

# Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome without atrioventricular block

Technology appraisal guidance

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This guidance partially replaces TA88.

# 1 Recommendations

This guidance partially updates NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block.

- 1.1 Dual-chamber pacemakers are recommended as an option for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block.

## 2 Clinical need and practice

- 2.1 Bradycardia is a slow heart rate, defined as a heart rate of less than 60 beats per minute. Bradycardia can be caused by 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, in which the sinus node occasionally does not generate electrical impulses, from a period lasting a couple of seconds to several minutes
    - sinoatrial exit block, in which 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 in which 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 due to sick sinus syndrome may also have or develop atrioventricular block.
- 2.2 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.
- 2.3 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 using electrocardiograms (ECGs). Because abnormalities may be intermittent, Holter monitoring (ECG monitoring for 24 to 48 hours) or event recorders may be used.

- 2.4 The prognosis of individuals with sick sinus syndrome is variable and difficult to predict, depending on 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 need 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.
- 2.5 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 due to sick sinus syndrome needing 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 2,490 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 people of any age, and affects men and women equally. The incidence of atrioventricular conduction abnormalities also increases with increasing age.

## Current management

- 2.6 Pacemakers are electrical devices that consist of a small battery-powered generator and 1 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 1 or 2 heart chambers. Dual-chamber pacemaker devices are attached to both chambers of the heart and may be used in either dual-chamber pacing mode (in which both the right atrium and ventricle are paced, which mimics the natural pacing rhythm of the heart) or single-chamber pacing mode (where only 1 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 (that is to pace the chamber) where the lead was

originally placed. Pacemakers may also be rate modulating (that is, able to sense and adapt the rate of pacing to the level of physical exertion).

- 2.7 NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block recommended the use of single-chamber atrial pacemakers for treating sick sinus syndrome in people in whom, after full evaluation, there was no evidence of impaired atrioventricular conduction. The purpose of this part review is to update this recommendation because the DANPACE trial, which was published after the publication of NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block, has provided additional evidence comparing dual- with single-chamber atrial pacemakers for this population.
- 2.8 In 2012 to 2013 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 people with a primary diagnosis of sick sinus syndrome (2,490 patients), 67.5% had implantation of a dual-chamber pacemaker, 14.8% had implantation of a single-chamber pacemaker and 2.2% had a re-operation of an existing implanted pacemaker.

### 3 The technology

- 3.1 Dual-chamber pacemakers 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 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 depending on whether they inhibit or trigger heart beats (in response to sensed electrical activity in the heart) and whether they are rate responsive (in which the pacing rate varies according to physical activity).
- 3.2 Dual-chamber pacemakers may be associated with a number of adverse reactions. The need 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 and infection of the pacemaker pocket or the leads. Complications arising after pacemaker implantation may include dysfunction of the pacemaker or of the leads (that is, failure to pace or sense appropriately), infection or erosion of the pacemaker site or its leads and the development of pacemaker syndrome, stroke, heart failure or atrial fibrillation. Re-operation may be needed as a result of a complication or end-of-battery life. The complication rate associated with a re-operation to remove or replace leads is higher than that associated with initial implantation. Battery replacement has a very low complication rate when the leads do not need to be removed or replaced.
- 3.3 The acquisition cost of pacemakers depends on the particular model. The Association of British Healthcare Industries estimates an average cost of dual-chamber pacemaker devices of £1,265, and for single-chamber atrial pacemaker devices a price of £718. Costs may vary in different settings because of negotiated procurement discounts.



## 4 Evidence and interpretation

The Appraisal Committee considered evidence from several sources.

### Clinical effectiveness

- 4.1 The Assessment Group 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 due to sick sinus syndrome with no evidence of atrioventricular block, identifying a total of 6 relevant randomised controlled trials. Three of the trials (Albertsen et al. 2008, DANPACE 2011 and Nielsen et al. 2003) were parallel group trials (see sections 4.2 to 4.5) and 3 of the trials (Gallick et al. 1994, Lau et al. 1994 and Schwaab et al. 2001) were crossover trials (see sections 4.6 to 4.9).

