NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

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

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- Are dual chamber pacemakers more clinically effective than single chamber atrial pacemakers for treating sick sinus syndrome with no evidence of atrioventricular block?
  - Dual chamber pacemakers statistically significantly reduce need for re-operation, however:
    - For most outcomes (including mortality, stoke, quality of life and heart failure), no statistically significant differences shown.
    - Dual chamber pacemakers may be associated with disadvantages including unnecessary ventricular pacing and longer operation times.
- Should subpopulations based on age be taken into account as a subgroup? In the largest study (DANPACE) those under 75 were

at statistically significantly higher risk of heart failure, and those over 75 were at lower risk of heart failure, with dual compared with single chamber atrial pacemakers.

Cost effectiveness

- For the cost of pacemaker devices, the Assessment Group (AG) used a weighted average of Healthcare Resource Group costs, rather than actual device costs:
  - Is the approach taken by the AG for costing pacemakers appropriate?
  - Has the AG appropriately taken the uncertainty of the cost of devices into account in its exploratory analyses?
- Is the incremental cost effectiveness ratio (ICER) for dual chamber pacemakers compared to single chamber atrial pacemakers robust given that it is dependent on both small incremental costs and small incremental quality adjusted life years (QALYs)?

1 Background: clinical need and practice

1.1 Bradycardia is a slow heart rate, defined as a heart rate of less than 60 beats per minute. Bradycardia can be caused a range of factors, including diseases such as:

- sick sinus syndrome – a number of abnormal heart rhythms caused by an irreversible dysfunction of the sinus node (the heart's natural pacemaker), including:
  - sinus arrest or pause, where the sinus node occasionally does not generate electrical impulses, from a period lasting a couple of seconds, to several minutes.
  - sinoatrial exit block, where the sinus node generates electrical impulses normally, but the signal is blocked before it leaves the sinus node.

  - alternating bradyarrhythmias and tachyarrhythmias (a fast heart rate) such as bradycardia-tachycardia syndrome.
- atrioventricular block (a condition where electrical impulses from the sinus node are slowed or blocked). Atrioventricular block can occur independently from sick sinus syndrome, and so people with symptomatic bradycardia because of sick sinus syndrome may also have or develop atrioventricular block.

1.2 The most commonly identified causes of abnormal heart rhythms are age, ischaemic heart disease, heart valve disorders and heart failure. If untreated, symptomatic bradycardia may lead to fatigue, fainting, palpitations, dizziness, heart failure and an increased risk of mortality.

1.3 Sick sinus syndrome is difficult to diagnose because of the intermittent symptoms, and also because symptoms are usually non-specific and observed in other disorders. Diagnosis is made by considering medical history and symptoms, and through the use of electrocardiograms (ECGs). As abnormalities may be intermittent, Holter monitoring (ECG monitoring for 24 to 48 hours) or event recorders may be used.

1.4 The prognosis of individuals with sick sinus syndrome is variable and difficult to predict, dependent upon the underlying cause and the presence and severity of comorbidities (such as ischaemic heart disease). For most people, the disease is idiopathic (that is, the cause is unknown) and progressive. People whose disease is not symptomatic do not require therapy; however once the disease becomes symptomatic it can have a significant impact on quality of life, and the only effective treatment is permanent implantation of a pacemaker. Most people who need a pacemaker implanted are older than 60 years of age.

1.5 The prevalence of sick sinus syndrome is thought to be about 0.03% of the whole population, and increases with age. However, both the prevalence of bradyarrhythmias because of sick sinus syndrome requiring permanent pacemaker implant, and the prevalence of sick sinus syndrome with atrioventricular block, is unknown. Hospital episode statistics data from October 2012 to September 2013 included 2490 patients with a primary diagnosis of sick sinus syndrome in NHS hospitals in England. Sick sinus syndrome usually occurs in older adults, but it can affect persons of all ages, and it affects men and women equally. The incidence of atrioventricular conduction abnormalities also increases with increasing age.

Current Management

1.6 Pacemakers are electrical devices that consist of a small battery–powered generator and one or more pacing leads that are in contact with the inner wall of the right atrium and/or the right ventricle. The primary aim of permanent pacing is to prevent the heart from beating too slowly. An important secondary aim is to reproduce, as far as possible, the function of the heart's normal electrical conduction system, which coordinates the way the heart muscle contracts. Pacemaker devices may be broadly classified as single or dual chamber, depending on whether leads are applied to one or two heart chambers, however there is complex nomenclature (that is, the naming conventions) depending on the specific subtype (see appendix B). Dual chamber pacemaker devices are attached to both chambers of the heart and may be used in either dual chamber pacing mode (where both the right atrium and ventricle are paced, which mimics the natural pacing rhythm of the heart) or single chamber pacing mode (where only one chamber of the heart is paced, either the atrium or the ventricle). Single chamber pacemaker devices may be either single chamber atrial devices or single chamber ventricular devices, and

may only be used in the mode for which they were originally programmed (re-operation is required to change pacing mode in a single chamber device). Pacemakers may also be rate modulating (that is, able to sense and adapt the rate of pacing to the level of physical exertion).

1.7 NICE technology appraisal 88 'Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block' (of which this appraisal is a part-review) contains a number of recommendations for the management of symptomatic bradycardia due to sick sinus syndrome or atrioventricular block. The following recommendations remain extant:

- Dual-chamber pacing is recommended for the management of symptomatic bradycardia due to sick sinus syndrome, atrioventricular block, or a combination of sick sinus syndrome and atrioventricular block
- Single-chamber ventricular pacing is recommended for the management of atrioventricular block for people with continuous atrial fibrillation
- Single-chamber ventricular pacing is recommended for the management of atrioventricular block (atrioventricular block alone, or in combination with sick sinus syndrome), when patient-specific factors, such as frailty or the presence of comorbidities, influence the balance of risks and benefits in favour of single-chamber ventricular pacing.

The following was recommended in TA88 however is being considered for review in this appraisal:

- Single-chamber atrial pacing is recommended for the management of sick sinus syndrome for people in whom, after

full evaluation, there is no evidence of impaired atrioventricular conduction

1.8 The British Pacing and Electrophysiology Group (BPEG) (1991) developed guidelines on pacemaker selection according to the type, programming and recommended pacing modes for different underlying conditions (see Table 1 below). Although atrial-based single-chamber ('AAI', or; 'AAIR' if rate-responsive) pacing is recommended for the treatment of sick sinus syndrome, people who go on to develop atrioventricular block may require a further procedure to upgrade their pacemaker to a dual chamber device – carrying increased costs and risks associated with re-operation. Therefore, sometimes in clinical practice, a dual chamber device may be implanted in people with sick sinus syndrome and no evidence of impaired atrioventricular conduction. The current European Society of Cardiology (ESC) guidelines on cardiac pacing and cardiac resynchronization therapy updated in 2013 recommend dual chamber pacemakers as a first choice for people with sick sinus syndrome and/or atrioventricular block, with the exception of people with persistent atrioventricular block and continuous atrial fibrillation, for whom a single chamber ventricular pacemaker is recommended.

Table 1 British Pacing and Electrophysiological Group recommendations for pacing mode (1991)

Diagnosis	Optimal	Alternative	Inappropriate
Sinus node disease	AAIR	AAI	VVI VDD
Atrioventricular block	DDD	VDD	AAI DDI
Sinus node disease and atrioventricular block	DDDR DDIR	DDD DDI	AAI VVI
Key: see appendix B			

1.9 During 2012-13 in England, more than 20,000 people had a single or a dual-chamber pacemaker fitted. Sick sinus syndrome was the

fourth most prevalent primary diagnosis (9.5%) after atrial fibrillation and flutter (22.5%), complete atrioventricular block (18.8%), and second degree atrioventricular block (10.6%). For those with a primary diagnosis of sick sinus syndrome (2490 patients) 67.5% had an implantation of a dual-chamber pacemaker, 14.8% had an implantation of a single-chamber pacemaker, and 2.2% had a re-operation of an existing implanted pacemaker.

2 The technology

2.1 Dual chamber pacemakers (non-proprietary) are a type of artificial pacemaker recommended for the treatment of sick sinus syndrome with atrioventricular block or atrioventricular block alone (see BPEG guidelines Table 1). They are small battery driven devices implanted in the chest with pacing leads inserted in the right atrium and ventricle. The pacing leads have sensors that detect the natural heartbeat and then send that information to a small computer in the pacemaker. The pacemaker uses this data to send signals back to the heart to help it beat regularly. There are several different types of dual chamber pacemaker (see appendix B) depending on whether they inhibit or trigger heart beats (in response to sensed electrical activity in the heart) and whether they are rate responsive (where the pacing rate varies according to physical activity).

2.2 All pacemakers must be granted a CE (Conformité Européene) mark before they are used in the UK which is granted by Notified Bodies following a safety and efficacy assessment. The MHRA monitor the safety of devices used in clinical practice.

2.3 Pacemakers may be associated with a number of adverse reactions. These may include pacemaker syndrome, stroke, heart failure and atrial fibrillation. The requirement for an additional lead in dual compared with single chamber pacemakers might lead to an

associated increased risk of complications, such as lead displacement, puncture of the lung when placing the leads, infection of the pacemaker pocket or the leads. Cardiac perforation is a serious but rare complication of the procedure. Later complications may include dysfunction of the pacemaker or of the leads (that is, failure to pace or sense appropriately) or infection or erosion of the pacemaker site or its leads. Re-operation may be required as a result of a complication, the need for pacemaker upgrade (single to dual), or end of battery life. The complication rate associated with a re-operation is substantially higher than that associated with initial implantation.

2.4 The acquisition cost of pacemakers depends on the particular model. The Association of British Healthcare Industries estimate an average cost of dual chamber pacemaker devices of £1265, and for single chamber atrial pacemaker devices a price of £718. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: appraise the clinical and cost effectiveness of dual-chamber pacemakers for treating symptomatic bradycardia in people with sick sinus syndrome in whom there is no evidence of impaired atrioventricular conduction.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	• People with symptomatic bradyarrhythmias due to sick sinus syndrome without atrioventricular block.	
Intervention	• Permanent implantable dual-chamber pacemakers	
Comparator	• Single chamber atrial pacemakers	
Outcomes	• Mortality • Morbidity (including incidence of heart failure, atrial fibrillation and stroke) • Exercise capacity • Cognitive function • Requirement for further surgery • Adverse effects of treatment (including pacemaker syndrome, atrial fibrillation and device replacement) • Health-related quality of life	
Economic evaluation	• The cost effectiveness of treatments should be expressed in terms of cost per quality adjusted life year • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	• The cost effectiveness of treatments will be expressed in terms of cost per quality adjusted life year, as well as the incremental cost per procedure avoided • There will be a lifetime time horizon for estimating clinical and cost effectiveness

4 Clinical-effectiveness evidence

Trial design and population

4.1 The Assessment Group (AG) conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of dual chamber pacemakers compared with single-chamber

atrial pacemakers for the treatment of symptomatic bradycardia because of sick sinus syndrome with no evidence of atrioventricular block, identifying a total of 6 relevant randomised controlled trials. 3 of the trials (Albertsen et al. [2008], DANPACE [2011], and Nielsen et al. [2003]) were parallel group trials (see sections 4.2 to 4.4) and 3 of the trials (Gallick et al. [1994], Lau et al. [1994] and Schwaab et al. [2001]) were crossover trials (see sections 4.5 to 4.7).

