studies show a statistically non-significant trend towards dual or physiologic pacing being more favourable regarding atrial fibrillation, stroke, heart failure and mortality. With regard to pacemaker syndrome, both the parallel studies and the crossover studies favour dual chamber pacing (parallel: OR=0.1, 95% CI=0.06-0.16; crossover: SMD=-0.74, 95% CI=-0.95-(-0.52)).

No individual studies reported a statistically more favourable outcome for any primary outcome in single chamber pacing

Clinical effectiveness: quality of life, exercise capacity and complication rate
One parallel study showed no overall significant difference in quality of life, whilst the crossover studies showed either no significant difference or a trend towards dual chamber pacing being more favourable for certain quality of life items.

Pooled data from crossover studies showed a statistically significant trend towards dual chamber pacing being more favourable in terms of exercise capacity (SMD=0.24, 95% CI=0.03-0.45)).

One parallel study showed an overall statistically significant higher rate of peri-operative complications for dual chamber pacing.

No studies reported a statistically significant more favourable outcome for quality of life or exercise capacity in single chamber pacing.

7 Economic evaluation

7.1 Methods

7.1.2 Search strategy

Information on cost effectiveness was sought from the following sources:

- Electronic bibliographic databases: MEDLINE, EMBASE and Science Citation Index between 1980 and present. Searches were carried out on 12/07/01. (see Appendix 1)

- Other databases: NHS Centre for Reviews and Dissemination, NHS Economic Evaluation Database (NHS EED) and Bandolier using terms *pacemaker(s)* and *pacing*.

- Checking citation lists from obtained cost effectiveness reviews and primary cost effectiveness references.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were applied as for the clinical effectiveness section of this report (see section 4.1). In addition, included studies had to include either assessment of resource implications and/or costs. There were no language restrictions. Exclusion and inclusion criteria were applied by two reviewers (JD and RT).

Synthesis of results and study quality

Identified studies were summarised at three levels: (1) study characteristics; (2) methodological details; (3) results. The headings used are adapted from Drummond & Jefferson's 'Guidelines for authors and peer reviewers of economic submissions to the BMJ checklist'.[64]

7.2. Results

Identification of primary studies

The selection of economic evaluation studies within this review is summarised in figure 20. 16 potentially relevant papers were identified. Five papers examined aspects of the costs of pacemakers but were not directly relevant to the policy question of this review (Ray et al, 1992[65]; Crossley et al, 1996[66]; Kupersmith et al, 1995[67]; Fabricius et al, 1978[68]; Clarke et al, 1998[69]). A further 3 studies assessed the potential budget impact of the implementation of differing pacemaker strategies (Cervellati et al, 1998[70]; De Belder et al, 1992[71]; Gillis et al, 1996[72]). The remaining 7 studies included 4 primary cost studies comparing single chamber to dual chamber pacemakers (Sutton & Bourgeois, 1996[73]; Eagle et al, 1986[74]; Brown Mahoney, 1996[75]; Hughes, 1994[76]), 3 reviews (ANAES, 1999[77]; Parsonnet, 1996[78]; Jillings, 1994[8]), each of which focused on one or more of these primary studies. One potentially relevant study (Mahoney, 1994[79]) was not obtained at the time of completion of this report. The remainder of this section will focus on the 4 primary economic evaluations of single and dual chamber pacemakers.

Characteristics of included primary cost studies

The characteristics of the included studies are summarised in Table 21. The 4 primary studies evaluated costs of an implementation strategy of dual chamber pacemakers compared to single chamber pacemakers, 3 of which are based on modelling exercises. Only one of the four studies also included patient costs. None undertook a full cost effectiveness analysis, i.e. assessed both benefits and costs, and none drew upon the randomised trials described in the clinical effectiveness section above.

Although all compared dual to single chamber pacing, there were some notable differences across the four studies. In terms of population, one of the studies was concerned with sick sinus syndrome, another with sick sinus syndrome and atrio-venticular block, one with bradycardia (which is a symptom of both sick sinus syndrome and atrioventicular block) and the third with all potential candidates for single/dual pacemakers. Three of the four studies incorporated potential downstream benefits of pacemakers by including the costs of follow up, complications and device failure. The period of follow up varied from 1 year to 12 years.

Findings of included primary studies

All four studies reported the implantation costs of dual chamber pacemakers to be greater than the implantation costs of single chamber devices (see Table 22). However, the conclusions on the overall cost (i.e. including 'downstream' costs) of the two pacemakers were conflicting. Two studies (Hughes, 1994[76]; Eagle et al, 1986[74]) concluded that the overall costs of dual chamber pacemakers were greater than the costs of single chamber pacemakers, and two studies (Sutton & Bourgeois, 1996[73]; Brown Mahoney, 1996[75]) reported the overall costs of dual chamber to be less than single chamber pacemakers.

Some of this difference can be explained by the variation in the costs included in each of the 4 studies, and the differences in incidence and type of complication modelled by each study. Both studies reporting the cost saving of dual chamber pacemakers included the cost of clinical complications such as atrial fibrillation, stroke, heart failure, pacemaker syndrome and upgrading to dual pacing after AV block, and ignored the cost of device malfunctioning or replacement of pacemaker hardware, such as batteries. One study that failed to show a cost saving (Eagle et al, 1986[74]) included both clinical complications and the cost of device malfunctioning and generator and battery replacement, whilst the other study that failed to show a cost saving (Hughes, 1994[76]) included only the latter.

Sutton and Bourgeois (1996)[73]demonstrated through sensitivity analysis that the favourable cost difference of dual chamber pacemakers compared to ventricular single chamber pacemakers in both SSS and AVB is reversed if the incidence of atrial fibrillation changes from 1% to 19%, with the switch occurring at ~7% incidence. The variation of findings may also reflect the limitations of the retrospective nature of the 4 studies.

7.3 Conclusions

The medical costs of the initial implantation of dual chamber technology are generally greater than for single chamber technology, this cost difference being primarily due to costs of pacemaker generator and leads. This finding is confirmed by current UK costs (average total cost for single chamber pacemaker £3044, and £5418 for a dual, rate-adaptive pacemaker [3]). Whether the 'downstream' complications, pacemaker failure and follow up of dual compared to single chamber pacemakers are sufficiently favourable to offset this increased initial cost, or result in a cost saving, remains uncertain from these 4 studies.

The economic evidence base of single versus dual chamber pacemakers identified within this review was small - only four costs studies, three of which were conducted in the US. The generalisability of this evidence to the UK is limited not only by the different currencies but also the potential different patterns of health service resource utilisation.

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 pacemakers, preferably in the context of a randomised controlled trial and with at adequate follow up i.e. 12 months or more.

Two trials currently underway will provide some key economic data to address the policy question of this review. UKPACE, a UK based trial, assesses quality of life (using both SF-36 and EuroQOL) at up to 3 years follow up and will report a cost per QALY of single versus dual pacing (Toff et al,1997[55]), whilst the US based MOST trial assesses health related quality of life and cost-effectiveness (Lamas et al., 2000[57]).

Figure 20. Summary of selection of health economics studies

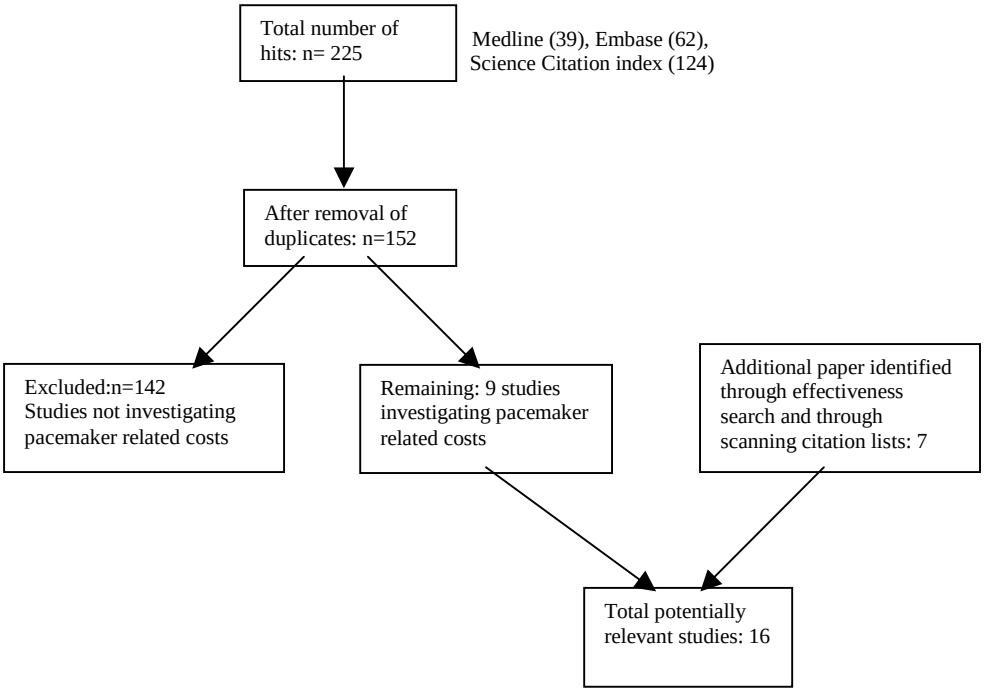


Table 21: Characteristics of included primary economic studies

	Eagle et al, 1986[80]	Hughes, 1994[76]	Sutton & Bourgeois, 1996[73]	Brown Mahoney, 1996[75]
Country	US	US	UK	US
Comparison(s)	Single ventricular chamber vs dual chamber	Single non programmable/ programmable versus dual chamber non rate responsive/rate responsive	VVI vs DDD (DDD, DDI, DVI and AAI combined for SSS)	VVI vs DDD
Population(s)/indication(s)	Not stated (probably all patients indicated for pacemaker implantation)	Bradycardia	Sick sinus syndrome or atrioventricular block	Not stated (probably all patients indicated for pacemaker implantation)
Perspective	Direct medical	Societal	Direct medical	Direct medical
Type of study	Retrospective cost analysis	Retrospective cost analysis	Retrospective cost analysis	Retrospective cost analysis
Medical costs considered (source)				
1. Implantation*	√	√	√	√
2. Routine follow up	√	√	√	√
3. Complications	√^	X	√^	√^
4. Generator survival	√^	√^	X	X
5. Battery survival**	√^	√^	X	X
6. Patient survival**	√^	X	√^	√^
Source of medical costs	Medicare & local hospital	Manufacturers, Medicare	NHS & local hospital	Medicare & weights for local city
Patient cost considered	None	Lost wages^^	None	None
Year of costs	Not stated	1993	1991	1992
Discount rate	5%	None applied	None applied	None applied
Time horizon	12 years	5 years	10 years	Not stated
Comments	^Rate estimates from published literature	^^As result of follow up attendance ^Estimate of overall pacemaker survival from previous literature	^Rates estimates from published literature	^Rate estimates from published literature – meta analysis of 52 studies

VVI: ventricular single chamber, DDD: dual chamber *Includes cost of pacemaker hardware (including leads) & operative costs ** and resultant reoperation