### Parallel group trials

- 4.2 The parallel group trials randomised participants to receive either a single-chamber atrial pacemaker device or a dual-chamber pacemaker device. The trials varied in size from 50 to 1415 randomised participants, the mean age was similar across the 3 parallel trials and between study arms (72 to 74 years), and either all or most of the 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. At baseline, most of the participants had their condition classed (according to the New York Heart Association [NYHA] class – used to classify the extent of heart failure according to the severity of symptoms) as I or II (96%) at the end of follow-up with no or mild symptoms of heart failure. The Assessment Group conducted random-effect model meta-analyses for the parallel trials where appropriate, generating odds ratios.

- 4.3 Albertsen et al. (2008) compared the impact of dual-chamber pacemaker devices (n=26) with single-chamber atrial pacemaker devices (n=24) on left ventricular desynchronisation in people with sick sinus syndrome, including those with sinus arrest or 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 or difference in the timing of contraction in the different segments within the left ventricle) from baseline to 12 months of follow-up. Secondary outcomes included the measurement of N-terminal prohormone of brain natriuretic peptide (a hormone released in response to heart problems) and a 6-minute walk test.
- 4.4 DANPACE (2011) compared rate-responsive dual-chamber pacemakers (n=708) with rate-responsive single-chamber atrial pacemakers (n=707) for treating sick sinus syndrome (including those with sino-atrial block or sinus-arrest, sinus bradycardia and bradycardia-tachycardia). The study was based in Denmark, the 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 or chronic atrial fibrillation, stroke, cardiovascular mortality, need for pacemaker re-operation and quality of life.
- 4.5 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 trial had 2 dual-chamber pacemaker arms, with different programmed atrioventricular block delay: short atrioventricular delay (less than 150 milliseconds, n=60) and long atrioventricular delay (a fixed delay of 300 milliseconds, n=63). The study was based in Denmark and mean follow-up was 2.9 years. The primary outcome was changes in left atrial size and left ventricular size and function during follow-up. Secondary outcomes were cardiographic (changes in left atrial volume, left ventricular volume and left ventricular ejection fraction) and clinical (atrial fibrillation, thromboembolism, all-cause and cardiovascular mortality, and congestive heart failure). The Assessment Group noted that there were some imbalances between the trial arms for the subtypes of sick sinus syndrome.

## Crossover trials

- 4.6 In the crossover trials, all participants had a dual-chamber pacemaker device implanted, and were then randomised to either single- or dual-pacing modes and then later crossed over to the alternative pacing mode. Lau et al. (1994) and Schwaab et al. (2001) randomised participants before implant by pacing programme, and Gallick et al. (1994) randomised participants who recently had a pacemaker fitted. The Assessment Group reported that they were unable to undertake meta-analyses on the crossover trials because of a lack of relevant data in all studies.
- 4.7 Gallick et al. (1994) compared dual-chamber pacing mode with single-chamber atrial pacing mode 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 1 pacing mode and, after 0.5 to 1 hour rest, after which the exercise was repeated in the other pacing mode. Gallick et al. excluded people with evidence of atrioventricular node disease or who were unable to exercise. The study location was not reported, and the follow-up was less than 1 day.
- 4.8 Lau et al. (1994) compared dual-chamber, single-chamber atrial and single-chamber ventricular 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 4 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.
- 4.9 Schwaab et al. (2001) compared dual-chamber with single-chamber atrial pacing mode for people with bradycardia-tachycardia syndrome (n=21). Participants spent 4 weeks in each pacing mode before crossing over to the other pacing mode. Participants had to have chronotropic incompetence (that is, an inability of the heart to increase its rate appropriately with increased activity, leading to exercise intolerance), have experienced at least 2 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 (to assess outcomes including exercise duration), number of episodes and total duration of atrial tachyarrhythmia, incidence of atrioventricular block type I, II or III and maximum duration of the longest atrioventricular pause, and percentage of paced atrial and ventricular beats.