Parallel group trials

4.2 The parallel group trials randomised participants (before implant) to receive either a single chamber atrial pacemaker device or dual chamber pacemaker device. The AG only considered parallel group design randomised controlled trials for dichotomous outcomes (mortality, heart failure, atrial fibrillation, stroke, further surgery, and adverse events). It excluded trials with a crossover design for dichotomous variables, stating that they are inappropriate when studying outcomes where an outcome event may alter the baseline risk. The trials varied in size from 50 to 1415 randomised participants, the mean age was similar across the three parallel trials and between study arms (72-74 years), and either all or the majority of people within each trial had the pacemakers programmed with the rate adaptive function activated. All parallel randomised controlled trials excluded patients if they had chronic atrial fibrillation, atrioventricular block, carotid sinus syndrome, vasovagal syncope, bundle branch block, surgery, short life expectancy, dementia or cancer. The vast majority of participants at baseline were New York Heart Association (NYHA) class (used to classify cardiac disease according to the severity of symptoms) I or II (96%) at end of follow up with no or mild symptoms of heart failure. The AG conducted random effect model meta-analyses for the parallel trials where appropriate, generating odds ratios.

4.3 The following is an overview of the included parallel trials. Please see Table 2 for further details of the baseline characteristics.

- Albertsen et al: Compared dual chamber pacemaker devices (DDD[R]) (n=26) with single chamber atrial pacemaker devices (AAI[R]) (n=24) for treating sick sinus syndrome (including those with sinus arrest/sino-atrial block, bradycardia-tachycardia syndrome, and sinus bradycardia). The study was based in Denmark, with a follow-up of 12 months. The primary outcome was changes in left ventricular dyssynchrony (that is, the level of delay/difference in the timing of contraction in the different segments within the left ventricle) from baseline to 12 months of follow-up. Secondary outcomes were measurement of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (that is, measurement of a hormone released in response to heart problems) and a 6 minute walk test. The AG noted that there were some imbalances between the trial arms for the sub-types of sick sinus syndrome. It also noted that there were few but uneven numbers of people with prior stroke.
- DANPACE: Compared rate responsive dual chamber pacemakers (DDDR) (n=708) with rate responsive single chamber atrial pacemakers (AAIR) (n=707) for treating sick sinus syndrome (including those with sino-atrial block/sinus-arrest, sinus bradycardia, and bradycardia-tachycardia). The study was based in Denmark, UK and Canada, and there was a mean follow-up of 5.4 years. The primary outcome was death by any cause. Secondary outcomes included paroxysmal/chronic atrial fibrillation; stroke; cardiovascular mortality; need for pacemaker re-operation, and quality of life.
- Nielsen et al. (2003): Compared rate responsive dual chamber pacemakers with rate responsive single chamber atrial pacemakers (n=54) for treating sick sinus syndrome (including those with sinus bradycardia, sino-atrial block and bradycardia-

tachycardia syndrome). The study was based in Denmark and there was a mean follow-up of 2.9 years. The trial had 2 dual chamber pacemaker arms, with different programmed atrioventricular block delay: short atrioventricular delay (<150 milliseconds) (DDDR-s) (n=60), and long atrioventricular delay (300 milliseconds) DDDR-l) (n=63). The AG combined the data for these two study arms for analyses in the review, and explored separate arms ether in sensitivity analyses or presented the results separately. The primary outcome was changes in left atrial size and left ventricle size and function during follow-up. Secondary outcomes were cardiographic end points (changes in left atrial volume and left ventricular volume and left ventricular ejection fraction) and clinical end points (atrial fibrillation, thromboembolism, all-cause and cardiovascular mortality, and congestive heart failure). The AG noted that there were some imbalances between the trial arms for the sub-types of sick sinus syndrome.

4.4 The population characteristics of the parallel group trials are shown in Table 2

Table 2: Population characteristics of parallel group trials

Patient characteristics		Albertsen 2008		DANPACE 2011		Nielsen 2003		
		DDDR	AAIR	DDDR	AAIR	DDDR-s	DDDR-l	AAIR
Location		Denmark		Denmark, UK, Canada		Denmark		
Follow-up (yrs)		1		Mean 5.4 ± 2.6		Mean 2.9 ± 1.1		
No. participants		26	24	708	707	60	63	54
AV block delay		Max 20–225 ms		Mean max 225±39ms		150ms	300ms	
Age (Mean)		73±13	72±10	72.4±11.4	73.5±11.2	74 ±9	74±9	74 ±9
Sex (male)		8 (31%)	10 (42%)	267 (37.7%)	235 (33.2%)	23 (43%)	26 (43%)	24 (38%)
Primary outcome		LV dyssynchrony change:baseline to 12 month		Death by any cause		Change in LA size, & change in LV size & function		
Sinus arrest/sinus-atrial block		16	14	NR	NR	17	16	19
Brady-tachy syndrome		12	11	NR	NR	38	36	27
Sinus bradycardia		8	4	NR	NR	5	11	8
History of AF(%)		NR	NR	318(44.9)	303 42.9)	NR	NR	NR
Previous stroke		1	5	53 (7.5%)	61 (8.6%)	NR	NR	NR
NYHA class, n	I	18	19	522 (73.9)	503 (71.4)	38	46	32
	II	8	3	158 (22.4)	172 (24.4)	22	14	18
	III	0	2	24 (3.4)	29 (4.1)	0	3	2
	IV	0	0	2 (0.3)	0	0	0	1
Anticoagulant drugs				89 (12.6)	108 (15.3)	5	11	5
Beta blockers		11	6	132 (18.7%)	159 (22.5%)	5	7	4
Diuretics		11	14	263 (37.2%)	304 (43.0%)			
Ca^{2+} channel blockers		5	5	142 (20.1%)	137 (19.4%)	7	11	14
ACE inhibitors		10	11	170 (24.0)	160 (22.6)			
Cardiac grycoside				62 (8.8)	73 (10.3)	9	11	11
Sotalol				44 (6.2)	43 (6.1)	8	10	7
Amiodarone				24 (3.4)	25 (3.5)			

Abbreviations: ACE inhibitor, angiotensin-converting-enzyme inhibitor; AV, atrioventricular; LA, left atrial; LV, left ventricular; ms, milliseconds NR, not reported; NYHA, New York Heart Association; SD, standard deviation;

Crossover trials

4.5 In the crossover trials, all participants had a dual chamber pacemaker device implanted, and were then randomised to either single or dual pacing modes, before crossing over to the alternative pacing mode. The AG noted that it used crossover trials primarily for continuous variables (exercise capacity, cognitive functioning, and quality of life). Lau et al. and Schwabb et al. randomised participants before implant by pacing programme, and Gallick et al. randomised participants who recently had a pacemaker fitted. The AG noted that participants in the crossover trials had a slightly lower mean age than the parallel group trials (61-70 years). The AG reported that they were unable to undertake meta-analyses on the crossover trials because of a lack of relevant data in all studies.

4.6 The following is an overview of the included crossover trials. Please see Table 3 for further details of the baseline characteristics.

- Gallick et al: compared rate responsive dual chamber pacing mode (DDDR) with rate responsive single chamber atrial pacing mode (AAIR) in people with sick sinus syndrome (including those with sinus node disease) (n=12), using ventricular function to study the immediate effects of pacing mode during exercise. Outcomes were exercise and haemodynamic parameters. The trial measured haemodynamic effects during bicycle exercise, initially in one pacing mode and, after 0.5 to 1 hour rest, the exercise was repeated in the other pacing mode. Gallick et al. excluded people with evidence of atrioventricular block node disease or who were unable to exercise. The study location was not reported, and the follow-up was less than 1 day.
- Lau et al: compared rate responsive dual chamber (DDDR), single chamber atrial (AAIR) and single chamber ventricular (VVIR) pacing modes for people with sick sinus syndrome (n=15), studying the effects of pacing modes and intrinsic

conduction on physiological responses, arrhythmias, symptoms and quality of life. Participants spent four weeks in each pacing mode before crossing over to the other pacing mode. Lau et al. did not report specific exclusion criteria. The study location was not reported, and follow-up was 3 months. Outcomes were Holter monitoring, ambulatory blood pressure monitoring, symptoms and quality of life assessments.

- Schwaab et al: compared rate responsive dual chamber (DDDR) with a rate responsive single chamber atrial pacing mode (AAIR) for people with sick sinus syndrome (including those with sinus bradycardia) (n=-21). Participants spent four weeks in each pacing mode before crossing over to the other pacing mode. Participants had to have chronotrophic incompetence (that is, an inability of the heart to increase its rate appropriately with increased activity, leading to exercise intolerance), have experienced at least two documented episodes of atrial tachyarrhythmia, and be on antiarrhythmic medication for prevention of atrial flutter or atrial fibrillation. The study was based in Germany, and the follow-up period was 3 months. Outcomes included quality of life, left ventricular outflow, bicycle cardiopulmonary exercise testing, number of episodes and total duration of atrial tachyarrhythmia, incidence of atrioventricular block type I, II or III and maximum duration of the longest pause, percentage of paced atrial and ventricular beats.

4.7 The population characteristics of the crossover trials are shown in

Table 3.