Table 22: Results of included primary economic studies

	Eagle et al, 1986[80]	Hughes, 1994[76]	Sutton & Bourgeois, 1996[73]		Brown Mahoney, 1996[75]
			Sick Sinus Syndrome	**Atrioventricular block**	
Implantation cost **Single chamber** **Dual chamber** **Incremental difference#**	 $US 6,924 $US 9,427 +$US 2,503	 $US 13,168* $US 17,585** +$US 4,417	 230 units* 340 units* +110 units*		 US$12,920* US$ 12,920* US$ 0*
Patient costs **Single chamber** **Dual chamber** **Incremental difference#**	Not collected	 $US 1,332 $US 1,442 +$US 110	Not collected		Not collected
Overall costs **Single chamber** **Dual chamber** **Incremental difference#**	 $US 11,339 $US 16,506 +$US 5,167	 $US 15,975^ $US 21,183^^ +$US 5,208	 2453 units* 1118 units* -1335 units*	 1642 units* 883 units* -760 units*	 US$ 13,048** US$ 10,489** -US$2,559**
Sensitivity analysis	None reported	None reported		Result sensitive to incidence of atrial fibrillation, stroke & heart failure) and cost of disability	Results insensitive to high or low costs of complications
Comments		*Non programmable single (programmable: $15,731 ^ $17,62) **Non rate responsive (rate responsive $18,232 ^^$ 21,859)	*Arbitrary currency units with cost of VVI = 100 units		*For patients with AMI, heart failure, or shock. Lower estimates without AMI, heart failure or shock **Estimates for low cost of complications

Positive values: dual chamber costs greater than single chamber
Negative values: dual chamber costs less than single chamber

8 Discussion

Implications for service provider
The policy question addressed by this review was the short-and long-term clinical and cost-effectiveness of dual chamber pacemakers compared to single chamber pacemakers.
The quality of the clinical effectiveness evidence was poorly reported and therefore the findings of this review are potentially subject to bias. Nevertheless a consistent benefit across studies of dual chamber pacing compared to single chamber pacing was observed for both primary and secondary outcomes. This included a statistically significant reduction in symptoms of pacemaker syndrome and increased exercise capacity.

These clinical effectiveness findings support the current British Pacing and Electrophysiology Group guidelines [1] that recommend dual chamber (over single chamber) pacing for AV block.

This review was unable to identify any studies formally assessing the cost effectiveness of dual compared to single chamber pacing. The results of the four costing studies of dual versus single pacing were inconclusive. Two studies reported an overall reduction in the incremental health service costs (including downstream costs such as complications and follow up clinics) with dual chamber pacing relative to single chamber while two studies reported an increase in overall incremental health service costs.

The review did not assess the evidence for potential benefits of atrial versus ventricular pacing, nor was the potential difference in effectiveness between rate-adaptive and non rate-adaptive pacemaker investigated. In order to inform the choice of the type of pacemaker for a given indication, the results of this review need to be considered in conjunction with these other pacing issues.

Implications for patients
Few studies have assessed the effect of dual or single chamber pacing using standardised patient health related quality of life measures. One parallel study showed no significant differences in effect between dual and single chamber pacing, whilst 4 crossover studies showed either no effect or a trend towards dual chamber pacing being more favourable for certain quality of life items.

However, fewer patients report symptoms of pacemaker syndrome during dual chamber pacing.

Only one study assessed the economic costs to patients reporting a modest reduction in costs with dual pacing as the result of a slight reduction in working days lost through attending follow-up clinics.

Limitations of study
Although only randomised controlled trials were included, it cannot be ruled out that the poor quality and potentially inappropriate design of some studies (e.g. in terms of mode randomisation, or choice of population and outcome for crossover studies) may have an influence on the effect size and direction. The quality was judged to be of a low standard for all studies, although this may be due to poor reporting.

Extensive searching was carried out in order to avoid publication bias, i.e. the failure to identify results that are not statistically significant or do not report a positive clinical effect. A funnel plot was generated for the results for total pacemaker symptoms (9 crossover studies) and exercise capacity (10 crossover studies). The statistical test for bias was not significant in both cases. However, as these plots are based on a small number of studies only, publication bias cannot be ruled out completely.

As there was heterogeneity between studies (for example in terms of pacemaker modes compared, populations or assessment tools) the clinical effects observed may not be solely due to the single versus dual chamber pacing aspect of the studies. However, the effects do appear to be consistent across studies.

Comparisons of effect according to patient condition (sick sinus syndrome or atrioventricular block) were limited as patient data was mainly presented in an aggregated form.

Implications for future research
Further clinical evidence is needed, particularly for the effect of dual and single chamber pacing on patient related quality of life, long-term adverse outcomes, mortality and the effect on patients with AV block and SSS respectively or other relevant indications.

Five large randomised controlled trials are currently ongoing in the UK, USA and Denmark and Canada (the Canadian trial referred to is a 3-year extension of the CTOPP trial, which has been included in this review, Connolly et al. 2000[26]) With over 8000 patients in total this is near double the number of patients included in this review and will provide important new evidence. The populations in these trials have AV block, SSS or both, and physiological pacemakers (dual chamber or atrial) are compared to ventricular pacemakers, with the exception of the Danish study, which compares dual to atrial modes. This systematic review will have to be updated once the new results have been fully reported. (see table 5 for details on all identified ongoing trials and expected report dates)

There is a need for further economic evidence. The results from the UK PACE trial and the US based MOST trial include formal cost-effectiveness as one of the outcomes investigated and will provide new evidence.

Appendix 1 - Search strategies

Scoping search/search for systematic reviews

MEDLINE (Ovid) search, 19th February 2001
1993-Present

Search history
1 (meta adj analy$).mp.
2 meta-analy$.mp.
3 metaanaly$.mp.
4 (systematic$ adj4 review$).mp.
5 review.ti.
6 (systematic$ adj4 overview$).mp.
7 guideline$.ti.
8 summar$.ti.
9 comparison$.ti.
10 exp cardiac pacing, artificial/
11 exp pacemaker, artificial/
12 10 or 11
13 or/1-9
14 12 and 13

Clinical effectiveness

MEDLINE (Ovid) search, 30th May 2001
1966-present

Search history
1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials.sh.
4 random allocation.sh.
5 double-blind method.sh.
6 single-blind method.sh.
7 or/1-6
8 (animal not human).sh.
9 7 not 8
10 clinical trial.pt.
11 exp clinical trials/
12 (clin$ adj25 trial$).ti, ab.
13 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti, ab.
14 placebos.sh.
15 placebo$.ti, ab.
16 random$.ti, ab.

17 research design.sh.
18 or/10-17
19 18 not 8
20 19 not 9
21 comparative study.sh.
22 exp evaluation studies/
23 follow up studies.sh.
24 prospective studies.sh.
25 (control$ or prospectiv$ or volunteer$).ti, ab.
26 or/21-25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28
30 exp pacemaker, artificial/
31 exp cardiac pacing, artificial/
32 pacemaker$.mp.
33 pacing.mp.
34 (dual adj chamber).mp.
35 (dual adj pac$).mp.
36 double adj chamber.mp.
37 physiologic$ adj pac$.mp.
38 (AV adj synchron$).mp.
39 (atrioventricular adj synchron$).mp.
40 (AV adj sequential).mp
41 (atrioventricular adj sequential).mp.
42 DDD.mp.
43 DDDR.mp.
44 DDI.mp.
45 DDIR.mp.
46 VDD.mp.
47 VDDR.mp.
48 VDI.mp.
49 VDIR.mp.
50 (single adj chamber).mp.
51 (single adj pac$).mp.
52 (atrial adj pac$).mp.
53 (ventricular adj pac$).mp.
54 VVI.mp.
55 VVIR.mp.
56 AAI.mp.
57 AAIR.mp.
58 or/30-33
59 or/34-39
60 or/50-57
61 29 and 58 and 59 and 60

EMBASE (Ovid) search, 30th May 2001

1980-present

Search history
1 exp controlled trial/
2 exp randomized controlled trial/
3 exp clinical trial/
4 exp controlled study/
5 exp clinical study/
6 exp prospective study/
7 exp double blind procedure/
8 exp crossover procedure/
9 exp randomization/
10 exp major clinical study/
11 exp pacemaker/
12 exp heart pacing/
13 pacemaker$.mp.
14 pacing.mp.
15 (dual adj chamber).mp.
16 (dual adj pac$).mp
17 (double adj chamber).mp
18 (physiologic$ adj pac$).mp.
19 (atrioventricular adj synchron$).mp.
20 (AV adj synchron$).mp.
21 (atrioventricular adj sequential).mp.
22 (AV adj sequential).mp.
23 DDD.mp.
24 DDDR.mp.
25 DDI.mp.
26 DDIR.mp.
27 VDD.mp
28 VDDR.mp.
29 VDI.mp.
30 VDIR.mp.
31 (single adj chamber).mp.
32 (single adj pac$).mp
33 VVI.mp.
34 VVIR.mp.
35 AAI.mp.
36 AAIR.mp.
37 (atrial adj pac$).mp
38 (ventricular adj pac$).mp.
39 or/1-10
40 or/11-14
41 or/15-30
42 or/31-38
43 39 and 40 and 41 and 42

Science Citation Index (Web of Science), search 30th May 2001
1980-present

Search history
(random* or blind* or comparative or comparison or prospective or controlled or trial or crossover or evaluation) and
(pacemaker* or pacing) and
(dual chamber or dual pac* or double chamber or DDD or DDDR or DDI or DDIR or VDD or VDDR or VDI or VDIR or physiologic* pac* or AV synchron* or atrioventricular synchron* or AV sequential or atrioventricualr sequential) and
(single chamber or single pac* or atrial pac* or ventricular pac* or AAI or AAIR or VVI or VVIR)

Cochrane Controlled Trials Register (CCTR), search 4th June 2001
2001 Issue 2

Search history
1 Pacemaker-artificial*:ME
2 Cardiac-Pacing-Artificial*:ME
3 Pacemaker*
4 Pacing
5 #1 or #2 or #3 or #4
6 Dual and Chamber
7 Dual and Pac*
8 Double and Chamber
9 Physiologic* and Pac*
10 Atrioventricular and Pac*
11 Atrioventricular and Sequential
12 Atrioventricular and Synchron*
13 DDD
14 DDDR
15 DDI
16 DDIR
17 VDD
18 VDDR
19 VDI
20 VDIR
21 #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
22 Single and Chamber
23 Single and Pac*
24 Atrial and Pac*
25 Ventricular and Pac*
26 VVI
27 VVIR
28 AAI
29 AAIR

#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#5 and #21 and #30

Cost-effectiveness

MEDLINE (Ovid) search, 12th July 2001
1966-present

Search history
1 economics/
2 health planning/
3 exp "costs and cost analysis"
4 cost of illness/
5 exp health care costs/
6 economic value of life/
7 exp economics medical/
8 exp economics hospital/
9 economics pharmaceutical/
10 exp "fees and charges"/
11 (cost or costs or costed or costly or costing).tw
12 (economic$ or pharmacoeconomic$ or price$ or pricing).tw
13 or/1-12
14 exp pacemaker, artificial/
15 exp cardiac pacing, artificial/
16 pacemaker$.mp.
17 pacing.mp.
18 (dual adj chamber).mp.
19 (dual adj pac$).mp.
20 double adj chamber.mp.
21 physiologic$ adj pac$.mp.
22 (AV adj synchron$).mp.
23 (atrioventricular adj synchron$).mp.
24 (AV adj sequential).mp
25 (atrioventricular adj sequential).mp.
26 DDD.mp.
27 DDDR.mp.
28 DDI.mp.
29 DDIR.mp.
30 VDD.mp.
31 VDDR.mp.
32 VDI.mp.
33 VDIR.mp.
34 (single adj chamber).mp.
35 (single adj pac$).mp.
36 (atrial adj pac$).mp.
37 (ventricular adj pac$).mp.