## Parallel and crossover trial quality

- 4.10 The Assessment Group 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 (2011) was considered to be a relatively large trial of good quality with a long follow-up, which represents the best available evidence comparing dual-chamber pacing with single-chamber atrial pacing for people with sick sinus syndrome without evidence of atrioventricular block. However, the Assessment Group noted several limitations of the trials. General limitations included that data were not reported consistently across the trials. 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) and the programmed atrioventricular block delay in the dual-pacing mode differed greatly between the trials and study arms, adding heterogeneity to the trials. In addition, new technologies in this area develop rapidly, therefore the implants used in the trials may now be superseded, limiting applicability of the results to current devices. Weaknesses of the parallel trials included that Albertsen et al. (2008) and Nielsen et al. (2003) had small sample sizes and short follow-up in comparison with DANPACE (2011; giving them little weight in meta-analyses), and both DANPACE and Nielsen et al. 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 ventricular size and function in Nielsen et al.) because they were terminated early. Recruitment for Nielsen et al. 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 1,415 patients (of a target of 1900) because of the increasing use of dual-chamber pacemakers with additional features that were not permitted in the trial. Limitations of the crossover trials included that the trials had a small number of participants (n=12 to 21) and short durations (up to 3 months), which limited the possible outcomes and reduced the power to detect differences between pacing modes.

## Clinical effectiveness

- 4.11 The Assessment Group presented the results of the clinical effectiveness of the trials. Where possible for dichotomous outcomes, the Assessment Group undertook meta-analyses and calculated odds ratios with 95% confidence intervals. The Assessment Group 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.

## Change in pacing mode

- 4.12 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. Some people randomised to the dual-chamber pacemaker device arm changed to single-chamber atrial or single-chamber ventricular mode. Some people randomised to the single-chamber atrial pacemaker device arm changed to a dual-chamber pacemaker device (if they developed atrioventricular block) or a single-chamber ventricular device (if they developed atrial fibrillation). A meta-analysis of all 3 parallel group trials comparing 857 people randomised to dual-chamber pacemaker devices with 785 people randomised to single-chamber atrial pacemaker devices, reported that statistically significantly fewer people with a dual-chamber pacemaker changed pacing mode than those in the single-chamber pacemaker group (odds ratio [OR] 0.50, 95% confidence interval [CI] 0.37 to 0.67). Most people who changed from a single-chamber atrial pacemaker changed to a dual-chamber pacemaker, 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 Assessment Group noted that in DANPACE, the results for change in pacing mode and re-operation were probably conservative because the incidence of atrioventricular block leading to these outcomes would have continued to increase over time beyond the follow-up period of the trial.

## Atrial and ventricular pacing

- 4.13 The proportion of atrial and ventricular pacing varied greatly between the studies, study arms and pacing mode, which may have been associated with differences in the level of atrial fibrillation across the trials. In the parallel trials, dual-chamber devices were associated with between 57% and 67% atrial pacing, and ventricular pacing between 17% and 90%. For single-chamber devices, the rate of atrial pacing ranged from 53% to 69%, and ventricular pacing ranged from 3% to 99% (Albertsen et al. [2008], for those who had upgraded from single to dual). In the crossover trials, the rate of dual-chamber atrial pacing was only reported by Schwaab et al. (2001; 95%), and the rate of ventricular pacing was reported by Lau et al. (1994; 64%) and Schwaab et al. (99%). For single-chamber devices, the rate of atrial pacing was not reported, and the rate of ventricular pacing was only reported by Schwaab et al. (95%). The Assessment Group noted that although the dual-chamber pacemakers in DANPACE (2011) were programmed in a way intended to reduce unnecessary ventricular pacing, ventricular pacing was still 65% (with a range of  $\pm 33\%$ ), which may have offset some of the benefit of implanting a dual-chamber pacemaker.

## All-cause mortality

- 4.14 All-cause mortality was reported in DANPACE (2011) and Nielsen et al. (2003), and for both studies there were no statistically significant results. DANPACE (for which the primary outcome was all-cause mortality) had an unadjusted hazard ratio for single- compared with dual-chamber pacemakers of 1.06 (95% CI 0.88 to 1.29), an adjusted (for patient characteristics) 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;  $p > 0.45$ ). For Nielsen et al., the Assessment Group 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.), there was no statistically significant difference in all-cause mortality between dual- ( $n=831$ ) and single-chamber atrial ( $n=761$ ) pacemakers (OR 0.97, 95% CI 0.67 to 1.41).