Table 3: Population characteristics of crossover trials

Patient characteristics	Gallick 1994	Lau 1994	Schwaab 2001
Number of participants	12	15	21
Location	NR	NR	Germany
Follow-up	<1 day	3 months	3 months
Atrioventricular block delay	100 ms	96±7 to 140±5 ms	Optimised based on max time velocity integral of aortic flow
Age (Mean)	61±4(SE)	62±2	70±7
Sex (male)	8 (67)	5 (42)	11 (58)
Main outcome	Haemodynamic effects during bicycle exercise	HRQL	Exercise capacity
Previous history of AF	NR	Some of the patients	NR
Previous stroke	NR	NR	NR
NYHA class, n	NR	NR	NR
Beta blockers	4	1	
Class I antiarrhythmics			2
Ca^{2+} channel blockers	4	2	
ACE inhibitors		1	
Cardiac grycoside	3	3	
K+ channel blockers		1	18
Aspirin		1	
Nitrates		2	
Abbreviations used in table: ACE inhibitor, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; HRQL, health related quality of life; ms, milliseconds NR, not reported; NYHA, New York Heart Association,			

Parallel and crossover trial quality

4.8 The AG noted that the quality of the trials was generally high, with appropriate trial design and methodology, and that the trials appeared to be appropriately randomised with a low number of participants excluded or lost to follow up. The baseline characteristics were similar between the trial arms and across the parallel and crossover trials. In particular, DANPACE is a relatively large trial of good quality with a long follow up, which gives a reasonable evidence base for dual-chamber pacing compared to single-chamber atrial pacing for people with sick sinus syndrome

without evidence of atrioventricular block. However the AG noted several issues with the trials:

- There were a limited number of trials available, and data was not reported consistently.
- There was a lack of detailed description of randomisation and allocation concealment.
- Trials were either open label, or blinding to pacing modes was unclear, possibly increasing the risk of bias to subjective outcomes such as quality of life and exercise capacity
- The programmed atrioventricular block delay in the dual pacing mode differed greatly between the trials and study arms, adding heterogeneity to the trials.
- The parallel trials Albertsen et al. and Nielsen et al. (2003) had small sample sizes and short follow-up in comparison to DANPACE, giving them little weight.
- Both DANPACE and Nielsen et al. (2003) were under-powered to show a statistically significant difference in the primary outcome (all-cause mortality in DANPACE; and changes in left atrial size, and left ventricle size and function, in Nielsen et al. [2003]) because they were terminated early. Recruitment for Nielsen et al. (2003) was stopped after randomisation of 177 patients (from a target of 450) because recruitment for DANPACE had started. Recruitment for DANPACE was stopped after randomisation of 1415 patients (of a target of 1900) because of the increasing use of dual-chamber pacemakers with additional features which were not permitted in the trial.
- The crossover trials included in the review had a small number of participants (12-21) and short durations (up to 3 months), which limited the possible outcomes and reduced the power to detect differences between pacing modes.

- New technologies in this area develop rapidly; therefore the implants used in the trials may be superseded prior to the completion of the trials.

Clinical effectiveness

4.9 The AG presented the results of the clinical effectiveness of the trials. Where possible for dichotomous outcomes, the AG undertook meta-analyses and calculated odds ratios (OR) with 95% confidence intervals (CI). The AG also presented trial data for individual trials, including the hazard ratios taken from the original trials where relevant, and in some instances using the individual trial data to calculate trial-specific odds ratios. To note, the hazard ratios presented in the trials are single compared with dual, whereas the odds ratios and meta-analyses derived from the trials by the AG were reported as dual compared with single. Selected aggregated results are shown in Table 4, and are discussed in more detail in sections 4.10 to 4.19.

Change in pacing mode.

4.10 People in the parallel group trials were randomised to receive a single or dual chamber device. During the trial, some participants changed pacing mode from the one to which they were randomised (in the single chamber arm, a change in pacing mode required a re-operation). Some people in the dual chamber arm changed to single chamber atrial or single chamber ventricular mode. Some people in the single chamber atrial arm changed to a dual chamber pacemaker device or a single chamber ventricular device (if they developed atrioventricular block or atrial fibrillation respectively). A meta-analysis of all 3 parallel group trials comparing 857 people randomised to dual chamber pacemaker devices (DDDR) with 785 to single chamber atrial pacemaker devices (AAIR) (see Table 5), reported that statistically significantly less people with a dual chamber pacemaker changed pacing mode than those in the single

chamber pacemaker group (OR 0.50, 95% CI 0.37 to 0.67). Most people who changed from a single chamber atrial pacing changed to dual chamber pacing, primarily because of the development of high degree atrioventricular block, or Wenckebach block during implantation. However, there were also a small number of people who switched from single chamber atrial pacing to single chamber ventricular pacing, primarily because of persistent atrial fibrillation. The AG noted that in DANPACE the results for change in pacing mode and re-operation were probably conservative as atrioventricular block leading to these outcomes would have increased over time beyond the length of follow up of the trial.

Percent atrial and ventricular pacing

4.11 The AG noted that the rate of atrial and ventricular pacing varied greatly between the studies, study arms and pacing mode, which may have been associated with differences in other outcome measures, and the AG cited research that ventricular pacing has been associated with an increased incidence of atrial fibrillation. The results from the trials were as follows:

- For the parallel trials:
  - For dual chamber devices, the rate of atrial pacing ranged from 57% (Nielsen et al. [2003] (DDDR-s arm) to 67% (Nielsen et al. [2003] DDDR-I arm), and ventricular pacing ranged from 17% (Nielsen et al. [2003] DDDR-I arm) to 90% (Nielsen et al. [2003] DDDR-s arm).
  - For single chamber devices, the rate of atrial pacing ranged from 53% (Albertsen et al.) to 69% (Nielsen et al. [2003]), and ventricular pacing ranged from 3% (Albertsen et al.) to 99% (Albertsen et al., for those who had upgraded from single to dual).
- For crossover trials:

- For dual chamber devices, the rate of atrial pacing was not reported in Gallick et al. and Lau et al. and was 95% in Schwabb et al., and the rate of ventricular pacing ranged from 64% (Lau et al.) to 99% (Schwabb et al.)
- For single chamber devices, the rate of atrial pacing was not reported, and the rate of ventricular pacing was not reported in Gallick et al. or Lau et al., and was 95% in Schwabb et al.

The AG noted that although the dual chamber pacemakers in DANPACE were programmed in a way intended to reduce unnecessary ventricular pacing, ventricular pacing was still 65% (with a range ± 33 %), which may have offset some of the benefit of implanting a dual-chamber pacemaker.

All-cause mortality

4.12 All-cause mortality was reported in DANPACE and Nielsen et al. (2003) and for both studies, there were no statistically significant results. DANPACE had an unadjusted hazard ratio for single compared with dual chamber pacemakers of 1.06 (95% CI: 0.88 to 1.29), an adjusted hazard ratio of 0.94 (95% CI: 0.77 to 1.14), and there were no statistically significant results in any of the pre-defined subgroups (age; gender; hypertension; left ventricular ejection fraction; history of atrial fibrillation; previous myocardial infarction; PQ interval; diabetes; NYHA classification; $p \geq 0.45$). Although DANPACE was not powered to detect a statistically significant difference in mortality (see section 4.8), the AG noted that a planned interim analysis of DANPACE (the largest study in the meta-analysis) calculated that no statistically significant difference would have been detected, even if the required numbers of participants had been recruited. For Nielsen et al. (2003), the AG derived an odds ratio from the trial for dual compared with single chamber pacemakers of 1.47 (0.64 to 3.38). In a meta-analysis of both trials (DANPACE and Nielsen et al [2003]), there was no

statistically significant difference in all-cause mortality between dual (n=831) compared with single atrial (n=761) pacemakers (OR 0.97, 95% CI: 0.67 to 1.41).

Heart failure

4.13 The AG noted that heart failure was reported in all 3 parallel trials. However, the outcome measures used as a proxy for heart failure varied between the studies, captured as:

- New York Heart Association (NYHA) class (used to classify cardiac disease according to the severity of symptoms) at end of follow up
- Number of people taking diuretics
- Heart failure leading to hospitalisation
- Number of cases of new heart failure, defined as new NYHA class IV or if two or more of the following indicators were present:
  - presence of oedema
  - presence of dyspnoea
  - and NYHA class III
- Number of people with an increase in consumption of diuretics
- Number of patient with an increase in at least one NYHA class.

The AG noted that all the outcome measures for heart failure consistently showed no statistically significant difference between dual and single atrial pacing (see page 58 of the Assessment Report). DANPACE conducted predefined subgroup analyses for single compared with dual chamber pacemakers for a younger (≤ 75 years) and older (> 75 years) population which showed that, in younger people, those with a single chamber pacemaker were at a statistically significantly lower risk of developing heart failure than those with dual chamber pacemakers (HR 0.72, 95% CI: 0.53 to 1.00), whereas in the older subgroup, those with single chamber

pacemakers were at a statistically significantly higher risk than those with dual chamber pacemakers (HR 1.34, 95% CI: 1.00 to 1.80). All other subgroup analyses were non-significant (p > 0.31).

Atrial fibrillation

4.14 DANPACE and Nielsen et al. (2003) reported results on the incidence of atrial fibrillation, diagnosed by standard 12-lead electrocardiogram (ECG) at planned follow up visits. In DANPACE, atrial fibrillation was defined as either paroxysmal (the first diagnosis of atrial fibrillation detected in the ECG and verified by the pacemaker telemetry at a planned follow-up visit) or chronic (atrial fibrillation at two consecutive follow-up visits and at all subsequent follow-up visit). The AG noted conflicting results in the 2 trials. Nielsen et al. (2003) showed that the risk of developing atrial fibrillation (paroxysmal and chronic combined) was statistically significantly higher for dual compared with single chamber pacemakers (OR 3.19, 95% CI: 1.05 to 9.67). DANPACE showed that the risk of paroxysmal atrial fibrillation was statistically significantly lower for dual compared with single chamber pacemakers (OR 0.78, 95% CI: 0.63 to 0.96), although there was no statistically significant difference for chronic atrial fibrillation (OR 0.96, 95% CI: 0.68 to 1.33). In addition subgroup analyses of paroxysmal atrial fibrillation in DANPACE showed that dual chamber pacing was associated with statistically significantly lower paroxysmal atrial fibrillation in subgroups of people without a prior history of atrial fibrillation, higher body-mass index, and a dilated left atrium at baseline (p<0.05). The AG noted that both DANPACE and Nielsen were good quality trials, but stated that, as DANPACE was the larger trial (almost 10 times the size of Nielsen et al. [2003]) and had a longer mean follow-up, it was reasonable to have more confidence in the results of DANPACE. Therefore, the AG concluded that dual-chamber pacing was associated with a lower risk of atrial fibrillation than single chamber pacing. In addition, the

AG outlined several possible reasons for the disparity in the results, including several differences in the trials (baseline patient characteristics and pacemaker programming).

Stroke

4.15 DANPACE and Nielsen et al. (2003) reported the effectiveness of single compared with dual chamber pacemakers for stroke. DANPACE reported a non-statistically significant unadjusted hazard ratio for stroke of 1.13 (95% CI: 0.72 to 1.80, p = 0.59) for people with single atrial pacing compared with dual pacing, and an adjusted hazard ratio of 1.11 (95% CI: 0.70 to 1.77, p = 0.65). The results of the Nielsen et al. (2003) study were also not statistically significant (p=0.32). A meta-analysis of both studies conducted by the AG reported no statistically significant difference between dual compared with single chamber pacemaker devices for stroke (OR 0.93, 95% CI: 0.60 to 1.45), however, the AG noted that the number of events was low, and therefore the uncertainty in the results was considerable.

Exercise capacity

4.16 Exercise capacity was reported in the parallel trial Albertsen et al. and the crossover trials Gallick et al. and Schwaab et al.

- Albertsen et al. used the 6-minute walking test to test exercise tolerance /capacity, measuring the distance an individual is able to walk over a total of six minutes on a hard, flat surface for dual compared with single chamber atrial pacemakers:
  - Baseline: no statistically significant difference
  - 12 months follow up: people with a single atrial pacemaker walked significantly further than patients with a dual-chamber pacemaker (p<0.05) (however the AG stated that the mean difference just reached the clinically important difference and

one person in the single chamber arm was lost to follow up, therefore there was substantial uncertainty around this value).