38 VVI.mp.
39 VVIR.mp.
40 AAI.mp.
41 AAIR.mp.
42 or/14-17
43 or/18-33
44 or/34-41
45 13 and 42 and 43 and 44

EMBASE (Ovid) search, 19th July 2001
1980-present

Search history
1 exp economic evaluation/ or exp fee/ or exp health care cost/ or exp health economics/ or exp health insurance/ or exp pharmacoeconomics/
2 cost$.mp
3 economic$.mp
4 price$.mp
5 fee$.mp
6 QALY.mp
7 exp Pacemaker/
8 exp heart pacing/
9 pacemaker$.mp.
10 pacing.mp.
11 (dual adj chamber).mp.
12 (dual adj pac$).mp.
13 double adj chamber.mp.
14 physiologic$ adj pac$.mp.
15 (AV adj synchron$).mp.
16 (atrioventricular adj synchron$).mp.
17 (AV adj sequential).mp
18 (atrioventricular adj sequential).mp.
19 DDD.mp.
20 DDDR.mp.
21 DDI.mp.
22 DDIR.mp.
23 VDD.mp.
24 VDDR.mp.
25 VDI.mp.
26 VDIR.mp.
27 (single adj chamber).mp.
28 (single adj pac$).mp.
29 (atrial adj pac$).mp.
30 (ventricular adj pac$).mp.
31 VVI.mp.
32 VVIR.mp.
33 AAI.mp.

34 AAIR.mp.
35 or/1-6
36 or/7-10
37 or/11-26
38 or/27-34
39 35 and 36 and 37 and 38

Science Citation Index (Web of Science) search, 12th May 2001
1980-present

Search history
(economic* or cost* or price* or pricing or value* or QALY) and
(pacemaker* or pacing) and
(dual chamber or dual pac* or double chamber or DDD or DDDR or DDI or DDIR or VDD or VDDR or VDI or VDIR or physiologic* pac* or AV synchron* or atrioventricular synchron* or AV sequential or atrioventricualr sequential) and
(single chamber or single pac* or atrial pac* or ventricular pac* or AAI or AAIR or VVI or VVIR)

Appendix 2 - Data Extraction Form

Data Extraction Form

1st Author, Year:
Reference Number:
Country:
Title of Study:
Reviewer:

A Inclusion/Exclusion Criteria:

Study Design
Is the study an RCT? *Yes/No/Can't tell*

Study Length
Is the length of time for one pacing mode in each study arm >/= 48 hours?

Yes/No/Can't tell

Population
Is the study population >/= 18 years with a majority having sick sinus syndrome or AV block?
Yes/No/Can't tell

Intervention/Comparator
Does the study only compare the effect of different pacing modes? *Yes/No/Can't tell*

Is at least one of the interventions a dual chamber sensing pacing pacemaker (e.g. DDD, DDDR, DDI, DDIR, VDD, VDDR)?

Yes/No/Can't tell

Is at least one of the comparators a single chamber sensing and pacing pacemaker (e.g. VVI, VVIR, AAI, AAIR)?

Yes/No/Can't tell

Outcomes (underline appropriate)

Does the study investigate one or more of the following outcomes?
Primary:
- morbidity (symptoms of pacemaker syndrome, onset of atrial fibrillation, stroke or other thromboembolic events, heart failure) and/or mortality (cardiovascular cause)

Secondary:
- quality of life (should measure: psychological/mental functioning; social functioning; physical status including ability to undertake everyday activities; and symptoms caused by disease and treatment)
- exercise assessment (exercise time and/or distance)

• complication(s) sever enough to warrant additional visit to hospital, surgical procedure or re-implantation of pacemaker

Yes/No/Can't tell

If *Yes* or *Can't tell* to all of the above, order full paper.
If *Yes* to all after reading full paper, extract remaining data.

B Quality Assessment

State Yes/No or Unclear

A Randomisation procedure A1 Was the trial described as "randomised"?	
A2 Was allocation truly random? A Was allocation quasi-random or B Was allocation systematic or C Was method of randomisation not stated or unclear? D	
B Allocation concealment B1 Was concealment adequate? A Was concealment inadequate? B Was concealment unclear? C	
C Method of blinding C1 Was the trial described as double blind?	
C2 Was the treatment allocation masked from the participants?	
C3 Was the treatment allocation masked from the investigators?	
C4 Was the treatment allocation masked at the outcome assessments?	
D Completeness of trial D1 Were the number of withdrawals (and crossovers) in each group stated?	
D2 Was an intention-to-treat analysis performed?	
D3 What were the drop-out (and crossover) rates in each group of the trial for each of the main outcomes?	
D4 Are there substantial differences in completeness between the groups?	
Jadad Score (0-5)	
Additional information parallel studies:	
Were the study arms comparable at entry?	
Were both arms treated identically?	
Were baseline measurements taken?	
Additional information crossover studies:	
Was a period effect test carried out?	

Was there a washout period? (state length)	
Were measurements taken at the start and end of both crossover periods?	

C Study Design

Is the study a crossover or parallel design?
Length of study (length of time in one pacing mode in one study arm):
Device or mode randomisation:

Population/Intervention/ Withdrawals and Crossovers

Indication(s) for pacing (according to group if applicable)/co-morbidity/drugs used:

Pacemaker present in patients before study? (length of time/type of pacemaker)

List additional groups if applicable.

Number of patients randomised:

	Group 1	Group 2	Total
Intervention/Comparator			
n (male/female)			
Mean age (SD) or (range)			
Withdrawals n (%)			
Unscheduled crossover to other study arm n (%) during 1st trial period			
n at end of first study period			

If crossover study, extract data for second part:

	Group 1	Group 2	Total
Intervention/Comparator			
n (male/female)			
Mean age (SD) or (range)			
Withdrawals n (%)			
Unscheduled crossover to other study arm n (%) during 2nd trial period			
n at end of second study period			

Comments:

Outcome: Morbidity/Mortality/Quality of Life/Exercise Assessment/Complications (underline relevant outcome)

If crossover trial, extract data separately for all crossover periods.

Intervention/ Comparator			Group 1:	Group 2:	Group 3:	Group 4:			
Outcome	Assessment tool	Total no of assessments/ frequency	Score(s) (SD or SE)	Score(s) (SD or SE)	Score(s) (SD or SE)	Score(s) (SD or SE)	Measure of statistical difference (p-value) confidence interval	Is there a statistically significant difference (Y/N)?	Type of statistical test used

Was subgroup analysis carried out?/Comments:

Appendix 3 - Quality assessment assumptions

Assumptions made when using quality assessment checklist:

Completeness: If total withdrawals were stated, a point was awarded, even if they were not stated separately for each study arm. If withdrawals were not stated, but it was evident from the data that none had occurred, a point was awarded.

Blinding: If there was no specific statement regarding patient or outcome blinding in the text, no point was awarded for patient or outcome blinding, even if it was stated that the trial was double-blind. If there was a statement regarding the outcome assessment blinding of at least one outcome, a point was awarded.

Intention to treat analysis (ITT): If there was no statement regarding ITT, but it was evident from the data that no withdrawals or unscheduled crossovers had occurred, a point was awarded. If there was a statement regarding ITT in the text, a point was awarded, even if ITT was not evident from the data.

Appendix 4 - Excluded studies

1. 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]. [Japanese]. *Journal of Cardiology* 1992;**22**:265-270.

2. Adinolfi E, Devita S, Genova L, et al. Radionuclide evaluation of DDD versus VVI pacing with a nonimaging probe - nuclear stethoscope. *Pace-Pacing And Clinical Electrophysiology* 1985;**8**:A98-A98

3. 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**:571-575.

4. 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 Electrophysiology* 1992;**15**:762-770.

5. Alpert MA, Curtis JJ, Sanfelippo JF, 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. *Journal of the American College of Cardiology* 1986;**7**:925-932.

6. Alpert MA, Curtis JJ, Sanfelippo JF, 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. *American Heart Journal* 1987;**113**:958-965.

7. Amici E, Neri R, Donati R, Gambelli G. Transesophageal echocardiographic color Doppler evaluation of pulmonary vein flow during ventricular pacing. *American Journal of Cardiac Imaging* 1996;**10**:23-28.

8. 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 & Electrophysiology* 1998;**8**:8-10.

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11. Batey RL, Sweesy MW, Scala G, Forney RC. Comparison of low rate dual chamber pacing to activity responsive rate variable ventricular pacing. *Pacing & Clinical Electrophysiology* 1990;**13**:646-652.

12. Been M, De Bono DP, Miller HC, Hillis WS . Effect of afterload reduction in patients with ventricular and physiological pacing. *British Heart Journal* 1984;**51**:292-297.

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16. BREN GB, WASSERMAN AG, ELBAYOUMI J, ROSS AM. COMPARISON OF DDD AND RATE RESPONSIVE-VVI PACING DURING EXERCISE. *Circulation* 1986;**74**:388-388.

17. Brignole M, Sartore B, Barra M, Menozzi C, Lolli G. Is DDD superior to VVI pacing in mixed carotid sinus syndrome? An acute and medium-term study. *Pacing & Clinical Electrophysiology* 1988;**11**:1902-1910.

18. Brignole M, Menozzi C, Lolli G, Sartore B, Bertulla A. [The choice of stimulation mode in patients with cardioinhibitory or mixed carotid sinus hypersensitivity, with or without associated sinus dysfunction]. [Italian]. *Giornale Italiano di Cardiologia* 1989;**19**:28-34.

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20. Brignole M, Menozzi C, Lolli G, Oddone D , Gianfranchi L, Bertulla A. Validation of a method for choice of pacing mode in carotid sinus syndrome with or without sinus bradycardia. *Pacing & Clinical Electrophysiology* 1991;**14**:196-203.

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24. 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 & Clinical Electrophysiology* 1996;**19**:815-821.

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patients with normal systolic function and complete atrioventricular block unchanged during exercise test]. [French]. *Archives des Maladies du Coeur et des Vaisseaux* 1993;**86**:69-74.

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28. Chauhan A, Grace AA, Newell SA, et al. Early complications after dual chamber versus single chamber pacemaker implantation. [see comments]. *Pacing & Clinical Electrophysiology* 1994;**17**:2012-2015.