## Heart failure

4.15 The outcome measures used as a proxy for heart failure varied between the 3 parallel studies, including:

- NYHA class 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 4 or if 2 or more of the following indicators were present:
  - presence of oedema
  - presence of dyspnoea
  - NYHA class 3
- number of people with an increase in consumption of diuretics
- number of people with an increase in at least 1 NYHA class.

There was no statistically significant difference between dual and single atrial pacing for the outcome of heart failure. DANPACE (2011) conducted predefined subgroup analyses for single- compared with dual-chamber pacemakers for a younger (75 years or under) and older (over 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 (hazard ratio [HR] 0.72,



95% CI 0.53 to 1.00,  $p=0.05$ ), 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 1.01 to 1.80,  $p=0.05$ ). All other subgroup analyses were non-significant ( $p>0.31$ ).

## Atrial fibrillation

4.16 DANPACE (2011) 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 2 consecutive follow-up visits and at all subsequent follow-up visits). DANPACE showed that the risk of paroxysmal atrial fibrillation was statistically significantly lower for dual- compared with single-chamber pacemakers (OR 0.75, 95% CI 0.59 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 BMI, and a dilated left atrium at baseline ( $p<0.05$ ). The Assessment Group noted that Nielsen et al. reported conflicting results: 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). The Assessment Group noted that both DANPACE and Nielsen were good-quality trials but stated that, because DANPACE was the larger trial (almost 10 times the size of Nielsen et al.) and had a longer mean follow-up, it was reasonable to have more confidence in the results of DANPACE.

## Stroke

4.17 DANPACE (2011) 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 (for patient characteristics) hazard ratio of 1.11 (95% CI 0.70 to 1.77,  $p=0.65$ ). The results of the Nielsen et al. study were also not statistically significant ( $p=0.32$ ). A meta-analysis of both studies reported no statistically significant difference between dual- and single-chamber pacemaker devices for stroke (OR 0.93, 95% CI 0.60 to 1.45).

## Exercise capacity

- 4.18 Exercise capacity was reported in the parallel trial Albertsen et al. (2008) and in the crossover trials Gallick et al. (1994) and Schwaab et al. (2001). Albertsen et al. reported that at 12 months' follow-up: people with a single atrial pacemaker walked statistically significantly further than patients with a dual-chamber pacemaker ( $p<0.05$ ) based on the 6-minute walking test to assess either exercise tolerance, capacity or both, measuring the distance a person is able to walk over a total of 6 minutes on a hard, flat surface. However, the Assessment Group noted significant uncertainty in this result, which almost did not reach the clinically important difference of 54 to 80 metres, and that no statistical significance had been demonstrated at baseline. Schwaab et al. reported 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. reported no statistically significant difference between the pacing modes when using the upright bicycle exercise to test exercise capacity ( $p=0.74$ ). The Assessment Group 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 the result from Schwaab et al.

## Further surgery

- 4.19 The need for pacemaker re-operation during follow-up was an outcome in DANPACE (2011), in which there were statistically significantly more participants in the single-chamber pacemaker arm needing a re-operation compared with the dual-chamber pacemaker arm (unadjusted HR 1.99, 95% CI 1.53 to 2.59; adjusted [for patient characteristics] HR 2.00, 95% CI 1.54 to 2.61). The only statistically significant difference in reason for re-operation was need for surgical change of

mode of pacing (dual n=4, single n=66,  $p<0.001$ ), primarily from single- to dual-chamber pacemaker because of the development of high-grade atrioventricular block.

## Adverse effects of pacemaker implantation

- 4.20 Only Albertsen et al. (2008) and DANPACE (2011) reported data on adverse effects linked to pacemaker implantation. Albertsen et al. considered complications around device implantation and did not report any adverse events in either dual- or single-chamber atrial pacemakers. DANPACE did not report adverse effects at implantation, but did consider the indications for re-operation during follow-up. Of 1,415 patients in both arms, 240 had 1 or more re-operations during the follow-up period. The more frequent indications for re-operation 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 only indication that was statistically significantly different between the dual and single atrial pacemaker arm was surgical change in pacing mode.