- Schwaab et al. used bicycle exercises to test exercise duration and workload, using workload increments of 15 Watt/min which showed:
  - a statistically significantly better exercise capacity with single atrial pacing mode compared with dual pacing mode, for bicycle exercise duration and workload (p= 0.05).
- Gallick et al. used the upright bicycle exercise to test exercise capacity for dual compared with single chamber atrial pacing modes. The initial workload was 200 kilopond metres (kpm), which was increased incrementally with 200 kpm every three minutes. The aim was to achieve a peak heart rate ≥85% predicted by age, and the outcome measure was exercise time.
  - Gallick et al. did not detect a statistically significant difference between the pacing modes (p=0.74) The AG noted that Gallick et al. was a very short term study, with both pacing modes tested in the same day with 0.5 to 1 hour rest in-between, which may partly explain the difference in result from Schwaab et al.

Further surgery

4.17 The need for pacemaker re-operation during follow-up was an outcome in DANPACE, where there were statistically significantly more participants in the single chamber pacemaker arm needing a re-operation compared to the dual chamber pacemaker arm (unadjusted HR 1.99, 95% CI 1.53 to 2.59; adjusted HR 2.00, 95% CI 1.54 to 2.61). An effect estimate generated by the AG based on DANPACE showed the same direction of effect, as there were statistically significantly fewer re-operations for dual compared with single chamber pacemakers (OR 0.48, 95% CI: 0.36 to 0.63, **Table 5**) during follow up (5.4 ± 2.6 years). The only statistically

significant difference in reason for re-operation was need for surgical change of mode of pacing, that is upgrade from and single to dual chamber pacemaker because of the development of high grade atrioventricular block [p<0.001) (Table 4). The AG noted that there was only modest uncertainty around the result.

Table 4 Reasons for re-operation in DANPACE

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

Adverse effects of pacemaker implantation

4.18 Only Albertsen et al. and DANPACE reported data on adverse effects linked to pacemaker implantation. Albertsen et al. (n=50) considered complications around device implantation, reporting that there were no adverse events, and specifically that there were no adverse events related to lead displacement, infection or haematoma at pacemaker implantation. No other peri- or postoperative adverse effects of pacemaker implantation were reported. DANPACE did not report adverse effects at implantation, but did consider the indications for re-operation during follow up. Of 1415 patients, 240 underwent one or more re-operations during the follow up period. The more frequent indications for re-operation (see Table 4) were battery depletion (dual n=42, single n=59)), lead complications (dual n=30, single n=37) and need for change of pacing mode (dual n=4, single n=66). Less common indications for re-operation were surgical or mechanical complications (dual n=7,

single n=10), infection (dual n-3, single n=3), skin erosion (dual n=3, single n=1), or device failure (dual n=2, single n=2). The AG noted that the only indication which was statistically significantly different between the dual and single atrial pacemaker arm, was surgical change in pacing mode.

4.19 Table 5 Summary of clinical effectiveness for dual compared with single chamber atrial pacemakers

	Study	Dual		Single		OR [95% CI]
		n	N	n	N	
Change in pacing mode						
	Albertsen	0	26	3	24	0.12 [0.01-2.37]
	DANPACE	69	708	122	707	0.52 [0.38-0.71]
	Nielsen	5	123	6	54	0.34 [0.10-1.16]
	Meta-analysis	**74**	**857**	**131**	**785**	**0.50 [0.37 to 0.67]**
All-cause mortality						
	Albertsen	NR		NR		NR
	DANPACE	193	708	209	707	0.89 [0.71-1.13]
	Nielsen	28	123	9	54	1.47 [0.64-3.38]
	Meta-analysis	**221**	**831**	**218**	**761**	**0.97 [0.67 to 1.41]**
Heart failure (events and ratios not shown)						
	Albertsen					NR
	DANPACE					p>0.43
	Nielsen					p>0.17
	Meta-analysis					**p>0.05**
Atrial fibrillation						
Both	Nielsen	25	123	4	54	3.19 [1.05-9.67]
Both	Albertsen	NR		NR		NR
Paroxysmal	DANPACE	163	708	201	707	0.75 [0.59-0.96]
Chronic	DANPACE	76	708	79	707	0.96 [0.68-1.33]
	Meta-analysis					**NR**
Stroke						
	Albertsen	NR	NR		NR	NR
	DANPACE	34	708	39	707	0.86 [0.54-1.39]
	Nielsen	11	123	3	54	1.67 [0.45-6.24]
	Meta-analysis	**45**	**831**	**42**	**761**	**0.93 [0.60-1.45]**
Exercise capacity (events and ratios not shown)						
	Albertsen	6 minute walking test 12mnth				<0.05
	Gallick	Exercise length				0.74
	Schwaab	Exercise length /max workload				<0.05
	Meta-analysis					**NR**
Further surgery						
	Albertsen	NR		NR		NR
	DANPACE	84	708	156	707	0.48 [0.36-0.63]
	Nielsen	NR		NR		NR
	Meta-analysis					**NR**

Health related quality of life

4.20 **Tools:** Quality of life was studied in the cross over trials Lau et al. and Schwaab et al.

- Lau et al. used the:
  - Visual analogue scale (VAS) for general well-being;
  - The Specific Activity Scale (SAS) functional questionnaire for physical capacity, a disease specific questionnaire for the functional classification of patients with cardiovascular disease
  - 12-item General Health Questionnaire, a measure of current mental health, where each item is rated on a four-point scale (less than usual, no more than usual, rather more than usual, or much more than usual)
  - symptom questionnaire, assessed the incidence and frequency of dyspnoea, palpitations, dizziness, chest pain and neck pulsations, rated between 1 (all the time) and 5 (never)
  - somatic symptoms inventory (SSI) adapted for local use from the Bradford Somatic Inventory, measures: adequacy of daily life activities, emotional adjustment, social interactions (frequency, range and quality), work adjustment, sleep, fatigue and appetite.
- Schwaab et al. used 3 different self-administered questionnaires relevant to this appraisal:
  - VAS for general well-being, physical, emotional, and cognitive functioning
  - VAS Karolinska questionnaire (contains 16 questions on cardiovascular symptoms relevant to pacemaker patients)
  - SAS functional questionnaire.

4.21 **Results**: The AG noted that results for both general well-being and functional status were similar across Lau et al. and Schwaab et al., with no statistically significant difference between dual or single

chamber pacing modes in either trial. For multi-dimensional measures, there was no statistically significant difference between the pacing modes for tests of mental well-being (12-GHQ, SSI), or for most symptoms in either Lau et al. or Schwaab et al. Schwaab et al. reported people experiencing less dizziness on single atrial pacing than dual-chamber pacing ($p < 0.05$), however Lau et al. 1994 did not find a difference for the same symptom. Schwaab et al. was the only included trial that used the multi-dimensional quality of life questionnaires (self-perceived health status) with a section on cognitive function and reported no statistically significant difference between dual and single atrial pacing mode. The AG noted that there was a substantial amount of uncertainty around all quality of life results, as both trials were relatively small and had limited follow up.

Summary

4.22 The AG concluded that dual-chamber pacing was associated with a lower risk of atrial fibrillation and fewer re-operations than single-chamber atrial pacing. No statistically significant difference was shown between the pacing modes for mortality, stroke, quality of life, or heart failure. However, for people younger than 75 years of age the risk of heart failure appeared to be higher with a dual-chamber pacemaker than a single-chamber atrial pacemaker, and lower for people older than 75 years. The AG concluded that in people with sick sinus syndrome without evidence of impaired atrioventricular conduction, the risk of developing complete atrioventricular block, and the lack of tools to identify those at risk of developing the condition, supports the implantation of a dual-chamber pacemaker programmed to minimise unnecessary ventricular pacing (although the AG noted that even though in DANPACE the dual chamber pacemakers were programmed to reduce ventricular pacing, ventricular pacing was still around 65%).

However, considerations should be made around the risk of developing heart failure which may depend on age and device.

4.23 The AG noted that there was limited opportunity to combine the results using meta-analysis from the 6 trials identified, but that where this was possible, the results were mainly influenced by the largest trial DANPACE which accounted for over 80% of the weight in change in pacing mode, all-cause mortality, and stroke. In no instance did the level of significance of an outcome from DANPACE change because of its combination in a meta-analysis of that outcome.

5 Comments from other consultees

5.1 The professional group noted that although an atrial-based single-chamber ('AAI') pacemaker should "theoretically suffice" for the treatment of sick sinus syndrome with no evidence of atrioventricular block, many heart rhythm specialists implant a dual chamber system. The reasons given why dual chamber pacemakers should be favoured were because:

- There is no robust way of identifying those people who will go on to develop atrioventricular block
- Those who go on to develop high-grade atrioventricular block will be protected by the presence of a ventricular lead and will not require re-operation. Consequences of premature device removal include:
  - inefficient use of the battery
  - additional cost of implant and device
  - additional risk of morbidity (the risk of complication is 5-6% and is higher for generator replacement/system revision than for a first time implant)
  - people found to have an occluded subclavian vein may need an implant on the opposite side of the heart, or lead

extraction, carrying associated costs and morbidity. Some people may need to be referred to a specialist pacing service resulting in another procedure.

5.2 The professional group noted a number of arguments against dual chamber pacemakers for people with sick sinus syndrome with no evidence of atrioventricular block, as dual chamber pacemakers:

- are a more complex system
- are more expensive
- have a longer procedure duration
- have more implant complications, such as cardiac perforation, pneumothorax and infection
- have a longer follow-up
- have two leads and are therefore more difficult to extract, and more likely to cause narrowing or obstruction of the great veins
- may have a higher incidence of atrial fibrillation
- may still cause unnecessary pacing (despite being designed to avoid this), which can impact cardiac function and reduce battery longevity.

5.3 The professional group concluded that although there are arguments in favour of both pacemakers for this indication, the high rate of progression to advanced atrioventricular block argues strongly in favour of dual-chamber pacing. It highlighted that dual chamber pacemakers implanted for sick sinus syndrome without atrioventricular block should use algorithms in order to minimize unnecessary ventricular pacing. This is because chronic right ventricular pacing has an adverse effect on cardiac structure and function, including ventricular remodelling, reduced left ventricular ejection fraction, atrial dilatation and an increased risk of atrial fibrillation.

6 Cost-effectiveness evidence

6.1 The Assessment Group (AG) undertook a systematic review of existing cost effectiveness evidence and identified 12 papers for inclusion in its review. It provided a narrative summary of the included studies (see section 6.2 to 6.4); however it stated that it had not been able to identify any UK based economic evaluations addressing the population in the scope (that is, dual-chamber versus single-chamber atrial pacemakers for those with symptomatic bradycardia caused by sick sinus syndrome and no evidence of atrioventricular block) since the publication of TA88. Therefore, the AG developed an independent economic model (see sections 6.5 to 6.21). No other submissions or economic models were provided by manufacturers as part of this appraisal.