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30. Copperman Y, Bornstein NM, Nissel T, Laniado S. The use of transcranial Doppler in the hemodynamic assessment of implanted pacemakers. *Pace-Pacing & Clinical Electrophysiology* 1993;**16**:2217-2221.

31. Daubert JC, Roussel A, Langella B. Haemodynamic and M mode echocardiographic study of the consequences of ventriculo-atrial conduction in man. *Archives des Maladies du Coeur et des Vaisseaux* 1984;**77**:413-425.

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33. Defilippi R, Bramucci E, Gavazzi A, 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. *Pace-Pacing And Clinical Electrophysiology* 1981;**4**:A41-A41

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41. Fananapazir L, Srinivas V, Bennett DH. Comparison of resting hemodynamic indices and exercise performance during atrial synchronized and asynchronous ventricular pacing. *Pacing & Clinical Electrophysiology* 1983;**6**:202-209.

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43. Fishberger SB, Wernovsky G, Gentles TL, et al. Long-term outcome in patients with pacemakers following the Fontan operation. *American Journal of Cardiology* 1996;**77**:887-889.

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Appendix 5 - Quality assessment crossover studies

Study, Year	Was trial described as randomised	Randomisation method stated	Adequate concealment described	Was trial described as double-blind	Statement regarding blinding of participants	Statement regarding blinding at outcome assessments	No of withdrawals	Intention to treat analysis performed	Jadad score (0-5)	Early crossover from a single mode (n/N)	Early crossover from a dual mode (n/N)	Was a period effect test carried out	Was there a washout period? At which point in trial were measurements taken?	Were patients paced before start of study?	Results for both crossover periods (I+II) or summarised (S) only?	Comments
Avery et al., 1994[35]	Y	N	N	Y	Y	Y	3/13	N	4	None	None	N	Tests at baseline and after each 1 month period. Baseline results not stated.	DDD or VDD mode (length of time not stated).	S	
Boon et al., 1987[36]	Y	N	N	N	N	N	3/18	N	2	None	None	N	Tests after each 4 week period. No tests at baseline.	Dual chamber pacemaker implanted 4 weeks before.	S	
Capucci et al., 1993[37]	Y	Y	N	N	N	Y/N	2/14	N	2	None	None	N	Tests after each 1 month period. No baseline tests.	1 month in DDD mode.	S	
Channon et al., 1994[38]	Y	N	N	Y	Y	Y	2/16	CT	4	3/16 VVI → DDD	None	N	Tests at baseline and after each 1 week period. Baseline results not stated.	DDD for average of 24.56 months (4 months to 8 years).	S	
Davis et al., 1985[39]	Y	N	N	Y	Y	Y/N	0/13	CT	4	None	None	N	Tests at baseline (symptom diary and exercise) and after each 3 week period (exercise). Symptom diary kept from day 1 of each period. Baseline results not stated.	DDD or VDD prior to December 1983.	S	
Deharo et al., 1996[81]	Y	N	N	N	Y	N	0/15	CT	2	1/15 VVIR → DDD	None	N	Tests after each 4 week period. Exercise tests before study commenced (no results).	At day 3-4 after implant, VVIR mode programmed for 2 weeks.	S	
Hargreaves et al., 1995[41]	Y	N	N	Y	N	N	0/20	Y	2	3/20 VVIR → DDD	None	Y	Baseline questionnaire and exercise tests (VVI mode, results stated). Tests (questionnaire and exercise) after each 2 week period.	1 month in VVI pacing.	I + II	
Heldman et al., 1990[15]	Y	N	N	N	Y	N	0/40	CT	2	17/42 VVI →DDD/I	None	N	Baseline questionnaire (results not stated). Questionnaire completed at end of each1 week period.	DDD or DDI mode for more than 3 months (4-72 months).	S	
Kenny et al., 1986[31]	Y	N	N	Y	Y	Y	0/10	CT	4	2/10 VVI → DDD	None	N	Baseline exercise test (no results stated). Exercise test and subjective comparison score after each 1 month period. Symptom diary kept from day 1 of each period.	DDD mode for minimum of 3 months, mean (SD)=17.9 (10.2) months.	S	
Kamalvand et al., 1997[32]	Y	Y	N	Y	N	Y/N	5/48	N	2	33% terminated VVIR mode early 19% terminated DDDR mode early 3% terminated MS DDDR mode early		N	Exercise test and questionnaires after each 4 week period.	DDIR mode for 30 days after implantation.	S	
Kristensson et al., 1985[42]	Y	N	N	Y	Y	Y	0/44	CT	4	None	None	N	Baseline questionnaire (no results). Questionnaire and exercise tests after each 3 week period. Questionnaire dealt only with symptoms from preceding week.	35 (+/-15) months with VDD pacemaker.	S	
Lau et al., 1994 (1)[30]	Y	N	N	Y	N	Y	3/15	N	2	1/15 VVIR →AAIR	None	N	Baseline questionnaire and questionnaire after each 4 week period.	Dual chamber pacemakers received at start of study.	S	
Lau et al., 1994	Y	N	N	Y	N	Y	0/33	CT	2	2/33	None	N	Baseline questionnaire (no results stated) and	1 month of pacing (mode	S	

Study, Year	Was trial described as randomised	Randomisation method stated	Adequate concealment described	Was trial described as double-blind	Statement regarding blinding of participants	Statement regarding blinding at outcome assessments	No of withdrawals	Intention to treat analysis performed	Jadad score (0-5)	Early crossover from a single mode (n/N)	Early crossover from a dual mode (n/N)	Was a period effect test carried out	Was there a washout period? At which point in trial were measurements taken?	Were patients paced before start of study?	Results for both crossover periods (I+II) or summarised (S) only?	Comments
(2)[43]										VVIR→DDD(R)			questionnaire after each 8 week period.	unclear) after implant.		
Linde-Edelstam et al., 1992 (1)[33]	Y	N	N	Y	Y	N	0/17	CT	2	1/17 VVIR → DDD	None	N	Questionnaires after each 2 month period. No baseline questionnaire.	DDD mode for 3 months after implant.	S	
Linde-Edelstam et al., 1992 (2)[34]	Y	N	N	Y	Y	Y	2/17	CT	4	1/17 VVIR → DDD	None	N	Exercise test after each 2 month period. No baseline test.	DDD mode for 3 months after implant.	S	
Lukl et al., 1994[44]	Y	N	N	Y	Y	Y	0/21	Y	4	None	None	N	Questionnaire at end of each 2 week study period.	Implant at start of study.	S	
Menozzi et al., 1990[45]	Y	N	N	Y	Y	Y	0/14	CT	4	5/14 VVIR→DDD	None	N	Symptom questionnaire and exercise test after each 6 wk period. Symptom diary throughout.	4 weeks in DDD mode after implant.	S	
Mitsuoka et al., 1988[46]	Y	N	N	Y	Y	Y	0/8	CT	4	2/16 VVI → DDD	None	N	Baseline exercise test (no results). Exercise tests after each 1 month period. Symptom diary cards kept throughout. Subjective comparison re symptoms made after each month.	DDD mode for a mean of 23 months.	S	
Oldroyd et al., 1991[47]	Y	N	N	Y	N	Y/N	0/10	CT	2	1/10 VVIR →DDD	None	N	Exercise tests and questionnaires after each 1 month period. Preliminary exercise tests (no results).	Implant at start of study.	S	
Perrins et al., 1983[48]	Y	N	N	Y	Y	Y	0/13	Y	4	None	None	N	Diary cards kept for I month with exercise test at the end as run-in period (in random mode, no results). Diary cards throughout and exercise tests after each 1 month period.	VDD or DDD mode for at least 3 months (3-27 months).	S	
Rediker et al., 1988[49]	Y	N	N	N	N	Y/N	0/19	N	2	8/19 VVI→ DDD after1.8 +/- 1.4 weeks; other 11 VVI→DDD after 6.2 +/- 3.7 weeks		N	Baseline questionnaire and exercise tests (no results). Questionnaires and exercise test after each 6 week period.	VDD or DDD mode between 3 and 55 months (mean 24.3 months).	S	
Saner & Fricker, 1996[50]	Y	Y	N	N	N	N	0/12	CT	2	4/12 VVIR → DDD	None	N	Questionnaire given out at beginning of each 6 week period & completed every week. Exercise tests after each 6 wk period. No baseline tests.	Dual chamber pacemakers-length of pacing time and mode not stated.	S	
Sulke et al., 1994[51]	Y	N	N	Y	N	N	0/10	CT	2	3/10 VVIR →DDDR	None	N	Questionnaire after each 4 week period. No baseline questionnaire.	DDIR mode for 6 weeks before study. Previous implantation time not stated.	S	
Sulke et al., 1991[53]	Y	Y	N	Y	Y	Y	0/22	CT	4	5/22 VVIR →dual	None	N	Questionnaire and exercise tests after each 4 week period. No baseline tests.	13 patients implanted at start of study, 9 previously implanted 9.6 months mean (range 3-12 months)	S	
Sulke et al, 1992[52]	Y	Y	N	Y	Y	Y	0/16	CT	4	3 early crossovers		N	Questionnaire after each 4 week period. No baseline questionnaire.	Chronic VVI pacing for at least 3 years. Upgrade to dual 2 weeks before study (in first randomised mode).	S	
Yee et al., 1984[54]	Y	N	N	N	Y	N	0/8	CT	2	None	None	N	Baseline questionnaire and exercise tests (results given). Questionnaire and exercise tests after each 3 month period.	Implantation at start of study in 7, upgrade from VVI for 1 patient.	S	

Appendix 6 - Clinical effectiveness results crossover studies (mortality and morbidity)