## Health-related quality of life

- 4.21 Quality of life was studied in the crossover trials Lau et al. (1994) and Schwaab et al. (2001). Lau et al. used the Visual Analogue Scale (VAS) for general wellbeing, the Specific Activity Scale (SAS) functional questionnaire, 12-item General Health Questionnaire (GHQ; a measure of current mental health), symptom questionnaire and Somatic Symptoms Inventory (SSI) adapted for local use from the Bradford Somatic Inventory (which assessed 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: the VAS for general wellbeing, VAS Karolinska questionnaire (contains 16 questions on cardiovascular symptoms relevant to pacemaker patients) and SAS functional questionnaire. The Assessment Group noted that results for both general wellbeing 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 wellbeing (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. 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 single atrial and dual pacing modes. The Assessment Group noted that there was a substantial amount of uncertainty around all quality-of-life results, because both trials were relatively small and had limited follow-up.

## Cost effectiveness

- 4.22 The Assessment Group carried out 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; 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 compared with single-chamber atrial pacemakers for people with symptomatic bradycardia caused by sick sinus syndrome and no evidence of atrioventricular block) since the publication of [NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block](#). Therefore, the Assessment Group developed an independent economic model. No other submissions or economic models were provided by the companies as part of this appraisal.

## Identified economic evaluations

- 4.23 The Assessment Group identified 12 papers of relevance in its systematic literature review, which included 2 cost-utility analyses that were relevant to the population in this appraisal: 1 NHS-based (Castelnuovo et al. [2005], developed for [NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for](#)

symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block and 1 non-NHS-based (Oddershede et al. [2014], partly based on DANPACE 2011). Castelnovo et al. compared dual- with single-chamber (atrial or ventricular) pacemakers over a 10-year time horizon for several subpopulations with bradycardia. The Castelnovo 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. Depending on the risk stratification, adjustment, and pooling of data used, the cost effectiveness of dual- compared with single-chamber atrial pacemakers (assessed by calculating net monetary benefit) ranged from £460 to £78,47 when assuming a maximum acceptable incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, and -£1,238 to £10,615 when assuming a maximum acceptable ICER of £30,000 per QALY gained.

## Model overview

- 4.24 The Assessment Group 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 Assessment Group conducted the economic analysis from the perspective of the NHS and Personal Social Services, 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

- 4.25 The model developed by the Assessment Group contained multiple health states. 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 (after re-operation)' health state. The Assessment Group noted that all re-operations were assumed to occur in the single-chamber atrial arm only (because the need to change pacing mode to dual-chamber pacing was the only reason for re-operation with a statistically significant difference between the 2 arms [see sections 4.12 and 4.19]), and all re-operations after the atrioventricular block health state were assumed to be an upgrade to a dual-chamber pacemaker. Only 1 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 need 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.

- 4.26 The Assessment Group populated the model with a cohort that had the same baseline characteristics of the DANPACE (2011) 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 on entry to the model. The Assessment Group stated that this assumption was made to simplify the model.

## Modelled treatment effectiveness

- 4.27 The treatment effect for dual- compared with single-chamber pacemakers was predominantly informed by results from the DANPACE (2011) trial only. The Assessment Group stated that it 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 people with atrial fibrillation, the Assessment Group carried out targeted literature searches.

- 4.28 **Re-operation:** Re-operation was assumed to only occur in the single-chamber arm of the model (see section 4.25). All re-operations following the development of atrioventricular block were assumed to be an upgrade to a dual-chamber pacemaker. For people with single-chamber atrial devices, the need to change pacing mode was predominantly a result of the development of atrioventricular block needing upgrade to a dual-chamber device (see sections 4.12 and 4.19). Therefore, the Assessment Group used the difference in event rates for re-operations between the single- and the dual-chamber arms in DANPACE (2011) that were because of a need for surgical change of pacing mode to estimate the risk of people 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. Because 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. To derive the transition probabilities for the model, the Assessment Group 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. People with single-chamber pacemakers in the stroke or heart failure health states could develop atrioventricular block at the same monthly rate as those not in the heart failure or stroke health states (0.142), and have a re-operation to receive a dual-chamber pacemaker. However, they remained in the stroke or heart failure health states, incurring the cost of re-operation but no change in utility. Re-operation was also possible for some people in the single-chamber atrial arm who developed atrial fibrillation and still needed pacing, where one-third of modelled patients had a re-operation to surgically change pacing mode and receive a single-chamber ventricular pacemaker. However, these patients remained in the atrial fibrillation health state and only incurred the costs of the health state with no change in utility. The Assessment Group 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 of their existing pacemaker.
- 4.29 **Atrial fibrillation, heart failure and stroke (all patients):** For the dual-chamber pacemaker arm, the Assessment Group derived event rates for atrial fibrillation, heart failure and stroke from DANPACE (2011) and Riahi et al. (2012; summary statistics from DANPACE). For the single-chamber arm, the Assessment Group 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 Assessment Group then transformed the event rates into monthly probabilities. The following monthly probabilities were used in the model: paroxysmal atrial fibrillation (dual 0.4%, single 0.5%), chronic atrial fibrillation (dual and single 0.18%), heart failure (dual 0.42%; single 0.46%) and stroke (dual and single 0.08%).