Identified economic evaluations

6.2 The AG stated that its systematic review of the literature allowed the inclusion of single-chamber ventricular pacemakers, as it was likely these papers would be informative for its economic evaluation. The 12 papers of relevance identified included 2 cost-utility analyses that were relevant to the population in this appraisal, 1 NHS based (Castelnuovo et al. [2005], developed for TA88) and 1 non-NHS based (Oddershede et al. [2014]). Castelnuovo et al. compared dual with single chamber (atrial or ventricular) pacemakers over a 10 year time horizon for several subpopulations with bradycardia. The Castelnuovo paper found single chamber atrial pacemakers to dominate (that is, were more effective and less costly than) dual chamber pacemakers for sick sinus syndrome. Oddershede et al. considered (from a Danish healthcare perspective) the cost-utility of dual- compared with single-chamber atrial pacemakers in people with sick sinus syndrome and no atrioventricular block, using data from DANPACE. Oddershede et al. presented adjusted results for DANPACE alone alongside

pooled data (DANPACE plus 2 other Danish trials), stratified by probability of survival, and also presented unadjusted non-stratified results for all patients combined. Depending on the risk stratification, adjustment, and pooling of data used, the cost-effectiveness of dual chamber compared with single chamber atrial pacemakers (assessed by calculating net-monetary benefit) ranged from £460 to £7847 when assuming a maximum acceptable ICER of £20,000 per QALY gained, and -£1238 to £10,615 when assuming a maximum acceptable ICER of £30,000 per QALY gained.

6.3 The AG described the other identified economic evaluations considered in the review, which were predominantly simple comparisons of costs and benefits (that is, differences in costs were not analysed in relation to benefits), in addition to an NHS based cost-utility analysis that was not relevant to the decision problem (Caro et al. [2006], which compared dual with single chamber ventricular pacemakers for bradycardia because of sinus node disease). The AG noted that based on the clinical evidence available at the time of TA88, single-chamber atrial pacing was estimated to dominate dual-chamber pacing for people with sick sinus syndrome and no atrioventricular block. However, since the publication of TA88, new clinical evidence (particularly DANPACE) of the relative effectiveness of dual- compared with single-chamber atrial pacing had emerged.

6.4 The AG noted that the following adverse events were commonly included in the economic literature, and were therefore incorporated into the economic evaluation: peri- and post-operative complications; the potential for upgrade requirements in people paced with single-chamber devices; onset of atrial fibrillation; heart failure; stroke; cardiovascular mortality, and; all-cause mortality.

Independent Assessment Group's economic model

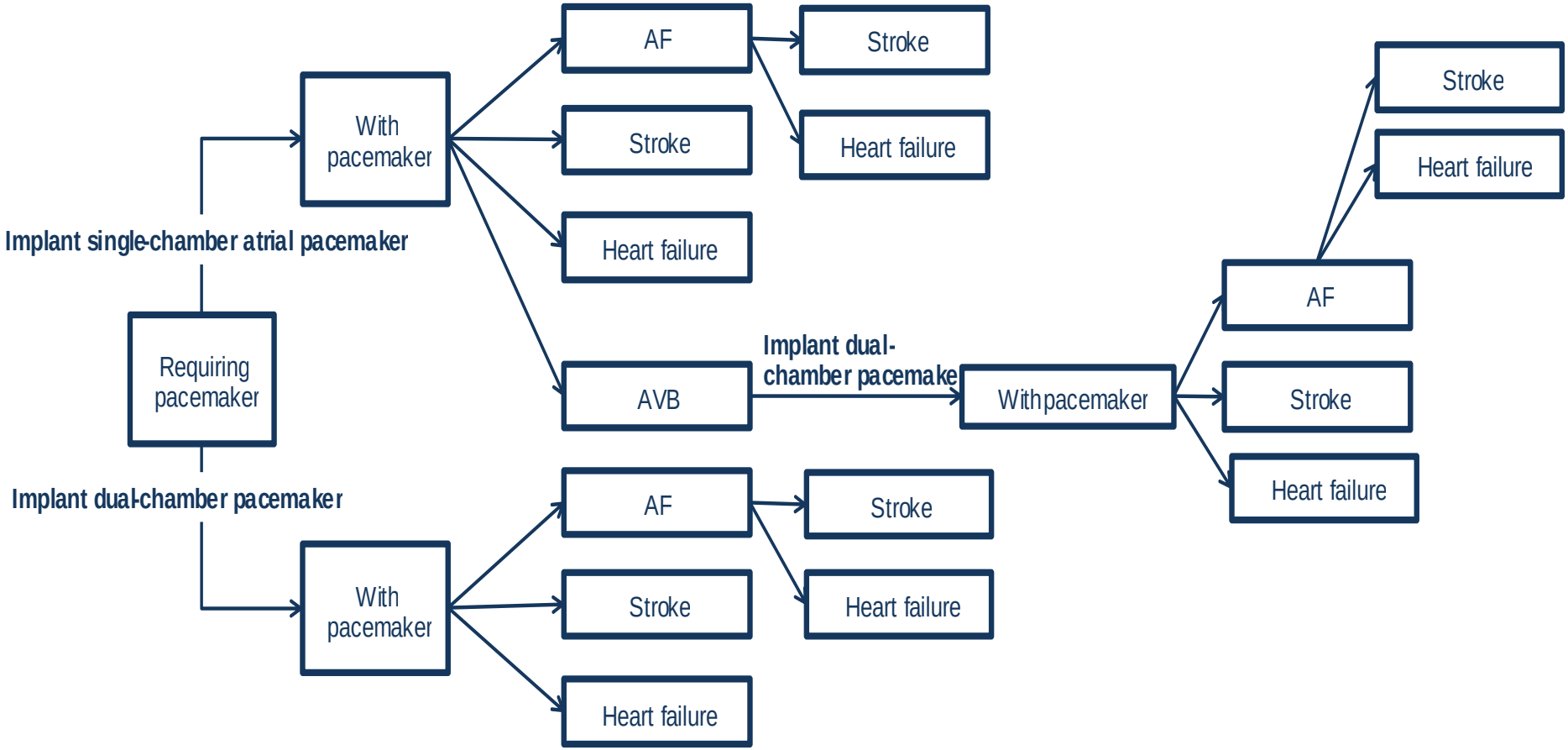
6.5 The Assessment Group (AG) constructed a Markov cohort model to estimate the cost-effectiveness of rate responsive dual-chamber pacemakers compared with rate responsive single-chamber atrial pacemakers in people with symptomatic bradycardia as a result of sick sinus syndrome without atrioventricular block. The AG conducted the economic analysis from the perspective of the NHS and Personal Social Services (PSS), and the model had a cycle length of 1 month. Costs and health effects were discounted at an annual rate of 3.5%.

Model structure

6.6 The model developed by the AG contained multiple health states (see Figure 1). Patients entered the model in the "requiring a pacemaker" health state, and then transitioned into either the "with dual-chamber pacemaker" or "with single-chamber atrial pacemaker" health state: In each arm patients could then experience adverse events and move on to the "atrial fibrillation", "stroke" or "heart failure" health states. In the single chamber pacemaker arm only, patients could move on to the "atrioventricular block" health state, and from there transition to the "with dual chamber pacemaker (following re-operation)" health state. The AG noted that all re-operations were assumed to occur in the single chamber atrial arm only (as the need to change pacing mode to dual chamber pacing was the only reason with a statistically significant difference between the two arms for re-operation [see sections 4.10 and 4.17]), and all re-operations were assumed to be an upgrade to dual chamber pacemaker. Only one instance of re-operation was permitted in the model. Patients who moved to the "heart failure" and "stroke" health states from the single chamber arm could have a re-operation; however they only incurred the costs of re-operation, and remained in the "heart failure" or "stroke"

health state. In the atrial fibrillation health state, modelled patients could require reprogramming of the device to act as a ventricular pacemaker in the dual-chamber arm, or re-operation in the single atrial arm to a single chamber ventricular device. However, in both arms, patients could transition from “atrial fibrillation” to “heart failure” or “stroke”. Patients were at risk of death in each health state.

Figure 1 Overview of model



6.7 The AG populated the model with a cohort that had the same baseline characteristics of the DANPACE trial: baseline age was 73 years, and 65% of participants were female. However, rather than using the prevalence of comorbidities from the DANPACE trial of atrial fibrillation (44%), stroke (8%) and heart failure (12%) these were assumed to be zero for all patients upon entry to the model. The AG stated this assumption was made in order to simplify the model.

Modelled treatment effectiveness

6.8 The treatment effect for dual compared with single chamber pacemakers was predominantly informed by results from the DANPACE trial only, including summary statistics for DANPACE taken from Nielsen et al. (2011) (risk of re-operation and risk of atrial fibrillation or stroke) and Riahi et al. (2012) (risk of heart failure). The AG stated that they did not combine the available trial data because of heterogeneity between the trials as a result of different patient populations (for example prior history of atrial fibrillation) and different device programming used (for example different proportions of ventricular pacing). For the risk of heart failure and stroke for those with atrial fibrillation, the AG carried out targeted literature searches.

Re-operation **(**

6.9 Table 6): Re-operation could only occur in the single chamber arm of the model (see section 6.6). For those with single-chamber atrial devices, the need to change pacing mode was predominantly a result of the development of atrioventricular block requiring upgrade to a dual-chamber device (see sections 4.10 and 4.17). Therefore the AG used the difference in event rates for re-operation between the single and the dual chamber arms in DANPACE to estimate the risk of those in the single chamber atrial arm developing atrioventricular block per patient per month, and applied this as a constant risk for the lifetime of the model. In order to derive the transition probabilities for the model, the AG converted the difference in monthly event rates into a monthly probability of atrioventricular block for those with single chamber pacemakers, generating a value of 0.142. The AG stated that this approach to modelling was taken so that the uncertainty associated with re-operation could be captured in one-way and probabilistic sensitivity analyses, however as the Kaplan-Meier plot suggested a non-linear relationship, re-operation as a time-dependent parameter (rather than assuming constant risk) was used in sensitivity analyses. The AG assumed that at 96 months post-implantation, based on an 8-year battery life, all patients who had not yet experienced re-operation or developed atrial fibrillation received a replacement dual-chamber device.

Atrial fibrillation, heart failure and stroke (all patients) **(**

6.10 Table 6): For the dual chamber pacemaker arm, the AG derived event rates for atrial fibrillation, heart failure and stroke from DANPACE and Riahi et al. For the single chamber arm, the AG derived event rates for atrial fibrillation, heart failure and stroke by taking the relevant hazard ratios from DANPACE and Riahi et al., and applying these to the associated event rates derived for the dual chamber arm. The AG then transformed the event rates into monthly probabilities.