Study	Assessment Tool	Outcome Measure	Single Mode(s)		Dual mode(s)		Statistical significance	Direction of effect
Avery et al., 1994[35]	Questionnaire on 11 symptoms based on Minnesota 'Living with heart failure' questionnaire re symptoms and ability to carry out daily tasks (0-5 score), max score 55. Low score = good sense of well-being.	Group mean (SD) for total symptom score	**VVI** 28 (10)		**DDD/VDD** 19 (5)		Yes (p<0.05)	Fewer symptoms of pacemaker syndrome and better ability to carry out daily tasks in DDD/VDD mode compared to VVI mode.
Boon et al., 1987[36]	Questionnaire on 4 symptoms (shortness of breath, dizziness, fatigue, general well-being) scored from 0-10 on visual analogue scale. Low score = good sense of well-being; less severe symptoms.	Group median, interquartile range (IR) and full range (FR) for individual symptoms [e] Shortness of breath Dizziness Fatigue General well-being	**VVI** 2.21 [e] IR 1.0-4.10 [e] FR 0-9.62 [e] 0.32 [e] IR 0-1.0 [e] FR 0-9.87 [e] 0.28 [e] IR 0.13-4.77 [e] FR 0-9.74 [e] 9.52 [e] IR 5.45-9.81 [e] FR 3.37-9.74 [e]		**DDD** 1.15 [e] IR 0-2.18 [e] FR 0-6 [e] 0.06 [e] IR 0-0.29 [e] FR 0-4.49 [e] 0.13 [e] IR 0-1.99 [e] FR 0-7.95 [e] 7.21 [e] IR 8.65-9.93 [e] FR 5.38-9.93 [e]	 Yes (p<0.05) Yes (p<0.05) Yes (p<0.05) Yes (p<0.05)	Fewer symptoms of pacemaker syndrome and higher level of well-being in DDD mode compared to VVI mode.
Capucci et al., 1993[37]	Questionnaire on 8 symptoms (shortness of breath at rest, shortness of breath on exercise, neck pulsation, palpitation, chest pain at rest, chest pain on exercises, fainting, dizziness) scored 1-5 for frequency or degree of discomfort. 1=least discomfort.	Group mean (?) for total symptoms. *NB: not clear whether SD calculated. No individual patient data.*	**VVIR** 25.5 (5.4)		**DDD** 19.0 (3.1)	**DDDR** 17.8 (1.8)	Yes for DDD vs VVIR (p<0.01) Yes for DDDR vs VVIR (p<0.01)	Fewer symptoms of pacemaker syndrome in DDD and DDDR mode compared to VVIR mode.
Channon et al., 1994[38]	Questionnaire on 7 symptoms (breathlessness, pulsation in neck, dizziness, blackout, wheeze, fatigue, palpitation) scored from 0-5 on visual analogue scale. (0=not at all, 5=very severe)	Group mean (SD) for total symptoms; group means (SD) for dizziness fatigue breathlessness	**VVI** 9.4 (5.67) 1.73 (1.71) 2.13 (1.69) 3.00 (1.89)		**DDD** 4.73 (4.40) 0.47 (0.92) 1.20 (1.42) 1.80 (1.66)		Yes (p<0.006) Yes (p<0.007) Yes (p=0.01) Yes (p<0.03)	Fewer symptoms of pacemaker syndrome in DDD mode compared to VVI mode.
Davis et al., 1985[39]	Daily symptom diaries on 10 symptoms (chest pain, chest discomfort, dizziness, blurred vision, palpitations, dyspnoea at rest, dyspnoea on exertion, disturbed sleep, pulsating sensation in neck, pulsating sensation in abdomen)	Group mean episodes per week chest pain and/or discomfort dizziness palpitations dyspnoea at rest dyspnoea on exertion *NB: no SD or SE stated, no individual patient data.*	**VVI** 1.7 2.2 1.0 1.5 7.3		**VDD** 1.5 0.8 1.0 0.2 2.2		 NS NS NS NS NS	Fewer episodes per week of 4 symptoms of pacemaker syndrome in VDD mode compared to VVI mode. One symptom of pacemaker syndrome occurred at equal frequency in both modes. Results not listed for all symptoms.

Deharo, et al., 1996[40]	5 symptoms (sleep disturbance, chest pain, palpitations, dizziness, neck pulsations) scored 0-3. (0=no symptoms, 3=very frequent symptoms)	Group mean (SD) for Sleep disturbance Chest pain Palpitations Dizziness Neck pulsations	**VVIR** 1.13 (1.46) 0.5 (0.91) 0.6 (1.3) 0.53 (0.91) 0.33 (0.72)		**DDD** 1.3 (1.44) 0.2 (0.56) 0.33 (0.72) 0.14 (0.52) 0.2 (0.56)		 NS NS NS NS NS	Lower overall symptom score for 4 symptoms (chest pain, palpitations, dizziness, neck pulsations) in DDD mode compared to VVIR mode. One higher overall symptom score in DDD mode compared to VVI mode (sleep disturbance). No statistical significance for any differences.
Hargreaves et al., 1995[41]	Questionnaire on frequency and severity of 8 symptoms (breathlessness pulsation, dizziness, blackout, wheeze, fatigue, palpitation, cough) scored 0-5 each on analogue scale. (0=none, 5=very severe) *NB: SD calculated by JD*	 Group mean (SE) *(SD)* Means (SE) for groups according to pacing order: DDD/VVIR Means (SE) for groups According to pacing order: VVIR/DDD	**VVIR** 5.2 (0.8) *(3.58)* 6.3 (1.0) 2.7 (2.0)		**DDD** 2.9 (0.8) *(3.58)* 2.9 (1.0) 3.9 (1.0)		 Yes (p<0.05) Yes (p<0.05) NS	Overall significantly lower score for 8 symptoms of pacemaker syndrome in DDD mode compared to VVIR mode. Difference not significant if paced in VVIR mode first.
Heldman et al., 1990[15]	Questionnaire on presence and severity of 16 symptoms (shortness of breath, fatigue, dizziness, apprehension, cough, pulsations in neck/abdomen, orthopnea, headache, palpitations, chest pain, choking sensation, confusion, pedal oedema, sensation of tachycardia, chest congestion, diaphoresis) scored 0-10. (0=not present, 10=very severe).	Group mean (SD) for total and individual symptoms. Total symptoms Shortness of breath Fatigue Dizziness Apprehension Cough Pulsation in neck/abdomen Orthopnea Headache Palpitations Chest Pain Choking Sensation Confusion Pedal Oedema Sensation of Tachycardia Chest Congestion Diaphoresis	**VVI** 29.0 (26.1) 3.3 (3.1) 4.8 (3.5) 2.9 (3.6) 3.0 (3.6) 1.7 (2.5) 2.0 (3.2) 1.3 (2.5) 1.3 (2.3) 1.5 (3.0) 1.4 (2.6) 1.3 (2.9) 0.9 (2.2) 0.9 (2.3) 1.1 (2.5) 1.1 (1.9) 0.7 (2.3)		**DDD/DDI** 7.3 (12.4) 0.8 (1.8) 1.3 (2.3) 0.8 (1.3) 0.3 (0.8) 0.4 (1.6) 0.4 (1.1) 0.3 (1.3) 0.5 (0.9) 0.5 (1.0) 0.4 (1.2) 0.3 (1.2) 0.2 (0.6) 0.3 (0.9) 0.4 (1.4) 0.5 (1.6) 0.1 (0.2)		 Yes (p<0.001) Yes (p<0.001) Yes (p<0.001) Yes (p<0.001) Yes (p<0.001) Yes (p=0.001) Yes (p=0.002) Yes (p<0.02) Yes (p<0.02) Yes (p<0.04) Yes (p<0.04) Yes (p<0.04) Yes (p<0.05) NS NS NS NS	Lower symptom score in DDD/DDI mode compared to VVI mode for all 16 symptoms. Significant difference for 12 out of 16 symptoms.
Kamalvand et al., 1997	Questionnaire on 11 cardiovascular related symptoms, score 0-84 (score >/= 25 indicative of pacemaker syndrome)	 Group mean (SD) total symptom score	**VVIR** 26.8 (15.3)		**DDDR** 22.3 (12.2)	**MS DDDR** 21.2 (12.4)	 Yes for MS DDDR versus VVIR (p=0.01)	Lower symptom score in both dual modes compared to single mode, significant difference between mode switching DDDR and VVIR.
Kenny et al., 1996[31]	Diary card on daily frequency of 3 symptoms (chest pain, dizziness, palpitations); Symptom score for 4 symptoms (chest pain, dizziness, palpitations, syncope) compared to previous crossover period (scale 1-5, 1=much worse, 5=much improved)	Group mean (SD) for episodes per week [e] Palpitations Dizziness Chest Pain Number of patients with specific score: 1 2 3 4 5	**VVI** 0 19.13 [e] 13.00 [e] 3 2 3 0 2		**DDD(100)** 0.94 [e] 4.25 [e] 7.09 [e] - 1 1 4 4	**DDD (150)** 0.60 [e] 4.96 [e] 25.75 [e] 2 1 3 1 3	Yes for VVI vs DDD (100) and DDD (150) for dizziness (p<0.01) Yes for DDD (150) vs DDD (100) for chest pain (p<0.01) Yes for VVI vs DDD (100) for chest pain (p<0.02)	Highest number of episodes per week in DDD (150) compared to DDD (100) and VVI. Fewer episodes per week for dizziness in dual modes compared to VVI. Similar levels for palpitations (dual modes slightly higher). Number of patients improving on their symptom score compared to previous crossover period is slightly higher in DDD (150) mode compared to VVI mode and highest in DDD (100) mode.

Kristensson et al., 1985[42]	Questionnaire on frequency and severity of 9 symptoms (palpitations, dizziness, syncope, pulsation in neck, fluttering before eyes, chest pain at rest, chest pain on exercise, dyspnoea at rest, dyspnoea on exercise) based on visual analogue scale (0-10). (0=no symptoms, 10=extreme symptoms). Total number of patients reporting symptoms.	Group means for individual symptoms [e] Palpitations Dizziness Syncope Pulsation in neck Eye flutter Chest pain at rest Chest pain on exercise Dyspnoea at rest Dyspnoea on exercise Total number of patients with symptoms in each group: Palpitations Dizziness Syncope Pulsation in neck Eye flutter Chest pain at rest Chest pain on exercise Dyspnoea at rest Dyspnoea on exercise	**VVI** 75.61 [e] 29.27 [e] 12.20 [e] 68.77 [e] 18.29 [e] 24.39 [e] 30.00 [e] 20.24 [e] 134.15 [e] 17 12 4 18 8 9 8 9 33		**VDD** 26.83 [e] 15.85 [e] 1.22 [e] 30.49 [e] 9.76 [e] 4.88 [e] 23.17 [e] 4.88 [e] 65.09 [e] 10 7 1 11 6 4 9 1 25		Yes (p<0.01) NS NS Yes (p<0.05) NS Yes (p<0.05) NS NS Yes (p<0.001)	Lower symptom score in VDD mode compared to VVI mode for 9 symptoms of pacemaker syndrome. Difference is significant for 4 symptoms (palpitations, pulsation in neck, chest pain at rest and dyspnoea on exercise). Fewer patients with symptoms in VDD group (for 8 of the 9 symptoms). One more patient with chest pain on exercise in the VDD group compared to the VVI group.
Lau et al., 1994 (1)[30]	Questionnaire on incidence and frequency of 6 symptoms (dyspnoea, palpitations, dizziness, chest pain, sleep disturbance, neck pulsations) scored 1-5 (1=all of the time, 5=never)	Group mean for individual symptoms Dyspnoea Palpitations Dizziness Chest pain Sleep disturbance Neck pulsations	**VVIR** 3.42 [e] 3.00 [e] 3.80 [e] 4.27 [e] 3.96 [e] 4.67 [e]	**AAIR** 4.00 [e] 4.00 [e] 3.90 [e] 4.67 [e] 4.67 [e] 5.00 [e]	**DDDR** 3.42 [e] 4.30 [e] 4.30 [e] 4.60 [e] 4.25 [e] 5.00 [e]		Yes for VVIR vs AAIR for palpitations (p<0.05) Yes for VVIR vs DDDR for palpitations (p<0.001)	Lower incidence of symptoms in DDDR and AAIR mode (for 5 out of 6 symptoms) compared to VVIR.
Lau et al., 1994 (2)[43]	Physical Malaise Inventory (41 items). Higher numerical score indicates less severe symptoms. Results given for pain, dyspnoea, temperature intolerance, epigastric pain and palpitations only.	Group mean for individual symptoms[e]: Pain Dyspnoea Temperature intolerance Epigastric pain Palpitations	**VVIR** 1.72[e] 1.83[e] 1.63[e] 1.85[e] 1.81[e]		**DDD** 1.55[e] 1.85[e] 1.63[e] 1.93[e] 1.84[e]	**DDDR** 1.89[e] 2.00[e] 1.91[e] 1.99[e] 1.98[e]	Yes for DDDR vs DDD for pain (p<0.01) Yes for DDDR vs DDD (p<0.05) and DDDR vs VVIR (p<0.01) for dyspnea Yes for DDDR vs DDD and DDDR vs VVIR for temperature intolerance (p<0.01) Yes for DDDR vs VVIR for epigastric pain (p<0.05) Yes for DDDR vs DDD (p<0.05) and DDDR vs VVIR (p<0.01) for palpitations	Overall lower incidence of symptoms in DDDR mode compared to VVIR and DDD mode. Significant difference for DDDR compared to VVIR mode for 4 out of 5 symptoms. Significant difference for DDDR compared to DDD for 4 out of 5 symptoms.