4.30 **Heart failure and stroke (those with atrial fibrillation):** The Assessment Group carried out targeted literature searches to estimate the increased risk of heart failure or stroke for those who also have atrial fibrillation. For heart failure, the Assessment Group 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, the Assessment Group identified a paper by Gallagher et al. (2014), which reported the results of a population-based cohort study of people with atrial fibrillation. Gallagher et al. presented incidence rates of stroke, adjusted for covariates such as risk of stroke, age and smoking status for various scenarios of warfarin therapy (currently exposed, recently exposed, history of exposure or no history of exposure). The Assessment Group 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. The Assessment Group noted this was similar to the monthly rate for those without atrial fibrillation.

4.31 **Mortality:** The Assessment Group 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. People in the 'with pacemaker' health states had the same risk of death as the age- and gender-matched UK general population (because the Assessment Group found no evidence of higher mortality risks for people needing or already implanted with a pacemaker [this assumption was tested in a scenario analysis]). The Assessment Group considered 2 overarching forms of mortality in the model: case fatality and all-cause mortality:

- **Case fatality:** Death directly from the health state experienced. For stroke (with and without atrial fibrillation), the Assessment Group 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 out of 545) and, of these, the number with atrial fibrillation (n=14). People 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 after heart failure for those without atrial fibrillation, the Assessment Group used 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 1 month after developing heart failure (therefore the Assessment Group assumed 19% of people with atrial fibrillation died after heart failure). For those with atrial fibrillation, the Assessment Group used a study by Mosterd et al. (2001, Rotterdam), which included prognostic analyses of a population-based cohort study. Mortality from heart failure in people with atrial fibrillation was associated with a hazard ratio of 2.08 compared with those with heart failure and no atrial fibrillation. The Assessment Group applied this hazard ratio to the probability of death without atrial fibrillation (19%), which generated a probability of death of 34.8%. No case fatality was applied to people with atrial fibrillation alone, as this was found to be non-significant in those older than 60 years in Miyasaka et al. (2007; a 21-year community-based study analysing the all-cause mortality risk of people with atrial fibrillation compared with an age- and gender-matched general population).

- **All-cause mortality:** In addition to death directly from the health state experienced, people within the health states of atrial fibrillation, stroke or heart failure were assumed to be at a generally increased risk of death when compared with the UK general population. Those with atrial fibrillation who also had either stroke or heart failure were assumed to be at further risk of death. The Assessment Group searched the literature for evidence of this increased risk, identifying studies by Pocock et al. (2006; an analysis of data from the CHARM [Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity] programme), Miyasaka et al. and Carter et al. The Assessment Group applied hazard ratios derived from these studies to the risk of death for the age- and gender-matched general population to represent the increased risk of death for heart failure (HR 1.32, taken from Pocock et al.), stroke (3.59 for males, 3.14 for females, taken from Carter et al.), and atrial fibrillation (HR 2.08, taken from Miyasaka et al.). For all-cause mortality for people with atrial fibrillation and heart failure or stroke, the Assessment Group applied hazard ratios derived from these studies to the



risk of death for those with stroke or heart failure without atrial fibrillation. The hazard ratio for stroke and atrial fibrillation was 1.33 (Carter et al.), and the hazard ratio for heart failure and atrial fibrillation was 1.11 (Pocock et al.).