Heart failure and stroke (those with atrial fibrillation) **(**

6.11 Table 6): People who develop atrial fibrillation are at risk of heart failure or stroke, therefore the AG carried out targeted literature searches to estimate risk. For heart failure, the AG did not identify any studies, therefore it assumed in the model that the risk of heart failure was the same in people with and without atrial fibrillation. For stroke, a paper Gallagher et al. (2014) was identified, which reported the results of a population-based cohort study of people with atrial fibrillation. Gallagher presented incidence rates of stroke, adjusted for covariates such as $CHADS_2$ score (a tool used to estimate the risk of stroke in those with atrial fibrillation), age, and smoking status for various scenarios of warfarin therapy (currently exposed, recently exposed, history of exposure or no history of exposure). The AG considered the incidence rate of stroke in people currently exposed to warfarin therapy (0.9 per 100 person years) the most suitable to inform the risk of stroke in people with atrial fibrillation, because current guidelines recommend effective anticoagulation therapy for stroke prevention in people with paroxysmal and persistent atrial fibrillation.

Mortality **(**

6.12 Table 6): The AG assumed (based on pooled estimates of all-cause and cardiovascular mortality identified in the clinical literature review) that the risk of death was consistent across all treatment arms, but varied by age and health state. Those in the "with pacemaker" health states had the same risk of death as the age and gender matched UK general population (as the AG found no evidence of higher mortality risks for people requiring or implanted with a pacemaker [this assumption was tested in a scenario analysis]). The AG considered 2 overarching forms of mortality within the model: case fatality and all-cause mortality. For all-cause mortality (which considered the change in the risk of death as a result of the event experienced), in addition to death from the event experienced, people with atrial fibrillation, stroke, or heart failure were assumed to be at increased risk of death compared with the UK general population, and those with atrial fibrillation who also had either stroke or heart failure were assumed to be at further risk of death (see Appendix C for sources of all-cause mortality). For case fatality (that is, death directly from the event itself), the AG calculated fatality from several sources. For stroke (with and without atrial fibrillation), the AG used data presented by Carter et al. (2007), which reported the number of people dying within 30 days of an acute stroke event (n=32/545) and, of these, the number with atrial fibrillation (n=14). Those with atrial fibrillation had a probability of stroke of 13.59%, and those without atrial fibrillation had a probability of stroke of 4.07%. For case fatality following heart failure (with and without atrial fibrillation), the AG used:

- Without atrial fibrillation: 19% patients without AF were assumed to die as a result of a study by Cowie et.al. (2000), a population based observational study (UK) of patients with a new diagnosis of heart failure in which 81% of patients were alive one month after developing heart failure.

- With atrial fibrillation: Mosterd et al. (2001, Rotterdam), which included prognostic analyses of a population based cohort study in which cardiac death in people with atrial fibrillation was associated with a hazard ratio of 2.08.

6.13 The following presents the effectiveness parameters used in the model:

Table 6 Summary of effectiveness used in the model

Parameter	Hazard ratio (HR)	Probability dual	Probability single	Source
Treatment effect (single v dual)				
AVB	N/A	N/A	0.142%	DANPACE
Paroxysmal AF	1.24	0.40%	0.50%	DANPACE
Chronic AF	1.01	0.18%	0.18%	DANPACE
Heart failure	1.09	0.42%	0.46%	DANPACE
Stroke	1.11	0.08%	0.08%	DANPACE
Probabilities not affected by device type				
With AF (vs non-AF)				
Parameter	**Hazard ratio**	**Probability**		**Source**
AF + stroke	N/A	0.08%		Gallagher
AF + Heart failure	N/A	Same as HF alone		DANPACE
Mortality: Case fatality (death from outcome itself)				
Parameter	**Hazard ratio**	**Probability**		**Source**
% HF fatal	N/A	19%		Cowie
% strokes fatal	N/A	4.07%		Carter
AF + fatal stroke	N/A	13.59%		Carter
AF + fatal HF	2.08 (vs HF alone)	34.8%		Cowie/ Mosterd
Mortality: All-cause mortality (increase in risk of death)				
Parameter	**Hazard ratio**	**Probability**		**Source**
Heart failure	1.32 (v general pop)	HR applied to population-based age and gender adjusted mortality		Pocock
Stroke	3.59 (M) 3.14 (F) (vs general pop)			Carter
Atrial fibrillation	2.08 (v general pop)			Miyasaka
Atrial fibrillation and stroke	1.33 (v stroke alone)			Carter
Atrial fibrillation and heart failure	1.11 (v HF alone)			Pocock
AF: atrial fibrillation; AVB: atrioventricular block; HF, heat failure				

6.14 **Adverse events**: The AG did not incorporate the effect of adverse events into the model because it did not identify any statistically significant differences in adverse events in the literature other than adverse events leading to re-operation).

6.15 **Health-related quality of life**: The AG carried out a systematic review to identify health-related quality of life evidence. The AG stated that, as with the economic evaluation searches, the inclusion

of ventricular pacing was allowed, as the evidence was likely to be transferable to the population in the decision problem. The AG identified 6 studies reporting generic, preference-based measures of quality of life and listed for final inclusion. The AG noted that all of the health related quality of life studies identified for inclusion reported time trade off (TTO) utility data collected directly from patients, and of these, 5 (Fleischmann et al. 2006; Fleischmann et al. 2009; Shulka et al. 2005; Link et al. 2004, and Lamas et al. 2002) reported the results of quality of life analyses carried out with the MOST clinical trial, and 1 (Lopez-Jimenez et al. 2002) from the PASE trial:

- The MOST trial was a UK based randomised controlled trial of 1841 people with sick sinus syndrome who received dual-chamber pacing systems and were randomised to either dual or single chamber ventricular pacing. The average age of patients was 73 years, 52% were male, approximately 45% had paroxysmal atrial fibrillation and 20% had some form of atrioventricular block. Health related quality of life was assessed using the Medical Outcomes Study 36-item Short Form (SF-36) General Health Survey, using the standard time trade-off methodology to generate utilities and the Specific Activity Scale (SAS) to generate functional status. Measurements were collected at baseline, 3 months and 12 months post-implantation.
- PASE was a randomised controlled trial of people who were in sinus rhythm and for whom permanent pacing was indicated as a result of bradycardia, with a primary endpoint of health related quality of life. People were randomised to single ventricular or dual pacing mode. The average age of patients was 76 years, 59% were male, 57% had atrioventricular block and 28% had New York Heart Association (NYHA) Class III or IV heart failure. Health related quality of life was assessed using the time trade

off, SF-36 and 0-100 scoring systems. In addition to health related quality of life, functional status was assessed with SAS. Measurements were collected at baseline, 3 months, 9 months and 18 months after enrolment.

6.16 The AG identified no utility data from the literature for those with atrial fibrillation who had a stroke, therefore it assumed in the base case that the utility of stroke is the same with and without atrial fibrillation. This assumption was tested in sensitivity analysis. Death was assumed to be associated with a utility of 0.

Table 7 Quality of life data selected for the economic model

Health state	Utility	Source/result	Rationale
Implant single	0.725	Fleischmann 2006: (Impact of pacemaker device & mode (DDDR/AAIR) on QoL) **TTO:** No statistically significant differences in utility **SF-36**: Small but measurable effect of a dual or single chamber pacemaker **Summary**: statistically significant improvements in QoL with pacemaker implant	Largest & most homogeneous utility study identified in people with SSS. Based on age & gender adjusted analysis.
Implant dual			
With single	0.825		
With dual			
AF	0.805	Fleischmann 2009 (Impact of AF on QoL & functional status following implant) **SF-36 & SAS:** Statistically significant difference in physical component of scores **Summary**: AF not a major determinant of most QoL measures, but may impair physical improvement	Only utility study of the impact of AF in people paced for bradycardia.
Stroke	0.64 month 1; 0.70 thereafter	Luengo-Fernandez 2013 (evaluated quality of life after TIA and stroke). **Results not described**	Most recent and robust study identified by targeted search.
AF & Stroke			Assumption
Heart failure	0.64	Lopez-Jimenez (2002) (results of PASE study) Lower utility for history of CHF v no CHF (0.64 vs 0.78; p<0.001) Lower utility for NYHA class III or IV v class I or II (0.62 vs 0.80, p=0.0001)	Only utility study identified reporting utility data for bradycardia patients with HF.
AF & Heart failure	0.64		Assumption
Death	0	Assumption	
Abbreviations: AF, atrial fibrillation; AVB, atrioventricular block; CHF, chronic heart failure; HSUV, health state utility value; NYHA, New York Heart Association; QoL, quality of life; SAS, Specific Activity Scale; SF-36, Short Form Health Survey, SSS, sick sinus syndrome, TTO, time trade off			

Costs

6.17 The AG identified studies for UK specific resource use and costing studies of atrial fibrillation, heart failure and stroke from the following sources:

- British Heart Foundation: Statistics on Coronary Heart Disease
- Luengo-Fernandez et al. (2012): a population-based cohort study of hospitalisation resource use and costs before and after stroke and transient ischemic attack
- Luengo-Fernandez et al. (2013): a population based study of acute and long term care costs after stroke in people with atrial fibrillation.

The resource use and costs were based on standard UK sources (NHS Reference costs 2012-2013, (NHS Reference costs 2012-2013, Electronic market information tool [eMit] or British National tool [eMit] or British National Formulary [BNF]) for the unit costs applied within the TAG applied within the TAG economic model and the above literature for the costs associated with the the costs associated with the treatment of atrial fibrillation, heart failure and stroke. Costs used failure and stroke. Costs used in the model are summarised in

Table 8

6.18 **Device and implantation costs**: The AG obtained procedure costs (including hardware costs) associated with implantation of a single- or dual-chamber device from a weighted average of episode costs associated with relevant Healthcare Resource Group (HRG) codes (NHS Reference costs 2012-2013). The AG assumed that upgrade procedures cost the same as an initial implantation of a dual-chamber device. In sensitivity analyses, the AG used spell level (rather than episode level) data for each HRG code. The AG assumed that at 96 months post-implantation, all patients who had not yet experienced re-operation or developed atrial fibrillation received a replacement dual-chamber device.

6.19 **Monitoring costs**: Modelled patients received follow up checks from a cardiologist following pacemaker implantation, for which the AG used HRG codes. Based on expert clinical opinion, the AG assumed initial follow up to be 1 week after implantation, and second follow up at 2 months post implantation and subsequent annual visits. Therefore, the AG applied the cost of a follow up visit upon entry into the "implant single-chamber atrial pacemaker", "implant dual-chamber pacemaker", "with single-chamber atrial pacemaker" and "with dual-chamber pacemaker" health states. The cost of a follow-up visit was also applied annually to all patients in the "With single-chamber atrial pacemaker" and "With dual-chamber pacemaker" health states.

6.20 **Episode costs**: Modelled patients were exposed to the risk of heart failure and stroke, with or without the presence of atrial fibrillation:

- Where atrial fibrillation was absent, the AG used a weighted average of episode level costs associated with relevant HRG codes for the occurrence of heart failure or stroke.
- Where atrial fibrillation was present, the episode cost of stroke was based on the population-based cohort study reported by Luengo-Fernandez et al. (2013) (see section 6.17). The AG found no evidence indicating that the episode cost of heart failure would differ in the presence of atrial fibrillation.