Linde-Edelstam et al., 1992 (1)[33]	Questionnaire on 4 symptoms (breathlessness, dizziness, chest pain, palpitations) on visual analogue scale (increasing no of mm=progressive severity of symptoms)	Group mean (SD) individual symptom score Breathlessness Dizziness Chest pain palpitations	**VVIR** 18.1 (14.3) 15.2 (22.6) 6.8 (8.9) 6.3 (15.2)		**DDD** 9.5 (8.5) 4.8 (8.5) 2.6 (2.5) 2.8 (8.1)		 Yes (p=0.02) Yes (p=0.04) Yes (p=0.06) Yes (p=0.03) NB p<0.1 considered significant by authors	Fewer symptoms of pacemaker syndrome (breathlessness, dizziness, chest pain, palpitations) in DDD mode than VVIR mode.
Lukl et al., 1994 [44]	Questionnaire consisting of 19 questions, 11 of which relate to cardiovascular symptoms, on 6 point scale (0=optimal state, 6=worst state)	Group mean (SD) individual symptom score Swollen ankles Breathlessness at rest Breathlessness during physical exertion Overexertion during household chores Fatigue Insomnia Dizzy spells Trouble with memory and concentration Tightness in chest Palpitation Sweating	**VVIR** 0.9 (1.3) 0.6 (1.3) 3.2 (1.5) 2.6 (1.4) 2.7 (1.5) 1.7 (1.5) 1.7 (1.6) 0.6 (0.9) 0.8 (1.3) 3.2 (1.8) 2.4 (1.8)		**DDD** 1.0 (1.3) 1.0 (1.3) 2.2 (1.6) 1.6 (1.3) 1.7 (1.6) 1.9 (1.7) 0.3 (0.8) 1.0 (1.2) 1.3 (1.7) 0.9 (1.2) 1.3 (1.3)		 NS NS Yes (p<0.02) Yes (p<0.01) Yes (p<0.02) NS Yes (p<0.005) NS NS Yes (p<0.005) Yes (p<0.005)	Significantly lower symptom score in DDD mode compared to VVIR mode for 6 out of 11 symptoms listed.
Menozzi et al., 1990 [45]	Questionnaire on 6 symptoms (palpitations, dizziness, pulsating sensation in neck or abdomen, shortness of breath at rest, shortness of breath on effort, chest pain) scored 1-5 (1=slight and occasional, 5=severe and almost persistent) *NB: no SD for individual symptoms stated, no individual patient data*	Group mean individual symptom score Palpitations Dizziness Pulsating sensation Shortness of breath (rest) Shortness of breath (effort) Chest pain	**VVIR** 19 9 14 9 27 1		**DDD** 5 2 0 1 11 0		 Yes (p=0.04) NS Yes (p=0.05) NS Yes (p=0.02) NS	Significantly lower scores in DDD compared to VVIR mode for 3 out of 6 symptoms.
Mitsuoka et al., 1988[46]	5 symptoms (general well-being, shortness of breath, chest pain, dizziness, palpitations) score 1-5 compared to previous month (1=much worse, 5=much improved) Weekly attack rates (chest pain, dizziness, palpitations) *NB: Means for total group, SD and significance calculated by JD from individual patient data*	 Group mean (SD) General well-being Shortness of breath Chest pain Dizziness Palpitations Attacks/week group mean (SD) Chest pain Dizziness Palpitations	**VVI** *2.06* *1.94 (0.85)* *3.06 (1.00)* *2.56 (0.51)* *2.44 (0.89)* *1.47* *0.5* *3.66*		**DDD** *3.37* *3.44 (0.73)* *2.87 (0.62)* *3.25 (0.45)* *3.25 (0.77)* *1.59* *0.34* *0.33*		 *Yes (p<0.01)* *Yes (p<0.01)* *NS* *Yes (p<0.01)* *Yes (p<0.01)* *NS* *NS* *Ns*	Higher level of general well-being in DDD mode compared to VVI mode. Fewer symptoms of shortness of breath, dizziness and palpitations in DDD mode. Higher symptom score for chest pain in DDD mode. Lower weekly attack rate for dizziness and palpitations in DDD mode compared to VVI mode. Higher weekly attack rate for chest pain in DDD mode.
Oldroyd et al., 1991[47]	Questionnaire comprising 3 sets of 8 questions relating to dyspnoea, fatigue and mood disturbance, scored on 100mm visual analogue scale. Maximum score of 800. *NB: SD calculated by JD from estimated SEM*	Estimated group mean (SEM) symptom score Dyspnoea Fatigue Mood disturbance	**VVIR** 153.12[e] (37.67)[e] 240.62[e] (61.98)[e] 106.94[e] (18.23)[e]	*SD* *(119.12)* *(196.00)* *(57.65)*	**DDD** 133.68[e] (35.24)[e] 170.14[e] (43.75)[e] 85.07 [e] (20.66) [e]	*SD* *(111.44)* *(138.35)* *(65.33)*	 NS NS NS	Lower symptom score in DDD mode compared to VVIR mode, although not significant.

Perrins et al., 1983[48]	Daily diary card of symptoms (chest pain, dizziness, palpitations, syncope) Subjective symptom score at end of crossover period regarding improvement (for chest pain, dizziness, shortness of breath, palpitation and general well-being) scored 1-5 (1=much worse, 5=much improved)	Group mean (SD) for weekly attack rates Chest pain Dizziness Palpitations Syncope Group mean (SD) symptom score General well-being Shortness of breath Syncope Dizziness Palpitations Chest pain	**VVI** 1.08 (1.30) 2.49 (4.7) 1.76 (2.86) 0 1.72 (0.6) 2.0 (0.91) 3.0 2.3 (0.91) 2.6 (0.69) 2.9 (0.31)		**VDD** 1.16 (2.01) 1.45 (2.67) 0.35 (1.22) 0 3.54 (0.80) 3.45 (0.80) 3.0 3.5 (0.70) 3.3 (0.67) 3.1 (1.1)		 NS NS p<0.05 NS Yes (p<0.01) Yes (p<0.01) NS Yes (p<0.02) Yes (p<0.05) NS	Similar weekly attack rates in VVI and VDD mode for 3 out of 4 symptoms. Higher rate of attack in VVI mode for palpitations. Improved symptom scores for general well-being, shortness of breath, dizziness and palpitations in VDD mode compared to VVI mode. No difference in symptom score for syncope and chest pain.
Rediker et al., 1988[49]	Questionnaire assessing 5 symptoms (dizziness, weakness, fatigue, shortness of breath, palpitations) scored 1-6 (1=all of the time, 6=none of the time)	Group mean (SD) symptom score Fatigue Shortness of breath Palpitations (NB no results given for dizziness or weakness)	**VVI** 3.7 (1.2) 4.5 (1.1) 4.7 (1.5)		**DDD** 4.3 (1.0) 5.2 (0.8) 5.8 90.4)		 Yes (p=0.046) Yes (p=0.01) Yes (p=0.006)	Symptoms (fatigue, shortness of breath, palpitations) occurred less frequently in DDD mode compared to VVI mode.
Saner & Fricker, 1996 [50]	Questionnaire on incidence and frequency of symptoms of heart failure and pacemaker syndrome (shortness of breath, palpitations, chest pain, dizziness)	Group mean (SD) total symptom score	**VVIR** 5.7 (3.2)		**DDD** 2.7 (1.6)		Yes (p=0.01)	Fewer symptoms of pacemaker syndrome in DDD mode compared to VVIR mode.
Sulke et al., 1994 [51]	Questionnaire on 11 cardiovascular related symptoms, score 0-84 (score >/= 25 indicative of pacemaker syndrome)	Group mean (SD) total symptom score	**VVIR** 23.7 (9.8)		**DDDR** 10.5 (5.5)		Yes (p=0.03)	Overall fewer symptoms in DDDR mode compared to VVIR mode.
Sulke et al., 1992[52]	Questionnaire on 11 cardiovascular related symptoms (memory, concentration, tiredness, lightheadedness, shortness of breath, orthopnea, cough, palpitations, fluttering in neck/abdomen, dizziness, ankle oedema) score 0-84 (score >/= 25 indicative of pacemaker syndrome)	Group mean for total symptoms [e]	**VVI** 10.45 [e]		**DDD** 4.59 [e]	**DDI** 10.22 [e]	Yes for DDD vs VVI and DDI (p<0.05)	Fewer symptoms of pacemaker syndrome in DDD mode compared to DDI and VVI mode.
Sulke et al, 1991[53]	Questionnaire assessing incidence and frequency of pacemaker syndrome symptoms (including shortness of breath, tiredness, neck flutter and lightheadedness; full symptom list not stated), score 1-5 (1=never, 5=all of the time)	Group mean (SD) total symptom score	**VVIR** 23.5 (11.5)	**Dual modes** **DDD DDDR DDIR** Mean score only stated: 14.4 (8.1)			Yes (p<0.01) for VVIR vs all dual modes.	Lower overall symptom score in dual modes compared to single mode.
Yee et al., 1984[54]	Questionnaire assessing functional capacity and presence and frequency of symptoms (including angina, chest pain, dyspnoea, lightheadedness at rest and during exercise) (0=severe limitation in function, 60=absence of symptoms)	Group mean (SD) symptom score	**VVI** 50.1 (8.4)		**VDD** 46.9 (8.9)		NS	Similar symptom and functional score for VDD and VVI modes.

e = data estimated from graph

Appendix 7 - Clinical effectiveness results parallel and crossover studies (quality of life)

1 Parallel study:

Lamas et al., 1998[28]: QOL assessments undertaken after 3, 9 and 18 months.

QOL Parameters/Assessment Tool	Outcome Measure		DDDR	VVIR	Statistical Significance	Direction of Effect
SF-36 used for assessment of:						Slightly higher score in DDDR mode compared to VVIR mode for 6/8 items at 3 and 9 months, and for 5/8 items at 18 months. No significant differences for any scores except for mental health at 9 months.
Physical function at 3 months	Mean score (0-100)	(+)	56.9	53.9	NS	
Social function at 3 months	Mean score (0-100)	(+)	75.3	73.0	NS	
Physical role at 3 months	Mean score (0-100)	(+)	62.8	53.6	NS	
Emotional role at 3 months	Mean score (0-100)	(+)	90.6	83.8	NS	
Mental health at 3 months	Mean score (0-100)	(+)	77.6	77.0	NS	
Energy at 3 months	Mean score (0-100)	(+)	55.0	53.0	NS	
Pain at 3 months	Mean score (0-100)	(+)	69.4	69.7	NS	
Health perception at 3 months	Mean score (0-100)	(+)	62.2	62.3	NS	
Physical function at 9 months	Mean score (0-100)	(+)	57.5	54.0	NS	
Social function at 9 months	Mean score (0-100)	(+)	69.2	67.3	NS	
Physical role at 9 months	Mean score (0-100)	(+)	53.2	49.0	NS	
Emotional role at 9 months	Mean score (0-100)	(+)	81.1	76.5	NS	
Mental health at 9 months	Mean score (0-100)	(+)	79.0	75.2	Yes (p<0.03)	
Energy at 9 months	Mean score (0-100)	(+)	50.5	50.3	NS	
Pain at 9 months	Mean score (0-100)	(+)	70.9	72.1	NS	
Health perception at 9 months	Mean score (0-100)	(+)	58.3	58.4	NS	
Physical function at 18 months	Mean score (0-100)	(+)	58.4	58.4	NS	
Social function at 18 months	Mean score (0-100)	(+)	69.9	68.0	NS	
Physical role at 18 months	Mean score (0-100)	(+)	55.1	53.7	NS	
Emotional role at 18 months	Mean score (0-100)	(+)	80.6	76.1	NS	
Mental health at 18 months	Mean score (0-100)	(+)	76.5	73.0	NS	
Energy at 18 months	Mean score (0-100)	(+)	50.1	50.1	NS	
Pain at 18 months	Mean score (0-100)	(+)	70.6	68.2	NS	
Health perception at 18 months	Mean score (0-100)	(+)	56.2	58.3	NS	
Disease specific cardiovascular functional status at 3 months using Specific Activities Scale functional questionnaire	Mean grading Class I-IV (SE)	(-)	1.91	1.99	NS	Significantly lower cardiovascular functional class in DDD mode at 18 months but not at 3 or 9 months.
Disease specific cardiovascular functional status at 9 months	Mean grading Class I-IV (SE)	(-)	1.72	1.87	NS	
Disease specific cardiovascular functional status at 18 months	Mean grading Class I-IV (SE)	(-)	1.66	1.94	Yes (p=0.02)	

(-) high score is unfavourable, (+) high score is favourable; [e] data estimated from graph, NS not significant, SD standard deviation, SE standard error

2 Crossover studies

Lau et al., 1994 (1)[30]: QOL assessment undertaken after 4 weeks in each mode.

QOL Parameters/Assessment Tool	Outcome Measure		DDDR	VVIR	AAIR	Statistical Significance	Direction of Effect
General well-being using visual analogue scale	Mean score (1-10)	(+)	7.17[e]	5.89[e]	6.83[e]	Yes for VVIR vs DDDR and VVIR vs AAIR (p<0.05) NS for AAIR vs DDDR	Significantly higher level of well-being in DDDR and AAIR modes compared to VVIR mode.
Incidence & Frequency of Symptoms:							Similar incidence of symptoms in all 3 modes. Significant difference only for palpitations, which occurred more frequently in VVIR mode, compared to AAIR and DDDR modes.
Dyspnoea	Mean quantitative score (1-5)	(-)	3.42[e]	3.42[e]	4.00[e]	NS	
Palpitations	Mean quantitative score (1-5)	(-)	4.30[e]	3.00[e]	4.00[e]	Yes for VVIR vs AAIR (p<0.05) Yes for VVIR vs DDDR (p<0.001) NS for AAIR vs DDDR	
Dizziness	Mean quantitative score (1-5)	(-)	4.30[e]	3.80[e]	3.90[e]	NS	
Chest pain	Mean quantitative score (1-5)	(-)	4.60[e]	4.27[e]	4.67[e]	NS	
Sleep disturbance	Mean quantitative score (1-5)	(-)	4.25[e]	3.96[e]	4.67[e]	NS	
Neck Pulsations	Mean quantitative score (1-5)	(-)	5.00[e]	4.67[e]	5.00[e]	NS	
Disease specific cardiovascular functional status using Specific Activities Scale functional questionnaire	Mean grading Class I-IV (SE)	(-)	1.5 (0.3)	1.5 (0.2)	1.4 (?)	NS	Similar level in all 3 modes.
Psychologist's assessment							Similar scores for 10/11 items assessed. Significant difference only for range of social interactions where a more favourable score was found in DDDR and AAIR modes compared to VVIR mode.
General health	Mean score (range 0-48) (SE)	(-)	14.3 (2.2)	14.9 (2.0)	15.2 (2.1)	NS	
Somatic symptoms	Mean score (range 41-82) (SE)	(+)	71.5 (3.3)	67.7 (3.6)	70.2 (3.5)	NS	
Activities of daily living	Mean score (range 0-36) (SE)	(+)	31.2 (2.0)	31.1 (2.2)	32.8 (2.1)	NS	
Emotional adjustment	Mean score (range 5-30) (SE)	(-)	24.2 (1.7)	23.5 (1.9)	23.2 (1.8)	NS	
Social interactions: Frequency	Mean score (range 0-12) (SE)	(+)	11.3 (1.1)	11.0 (1.0)	11.8 (1.2)	NS	
Social interactions: Range	Mean score (range 0-4) (SE)	(+)	2.1 (0.2)	1.3 (0.2)	2.2 (0.3)	Yes for VVIR vs AAIR (p<0.02) Yes for VVIR vs DDDR (p<0.02) NS for AAIR vs DDDR	
Social interactions: Quality	Mean score (range 5-25) (SE)	(-)	21.5 (1.2)	21.1 (1.3)	22.4 (1.1)	NS	
Work adjustment	Mean score (range 0-2) (SE)	(-)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	NS	
Sleep	Mean score (range 0-2) (SE)	(-)	0.3 (0.1)	0.7 (0.1)	0.3 (0.1)	NS	
Fatigue	Mean score (range 0-2) (SE)	(-)	0.6 (0.1)	0.8 (0.1)	0.6 (0.1)	NS	
Appetite	Mean score (range 0-2) (SE)	(-)	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	NS	

(-) high score is unfavourable, (+) high score is favourable; [e] data estimated from graph, NS not significant, SD standard deviation, SE standard error

Lau et al., 1994 (2)[43]: QOL assessment undertaken after 8 weeks in each mode.

QOL Parameters/Assessment Tool	Outcome Measure		DDD	DDDR	VVIR	Statistical Significance	Direction of Effect
Subjective physical malaise assessed by Physical Malaise Inventory (41 items); scale not given (lower numerical value = increased malaise)							Overall significantly lower symptom scores in DDDR mode compared to VVIR and/or DDD mode. No significant differences between VVIR and DDD modes.
Pain	Mean symptom score (estimated from graph)	(+)	1.55 [e]	1.89 [e]	1.72 [e]	Yes for DDD vs DDDR (p<0.01)	
Dyspnoea	Mean symptom score (estimated from graph)	(+)	1.85 [e]	2.00 [e]	1.83 [e]	Yes for DDD vs DDDR (p<0.05) Yes for DDDR vs VVIR (p<0.01)	
Temperature intolerance	Mean symptom score (estimated from graph)	(+)	1.63 [e]	1.91 [e]	1.63 [e]	Yes for DDDR vs DDD (p<0.01) Yes for DDDR vs VVIR (p<0.01)	
Epigastric pain	Mean symptom score (estimated from graph)	(+)	1.93 [e]	1.99 [e]	1.85 [e]	Yes for DDDR vs VVIR (p<0.05)	
Palpitations	Mean symptom score (estimated from graph)	(+)	1.84 [e]	1.98 [e]	1.81 [e]	Yes for DDDR vs VVIR (p<0.01) Yes for DDDR vs DDD (p<0.05)	
Quality of life (48 items) assessed by clinical psychologist regarding: adequacy of daily life activities, emotional adjustment, social adjustment, work adjustment, general well-being (sleep, appetite and fatigue), patients' own self rating of symptomatic level, subjective well-being. Scale not given (higher score = poorer quality of life)							Overall lower scores (better quality of life) for 3/4 symptoms and total symptoms score in DDDR mode. Significantly lower scores in VVIR mode for all symptoms compared to a dual mode.
Stress	Mean estimated score for this item	(-)	1.88 [e]	1.32 [e]	1.83 [e]	Yes for DDDR vs DDD (p<0.01) Yes for VVIR vs DDDR (p<0.018)	
Mobility	Mean estimated score for this item	(-)	1.67 [e]	1.24 [e]	2.00 [e]	Yes for VVIR vs DDDR (p<0.01)	
Illness impact	Mean estimated score for this item	(-)	3.08 [e]	2.81 [e]	3.24 [e]	Yes for VVIR vs DDDR (p<0.05)	
Worries	Mean estimated score for this item	(-)	1.33 [e]	1.73 [e]	2.02 [e]	Yes for DDD vs VVIR (p<0.002)	
Total sum	Mean total quality of life score (SEM)	(-)	105 (2)	102 (2)	113 (2)	Yes for VVIR vs DDDR (p<0.003) Yes for DDD vs VVIR (p<0.018)	
Illness perception assessed by illness perception score (43 items) including items on illness-related anxiety and depressive problems. Scale not given (lower numerical score = lower severity of illness perception). Results only stated for 5/43 items.							Lowest scores (lowest severity of illness perception) for DDDR mode for 4/5 items. Statistically significant higher scores for VVIR mode for all symptoms compared to a dual mode.
Diet	Mean estimated score for this item	(-)	1.21 [e]	1.00 [e]	1.27 [e]	Yes for DDDR vs DDD (p<0.05) Yes for DDDR vs VVIR (p<0.01)	
Volition	Mean estimated score for this item	(-)	2.00 [e]	1.16 [e]	1.83 [e]	Yes for DDDR vs DDD (p<0.01) Yes for DDDR vs VVIR (p<0.01)	
Concentration	Mean estimated score for this item	(-)	2.57 [e]	2.31 [e]	3.30 [e]	Yes for DDDR vs VVIR (p<0.05)	
Work	Mean estimated score for this item	(-)	1.59 [e]	1.30 [e]	1.92 [e]	Yes for DDDR vs VVIR (p<0.05)	
Contentment	Mean estimated score for this item	(-)	1.52 [e]	1.71 [e]	2.14 [e]	Yes for DDD vs VVIR (p<0.05)	

(-) high score is unfavourable, (+) high score is favourable; [e] data estimated from graph, NS not significant, SD standard deviation, SE standard error

Linde-Edelstam et al., 1992 (1)[33]: QOL assessment undertaken after 2 months.