The AG applied the episode cost of heart failure to people entering the "heart failure" and "atrial fibrillation and heart failure" health states. The AG applied the episode cost of stroke to people entering the "stroke" health state, and the episode cost of stroke following atrial fibrillation to people entering the "atrial fibrillation & stroke" health state. If people developed atrial fibrillation which required reprogramming to ventricular mode:

- Dual chamber device: modelled patients accrued the costs of a consultation with a cardiologist and an electrocardiogram (ECG), based on HRG codes.
- Single chamber atrial device: modelled patients accrued the cost of a replacement single ventricular device (the AG assumed an equivalent cost to the single atrial pacemaker of £1,875).

The AG applied (based on expert clinical opinion) the cost of reprogramming and device replacement to one third of people developing atrial fibrillation. The impact of this assumption was tested in sensitivity analysis.

6.21 **Long-term costs**: Following the onset of heart failure, stroke or atrial fibrillation, the AG assumed modelled patients accrued costs over the long-term, for example medication, hospitalisation and primary care costs.

- Heart failure: the AG used national prevalence and cost statistics reported in the 2012 BHF coronary heart disease statistics publication, calculating the relative prevalence of heart failure as a percentage of CVD, and estimating the 2011 UK direct healthcare costs of CVD and heart failure. The AG applied these costs monthly to people in the “heart failure” and “atrial fibrillation and heart failure” health states.
- Stroke: the AG used the cost of hospitalisation estimated from a population-based cohort study reported by Luengo-Fernandez et al. (2012) and the cost of medication and primary care reported by Townsend et al. (2012). The AG applied the costs monthly to people residing in the “stroke” and “atrial fibrillation and stroke” health states.
- Atrial fibrillation: the AG identified long-term costs of primary care and hospitalisation from a predictive study carried out by Stewart et al. (2004) (which evaluated the UK health and social services cost of atrial fibrillation in 1995, and projected costs to 2000 based on epidemiological trends). The AG also assumed people with atrial fibrillation received effective anticoagulation therapy with apixaban, dabigatran etexilate, rivaroxaban or warfarin in addition to the costs of primary and hospital care (as the AG stated this reflected current clinical guidance). The AG noted that it used current market shares for anticoagulation in the base case, but that these may be subject to change over time, therefore it used additional scenarios in sensitivity analyses. The long-term costs were applied monthly to people residing in the "atrial fibrillation", "atrial fibrillation and stroke" and "atrial fibrillation and heart failure" health states.

Table 8 Costs used in the AG model

Health state	Cost	Frequency	Dual (£)	Single (£)	Source
Implant device	Device/implant	Unit cost	2438	1875	HRG
	Cardiologist F-up	Unit cost	86		HRG
With device	Cardiologist F-up	Annual	86		HRG
Atrial fibrillation	Ventricular reprogramming	Episode/unit cost (33% patients)	86 (Cardiology consult); 41 (ECG)	1875 (new device)	HRG
	Anticoagulation	Monthly	6.45		BNF/eMIT
	Cost per person	Annual	955		Stewart
	Cost per cycle	**Monthly**	**86.01**		
Heart failure	Episode	Unit	1228		HRG
	Cost per cycle	Per cycle	343		
Stroke	Episode	Unit	1427		HRG
	Hospitalisation	Unit	1564		L-Fernandez
	Medication	Unit	81		Townsend
	Primary care	Unit	38		Townsend
	Cost per cycle	**Per cycle**	**140**		
AF+stroke	Episode	Unit	11,275		L-Fernandez
	Hospitalisation	Unit	3649		L-Fernandez
	Medication	Unit	81		Townsend
	Cost per cycle	**Per cycle**	**400**		
AF+HF	Episode	Unit	1228		HRG
	Cost per cycle	**Per cycle**	**343**		
Reoperation	Device/implant	Unit	N/A	2438 dual 1875 single V	HRG
Abbreviations used in table: AF, atrial fibrillation; AVB, atrioventricular block; BNF, British National Formulary; eMIT, electronic market information tool; HF, heart failure; HRG, Healthcare Resource Group codes					

Results of the economic analyses

6.22 The deterministic base case incremental cost effectiveness ratio (ICER) for dual compared with single chamber atrial pacemakers was £10,288 per quality adjusted life year (QALY) gained (incremental costs £470, incremental QALYs 0.04), and the mean probabilistic ICER across 1000 simulations was £5989 per QALY gained (incremental costs £270, incremental QALYs 0.05). The AG

noted that difference between the probabilistic and deterministic ICER was mainly because of the non-linearity of the minimum and maximum cost of implantation a single chamber atrial or dual chamber pacemaker. The probability of dual chamber pacemakers being cost effective at a maximum acceptable ICER of £20,000 per QALY gained was 72.3%, and at £30,000 per QALY gained was 76.6%. The AG noted that in 63.4% of simulations, dual chamber devices had both greater costs and greater QALYs than single atrial pacemakers, and in 25.8% of simulations, dual chamber pacemakers dominated single chamber atrial pacemakers (that is, produced more QALYs at a lower cost.) Single chamber devices dominated dual in 10% of cases.

Table 9 Base case incremental cost effectiveness ratio (ICERs)

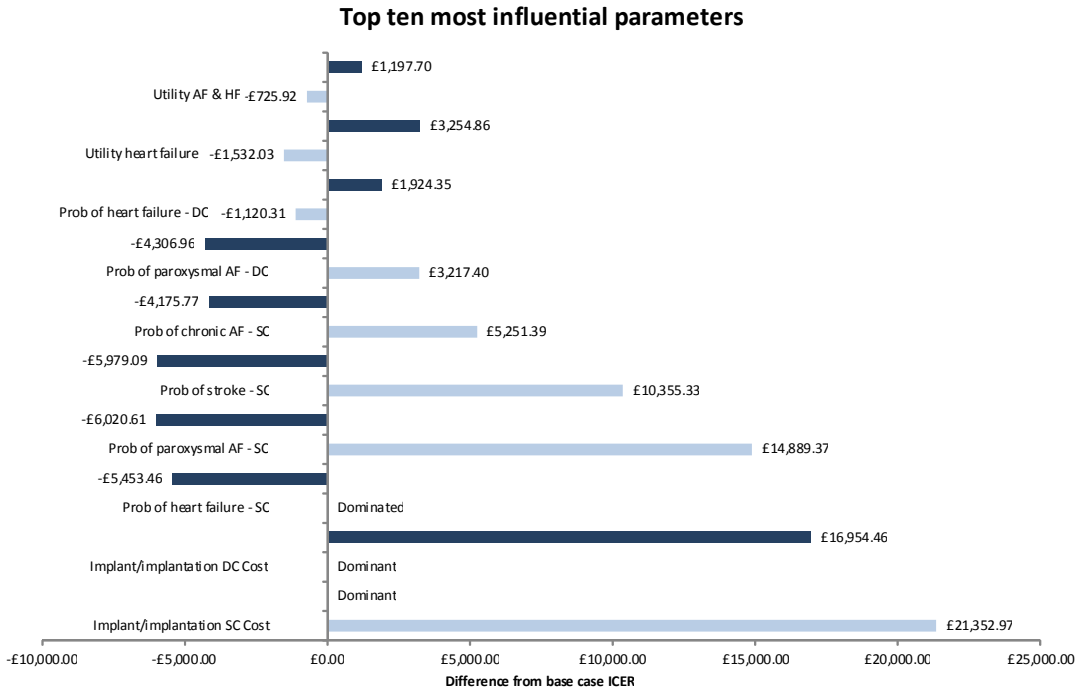
Intervention	**Total costs**	**Total QALYs**	**Inc. costs**	**Inc.QALYs**	**ICER**
Deterministic results					
Single atrial	£5,566.11	5.51	–	–	–
Dual	£6,023.21	5.56	£457.10	0.04	£10,288
Probabilistic results					
Single atrial	£8,720.68	5.25	–	–	–
Dual	£8,991.02	5.29	£270.34	0.05	£5,989

6.23 The AG carried out one-way sensitivity analysis on the following parameters by using the lower and upper limits of the 95% confidence intervals: age; efficacy values; utility values; costs; all-cause mortality; and heart failure hospitalisation. The AG presented a tornado diagram of the 10 most influential results in the deterministic sensitivity analysis (see Figure 2), which showed the variance from the base case, and noted that many of the parameters tested had minimal impact on the deterministic cost-effectiveness results. The ICER was most sensitive to the probability of heart failure and probability of paroxysmal atrial fibrillation in people with single chamber atrial pacemakers. When the AG applied the minimal probability of heart failure to those with

single chamber devices, dual chamber pacemakers become dominated (however the AG noted that this was driven by a modest increase in costs (£391) and a modest reduction in utility (-0.01). The ICER was also sensitive to the implantation costs for both dual and single chamber pacemakers with both becoming dominant when their respective minimum costs are used. The AG noted that the parameters most likely to increase the deterministic ICER over £20,000 per QALY gained were:

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

Figure 2 Tornado diagram of parameters to which the cost-effectiveness results were most sensitive (variance from base case)



6.24 The AG conducted structural sensitivity analyses (Table 10). When using a 5-year time horizon, the deterministic ICER was £19,549 per QALY gained, and the probabilistic ICER was £14,002 per QALY gained. When using Kaplan-Meier data as the basis for reoperation, the ICER was £7,691 per QALY gained.

6.25 The AG conducted scenario analyses on the base case results (Table 10), including varying efficacy sources, cost estimates (using spell costs of pacemaker device and implantation [dual cost: £4,142.11; single cost: £3,362.18]), discount rates, and differing risk of developing heart failure by age. Most of the scenarios explored had a minor impact on the resulting ICER with the exception of:

- assuming no difference in risk of developing heart failure (£20,948 per QALY gained);

- monthly cost for heart failure taken from TA88 (£1,892 per QALY gained);
- reprogramming/device replacement for atrial fibrillation in 0% patients (£14,806 per QALY gained);
- reprogramming/device replacement for atrial fibrillation in 100% patients (£1,251 per QALY gained).