QOL Parameters/Assessment Tool	Outcome Measure		DDD	VVIR	Statistical Significance	Direction of Effect
Cardiovascular Symptomatology. No maximum score stated (0=no symptoms, increasing mm on visual analogue scale = increasing symptoms)						Significantly lower symptom score in DDD mode compared to VVIR mode.
Breathlessness	Mean visual analogue scale score (SD)	(-)	9.5 (8.5)	18.1 (14.3)	Yes (p=0.02)	
Dizziness	Mean visual analogue scale score (SD)	(-)	4.8 (8.5)	15.2 (22.6)	Yes (p=0.04)	
Chest Pain	Mean visual analogue scale score (SD)	(-)	2.6 (2.5)	6.8 (8.9)	Yes (p=0.06)	
Palpitations	Mean visual analogue scale score (SD)	(-)	2.8 (8.1)	6.3 (15.2)	Yes (p=0.03)	
Sleep Disturbance						Similar alertness and quality of sleep scores.
Alertness in last 15 min	Mean visual analogue scale score (SD)	(-)	3.4 (1.6)	3.5 (1.2)	NS	
Quality of Sleep	Mean sleep quality scale score (SD)	(-)	24.2 (7.4)	26.0 (7.0)	NS	
Cognitive Functioning						Significantly better memory score in DDD mode, similar decision making and concentration skills.
Decision Making	Mean visual analogue scale score (SD)	(-)	2.8 (4.8)	4.0 (6.0)	NS	
Memory	Mean visual analogue scale score (SD)	(-)	4.4 (4.9)	10.5 (12.0)	Yes (p=0.001)	
Concentration	Mean visual analogue scale score (SD)	(-)	2.6 (2.5)	6.1 (12.0)	NS	
Physical & Social Functioning						Similar physical and social functioning scores.
Physical Ability	Mean 5-point category scale score (SD)	(+)	34.1 (2.7)	34.6 (2.4)	NS	
Social Participation	Mean 5-point category scale score (SD)	(+)	11.6 (1.1)	11.9 (0.3)	NS	
Depressive Feelings						Similar score for depression.
Depressive Score	Mean questionnaire score (max 9) (SD)	(-)	1.2 (2.1)	0.9 (2.1)	NS	
Mood States						Similar score for mood states.
Activation/Deactivation	Mean 4-point category scale score (SD	(+)	3.2 (0.6)	3.2 (0.4)	NS	
Calmness/Tension	Mean 4-point category scale score (SD)	(+)	3.3 (0.5)	3.2 (0.6)	NS	
Pleasantness/Unpleasantness	Mean 4-point category scale score (SD)	(+)	3.3 (0.6)	3.3 (0.6)	NS	
Self-perceived Health Status (2 questions on general health and well-being derived from Cornell heart Study Ref)						Similar self-perceived health status.
Question A	Mean category scale score (SD)	(-)	1.4 (0.5)	1.6 (0.8)	NS	
Question B	Mean category scale score (SD)	(-)	1.5 (0.8)	1.7 (1.0)	NS	
Other Influencing Factors						Scores not stated. No significant differences in patients' comments.
Patients' Comments	Interpretation/scoring by independent observers				NS	

(-) high score is unfavourable, (+) high score is favourable; [e] data estimated from graph, NS not significant, SD standard deviation, SE standard error

Lukl et al., 1994[44]: QOL assessment undertaken after 2 weeks in each mode (only last week evaluated)

QOL Parameters/Assessment Tool	Outcome Measure		DDD	VVIR	Statistical Significance	Direction of Effect
19 question quality of life questionnaire; each question scored 0-5 (0=optimal state, 5=worst state)						Lower scores (better quality of life) in DDD mode compared to VVIR mode. Significantly lower scores in DDD mode for 12 out of 19 symptoms.
Have you felt ill?	Group mean (SD) score	(-)	1.6 (1.6)	2.5 (1.7)	P<0.05	
Have you lost interest in your hobbies?	Group mean (SD) score	(-)	0.4 (0.9)	1.1 (1.7)	P<0.05	
Have you felt lethargic?	Group mean (SD) score	(-)	1.7 (1.5)	2.8 (1.8)	P<0.02	
Have you been depressed?	Group mean (SD) score	(-)	0.6 (1.3)	1.4 (1.7)	P<0.05	
Have you considered your state of health worse than that of your contemporaries?	Group mean (SD) score	(-)	1.1 (1.4)	1.8 (1.8)	P<0.05	
Have you eaten less, even the things you like?	Group mean (SD) score	(-)	1.1 (1.4)	1.9 (1.4)	NS	
Have you had any emotional problems?	Group mean (SD) score	(-)	0.2 (0.5)	0.9 (1.3)	P<0.05	
Has your disease prevented you from leading the life you were used to?	Group mean (SD) score	(-)	2.0 (1.4)	1.5 (1.5)	NS	
Have you had:						
Swollen ankles?	Group mean (SD) score	(-)	1.0 (1.3)	0.9 (1.3)	NS	
Breathlessness while at rest?	Group mean (SD) score	(-)	1.0 (1.3)	0.6 (1.3)	NS	
Breathlessness during physical exertion?	Group mean (SD) score	(-)	2.2 (0.6)	3.2 (1.5)	P<0.02	
Overexertion when doing household chores?	Group mean (SD) score	(-)	1.6 (1.3)	2.6 (1.4)	P<0.01	
Fatigue?	Group mean (SD) score	(-)	1.7 (1.6)	2.7 (1.5)	P<0.02	
Insomnia?	Group mean (SD) score	(-)	1.9 (1.7)	1.7 (1.5)	NS	
Dizzy spells?	Group mean (SD) score	(-)	0.3 (0.8)	1.7 (1.6)	P<0.005	
Troubles with your memory and concentration?	Group mean (SD) score	(-)	1.0 (1.2)	0.6 (0.9)	NS	
Tightness in your chest?	Group mean (SD) score	(-)	1.3 (1.7)	0.8 (1.3)	NS	
Palpitation?	Group mean (SD) score	(-)	0.9 (1.2)	3.2 (1.8)	P<0.005	
Sweating?	Group mean (SD) score	(-)	1.3 (1.3)	2.4 (1.8)	P<0.005	

(-) high score is unfavourable, (+) high score is favourable; [e] data estimated from graph, NS not significant, SD standard deviation, SE standard error

Appendix 8 - Clinical effectiveness results crossover studies (exercise capacity)

Exercise duration

Study	Population Size (n)	Type of exercise test	Outcome Measure	Single mode(s)		Dual mode(s)		Statistical significance
Kamalvand et al., 1997[32]	48	Chronotropic assessment exercise protocol (CAEP) (treadmill test)	Group mean (SD) exercise duration (minutes)	**VVIR** 7.0 (3.8)		**DDDR** 7.6 (3.6)	**MS DDDR** 8.1 (3.6)	MS DDDR vs VVIR (p<0.01)
Sulke et al., 1991[53]	22	Chronotropic assessment exercise protocol (CAEP) (treadmill test)	Group mean (SD) exercise duration (minutes)	**VVIR** 10.2 (3.6)	**Dual Modes** **DDD** 10.0 (3.2)	**DDDR** 11.3 (3.4)	**DDIR** 10.15 (3.4)	DDDR vs other modes only (p<0.01)
Rediker et al., 1988[49]	19	Symptom limited treadmill test (Balke-Ware protocol)	Group mean (SD) exercise duration (minutes)	**VVI** 10.1 (3.7)		**DDD** 11.3 (3.7)		p=0.006
Deharo et al., 1996[40]	18	Symptom limited treadmill test (Naughton Protocol)	Group mean (SD) exercise duration (minutes)	**VVIR** 10.0 (3.8)		**DDD** 10.0 (3.6)		NS
Linde-Edelstam et al., 1992 (2)[34]	17	Treadmill test up to Borg exertion rating of 5	Group mean (SD) exercise duration (minutes)	**VVIR** 10.1 (5.5)		**DDD** 10.5 (4.7)		NS
Sulke et al., 1992[52]	16	Chronotropic assessment exercise protocol (CAEP) (treadmill test)	Group mean (SD) exercise duration (minutes)	**VVI** 8.99[e]		**DDD** 10.9 (1.0)	**DDI** 9.39[e]	NS
Capucci et al., 1993[37]	14	Symptom limited exercise test, bicycle ergometer	Group mean (?) exercise duration (minutes)	**VVIR** 11.4 (3.4)		**DDD** 11.0 (2.9)	**DDDR** 12.6 (3.1)	DDDR vs VVIR (p<0.01) DDDR vs DDD (p<0.01)
Davis et al., 1985[39]	14	Maximal treadmill exercise test (Bruce Protocol)	Group mean (SD) exercise duration (minutes)	**VVI** 7.2 (3.0)		**VDD** 8.4 (3.0)		p<0.001
Saner & Fricker, 1996[50]	12	Symptom limited treadmill test (modified Bruce protocol)	Group mean (SD) exercise duration (minutes)	**VVIR** 12.55 (5.82)		**DDD** 15.83 (6.45)		p=0.01
Oldroyd et al., 1991[47]	10	Symptom limited treadmill test *NB: SD calculated by JD*	Group mean (SEM) *(SD)* exercise duration (minutes)	**VVIR** 7.95 (0.53) *(1.68)*		**DDD** 8.15 (0.52) *(1.64)*		NS
Yee et al., 1984[54]	8	Symptom limited treadmill test (modified Bruce protocol)	Group mean (SD) exercise duration (minutes)	**VVI** 5.53 (2.9)		**VDD** 6.9 (3.1)		p<0.001

Walking distance

Study, Year	Population size (n)	Type of exercise test	Outcome measure	Single mode	Dual mode	Statistical significance
Hargreaves et al., 1995[41]	20	6 minute (or symptom limited) length walking 1 length ~25 metres *NB: SD calculated by JD*	 Group mean (SE) *(SD)* total number of lengths walked approximate distance (m) Means (SE)/approximate distance (m) for groups according to pacing order: DDD/VVIR VVIR/DDD	**VVIR** 19 (1) *(4.47)* 475 20 (1)/500 18 (2)/450	**DDD** 20 (1) *(4.47)* 500 20 (1)/500 20 (2)/500	 NS NS NS
Channon et al., 1994[38]	16	6 minute (or symptom limited) length walking 1 length ~25 metres *NB: SD calculated by JD*	 Group mean (SE) *(SD)* total number of lengths walked Approximate distance (m)	**VVI** 16.43 (5.68) *(22.72)* 410.75	**DDD** 18.7 (3.95) *(15.8)* 467.5	 Yes (p=0.013)
Avery et al., 1994[35]	13	6 minute walking at own pace	 Group mean (SD) total distance walked (m)	**VVI** 327 (69)	**VDD/DDD** 360 (65)	 Yes (p<0.01)

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