Table 10 Summary of deterministic structural sensitivity analyses and deterministic scenario analyses (see page 158 of Assessment Report)

Analysis	Inc. cost	Inc. QALY	ICER
Base case	£457.10	0.04	£10,288
Structural sensitivity analyses			
Time horizon reduced to 5 years	£307.79	0.02	£19,549
KM data as basis for re-operation	£306.37	0.04	£7,691
Scenario analyses			
Efficacy scenarios			
No impact on HF (HR=1)	£429.13	0.02	£20,948
Stroke used from AG meta-analysis	£466.04	0.04	£10,912
Cost scenarios			
Spell level costs of pacemaker implantation NHS Reference costs	525.94	0.04	£11,837
Cycle cost for heart failure from TA88	£84.08	0.04	£1,892
Cycle cost for stroke from TA88	£393.92	0.04	£8,866
Cycle cost for stroke from Saka 2009 (UK study cost of stroke)	£484.37	0.04	£10,901
Reprogramming/device replacement for AF in 0% patients	£657.85	0.04	£14,806
Reprogramming/device replacement for AF in 100% patients	£55.60	0.04	£1,251
Other scenarios			
Discount rate 0%	£495.35	0.05	£9,202
Discount rate 6%	£438.40	0.04	£11,224
Market share 55% warfarin 45% NOAC	£407.60	0.04	£9,174
'Worst case' scenarios			
All worst case scenarios cumulative	£917.71	0.02	£49,018
Additional scenarios for HF			
HF adjusted by age >75 years	£531.86	0.11	£4,918
HF adjusted by age ≤75 years	£338.35	-0.06	Dominated
HF, heart failure, NOAC, novel oral anticoagulants			

Base-case A: Post-consultation analyses

6.26 Following consultation on the AG report, an error was noted in the calculation of total UK direct costs of cardiovascular disease, which had been underestimated in both arms of the model. This changed the base case ICER and all scenario and sensitivity analyses. These corrected ICERs are described in sections 6.27 to 6.30 and are hereafter referred to as base-case A. The AG noted the error had a minimal effect on the ICERs.

6.27 The deterministic base case A ICER for dual compared with single chamber atrial pacemakers was £6056 per QALY gained (incremental costs £269, incremental QALYs 0.04), and the mean probabilistic ICER across 1000 simulations was £6068 per QALY gained (incremental costs £277, incremental QALYs 0.05). The probability of dual chamber pacemakers being cost effective at a maximum acceptable ICER of £20,000 per QALY gained was 72.9%, and at £30,000 per QALY gained was 78.7%. The AG noted that in 66% of simulations, dual chamber devices had both greater costs and greater QALYs than single atrial pacemakers, and in 24.1% of simulations, dual chamber pacemakers dominated single chamber atrial pacemakers (that is, produced more QALYs at a lower cost.) Single chamber devices dominated dual in 9% of cases.

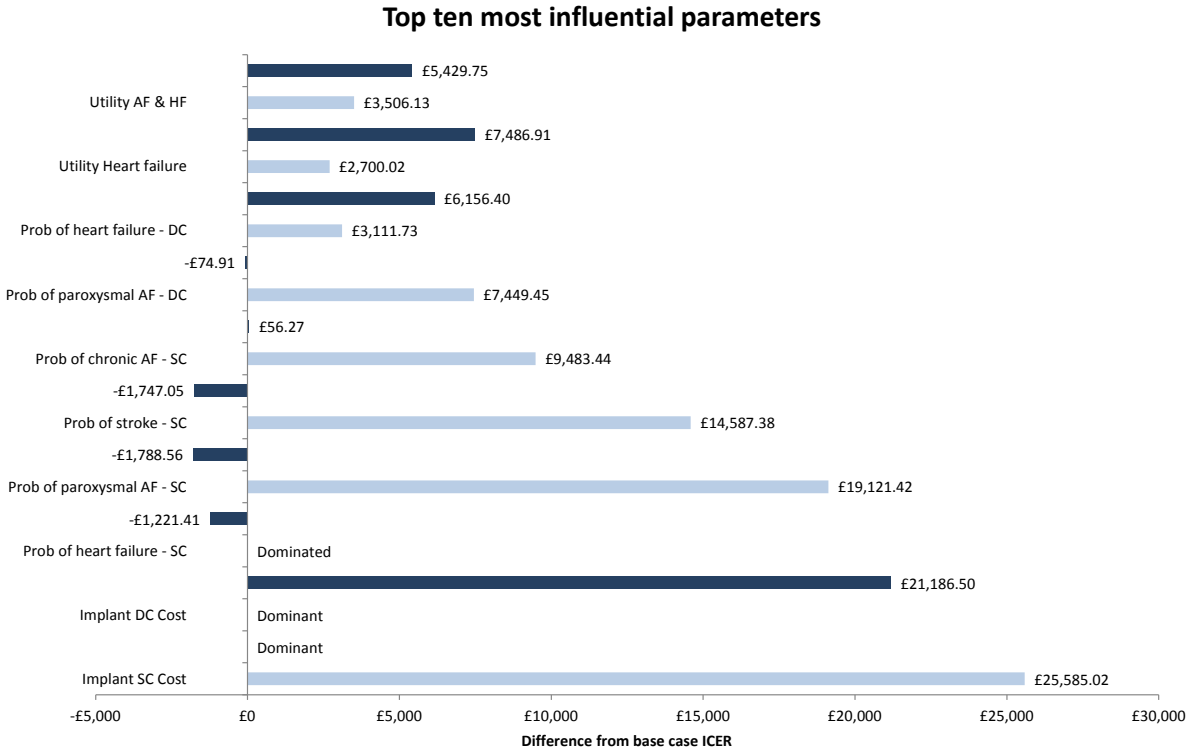
Table 11 Base case A incremental cost effectiveness ratio (ICERs)

Intervention	**Total costs**	**Total QALYs**	**Inc. costs**	**Inc. QALYs**	**ICER**
Deterministic results					
Single atrial	£9,211.41	5.51	–	–	–
Dual	£9,480.47	5.56	£269.06	0.04	£6,056
Probabilistic results					
Single atrial	£8,828.23	5.25	–	–	–
Dual	£9,104.81	5.3	£276.59	0.05	£6,068

6.28 The AG carried out one-way sensitivity analysis on the following parameters by using the lower and upper limits of the 95% confidence intervals: age; efficacy values; utility values; costs; all-cause mortality; and heart failure hospitalisation. The AG presented a tornado diagram of the 10 most influential results in the deterministic sensitivity analysis (see Figure 3), which showed the variance from the base case, and noted that many of the parameters tested had minimal impact on the deterministic cost-effectiveness results. The AG noted that the parameters most likely to increase the deterministic ICER over £20,000 per QALY gained were:

- lowest risk of stroke (£20,643 per QALY gained)
- lowest risk of paroxysmal atrial fibrillation (£25,177 per QALY gained)
- highest implant/procedure cost for dual-chamber pacemaker (£27,242 per QALY gained)
- lowest cost of implant procedure cost for single-atrial pacemaker (£31,641 per QALY gained)
- lowest risk of heart failure (single chamber atrial pacemakers dominated dual) (the AG noted that this result was driven by an increase in cost of £710 and a modest reduction in benefit (–0.01).

Figure 3 Tornado diagram of parameters to which the cost-effectiveness results were most sensitive (variance from base case)



6.29 The AG conducted structural sensitivity analyses (Table 12). When using a 5-year time horizon, the deterministic ICER was £14,261 per QALY gained, and the probabilistic ICER was £13,837 per QALY gained. When using Kaplan-Meier data as the basis for re-operation, the ICER was £3,425 per QALY gained.

6.30 The AG conducted scenario analyses on the base case results (Table 12), including varying efficacy sources, cost estimates (using spell costs of pacemaker device and implantation [dual cost: £4,142.11; single cost: £3,362.18]), discount rates, and differing risk of developing heart failure by age. Most of the scenarios explored had a minor impact on the resulting ICER with the exception of:

- assuming no difference in risk of developing heart failure (£22,213 per QALY gained)

- reprogramming/device replacement for atrial fibrillation in 0% patients (£10,872 per QALY gained)
- reprogramming/device replacement for atrial fibrillation in 100% patients (dual-chamber pacemakers dominated single atrial).

Table 12 Base case A: summary of deterministic structural sensitivity analyses and deterministic scenario analyses

Analysis	Inc. cost	Inc. QALY	ICER
Base case	£269.06	0.04	£6056
Structural sensitivity analyses			
Time horizon reduced to 5 years	£224.53	0.02	£14,261
KM data as basis for re-operation	£136.43	0.04	£3425
Efficacy scenarios			
Stroke used from AG meta-analysis	£274.96	0.04	£6438
No impact on HF (HR=1)	£455.05	0.02	£22,213
Cost scenarios			
Spell level costs implant NHS Ref costs	£337.9	0.04	£7605
Cycle cost for heart failure from TA88	£317.22	0.04	£7140
Cycle cost for stroke from TA88	£154.44	0.04	£3476
Cycle cost for stroke from Saka 2009 (UK study cost of stroke)	£244.95	0.04	£5513
Reprogramming/replacement AF 0%	£483.05	0.04	£10,872
Reprogramming/replacement AF 100%	-£158.92	0.04	Dominant
"Worst case" scenario			
All, cumulative	£912.47	0.02	£48,738
Other scenarios			
Discount rate 0%	£271.58	0.05	£5,045
Discount rate 6%	£271.00	0.04	£6,938
Market share: 55% warfarin/45% NOAC	£219.57	0.04	£4,942
Additional scenarios for heart failure			
HF adjusted by age >75 years (HR single v dual 1.34)	-£225.94	0.11	Dominant
HF adjusted by age ≤75 years (HR single v dual 0.72)	£1061.81	-0.06	Dominated
HF, heart failure; HR, hazard ratio; NOAC, novel oral anticoagulants			

7 Equality issues

7.1 No potential equalities issues have been raised.

8 Innovation

8.1 No submissions have been submitted which support innovation.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2007). A combined update of TA95 and TA120 is in progress, expected date of issue June 2014.
- Implantable cardioverter defibrillators for arrhythmias. NICE technology appraisal guidance 95 (2006). A combined update of TA95 and TA120 is in progress, expected date of issue June 2014.

Appendix B: Pacemaker naming conventions

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

Appendix C: All-cause mortality used in the TAG economic model

Health state	Rate of all-cause mortality[a]	Source (Country)
Implantation health states	Age specific rate of all-cause mortality from UK general population; weighted by the proportion of male and female patients modelled.	ONS 2012 (UK)[86]
With pacemaker health states		
AF	HR of 2.08 versus the general population all-cause mortality rate	Miyasaka 2007, a 21 year community-based study analysing the all-cause mortality risk of people with AF versus an age and gender matched general population (US). [87]
Stroke	HRs of 3.59 and of 3.14 versus the general population for males and females, respectively.	Carter 2007, a hospital-based cohort study to determine all-cause mortality with ischemic stroke compared with an age-matched healthy cohort (UK). [88]
AF and stroke	HR of 1.33 versus people with stroke and no AF	
Heart failure	HR of 1.32, calculated from a weighted average of HR for people with NYHA Class III (1.30, n = 3,985) and NYHA Class IV (1.68, n = 197).	Pocock 2006, an analysis of data from the CHARM programme to develop predictive models of all-cause mortality (International) [89]
AF and heart failure	HR of 1.11 versus people with heart failure and no AF	

[a] Converted into monthly probabilities for use in the model; prob=1-exp(-rate*time).

Abbreviations used in table: AF, atrial fibrillation; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; HR, hazard ratio; NYHA, New York Heart Association; ONS, Office of National statistics; SMR, standardised mortality rate; TAG, Technology Assessment Group.