- 4.32 **Adverse events:** The Assessment Group 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.
- 4.33 **Health-related quality of life:** The Assessment Group carried out a systematic review to identify health-related quality-of-life evidence, identifying 6 relevant studies reporting generic, preference-based measures of quality of life. The Assessment Group noted that all of the health-related quality-of-life studies identified for inclusion reported time trade-off 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 comparing 2010 people with sick sinus syndrome who were randomised to either dual- or single-chamber ventricular pacing. PASE was a randomised controlled trial of 407 people comparing dual- with single-chamber ventricular pacing for people with bradycardia, with a primary end point of health-related quality of life. In both trials, patients received dual-chamber pacemakers before randomisation to either dual- or single-chamber ventricular mode. In addition to the identified utility studies, the Assessment Group carried out a targeted literature search for utility associated with stroke (with or without atrial fibrillation), identifying a study by Luengo-Fernandez et al. (2013), which evaluated quality of life after transient ischaemic attack and stroke. People in the dual and single 'requiring pacemaker' health states were assumed to have a utility of 0.725 and those in the dual and single 'with pacemaker' health states had a utility of 0.825 (both utilities taken from Fleischmann et al. [2006], which considered the impact of pacemaker device and mode on quality of life). People in the 'atrial fibrillation' health state had a utility of 0.805 (Fleischmann et al. [2009], which considered the impact of atrial fibrillation on quality of life and functional status after implantation). 'Stroke' (with or without atrial fibrillation) was associated with a utility of 0.64 in month 1 and 0.70 thereafter (Luengo-Fernandez et al. [2013],). 'Heart failure' (with or without atrial fibrillation)

was associated with a utility of 0.64 (taken from Lopez-Jimenez et al. [2002], which described the results of the PASE study). Death was assumed to be associated with a utility of 0.

## Costs

4.34 The Assessment Group identified studies for UK-specific resource use and costing studies of atrial fibrillation, heart failure and stroke from the following sources:

- Townsend et al. (2012): 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.

In addition, the resource use and costs were based on standard UK sources (NHS reference costs 2012 to 2013, Electronic market information tool [eMit] or BNF) for the unit costs applied within the Assessment Group economic model.

4.35 **Device and implantation costs:** The Assessment Group obtained procedure costs (including hardware costs) associated with implantation of a single- (£1,875) or dual-chamber (£2,438) device from a weighted average of episode costs associated with relevant Healthcare Resource Group (HRG) codes (NHS reference costs 2012 to 2013). The Assessment Group assumed that upgrade procedures cost the same as an initial implantation of a dual-chamber device. In sensitivity analyses, the Assessment Group used spell level (rather than episode level) data for each HRG code. The Assessment Group 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.

4.36 **Monitoring costs:** Modelled patients received follow-up checks from a

cardiologist (£86) after pacemaker implantation, for which the Assessment Group used HRG codes. Based on expert clinical opinion, the Assessment Group assumed initial follow-up to be 1 week after implantation, and a second follow-up at 2 months post-implantation and subsequent annual visits. Therefore, the Assessment Group applied the cost of a follow-up visit on entry into the dual and single 'requiring pacemaker' and 'with pacemaker' health states. The cost of a follow-up visit was also applied annually to all patients in the dual and single 'with pacemaker' health states.

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

- If atrial fibrillation was absent, the Assessment Group used a weighted average of episode level costs associated with relevant HRG codes for the occurrence of heart failure (£1,228) or stroke (£1,427).
- If atrial fibrillation was present, the episode cost of stroke (£11,275) was based on the population-based cohort study reported by Luengo-Fernandez et al. (2013). The Assessment Group found no evidence indicating that the episode cost of heart failure would differ in the presence of atrial fibrillation.

The Assessment Group applied the episode cost of heart failure to people entering the 'heart failure' and 'atrial fibrillation and heart failure' health states. The Assessment Group applied the episode cost of stroke to people entering the 'stroke' health state, and the episode cost of stroke after atrial fibrillation to people entering the 'atrial fibrillation and stroke' health state. If people developed atrial fibrillation and needed their device reprogramming to ventricular mode, they accrued the following costs:

- People with a dual-chamber device: modelled patients accrued the costs of a consultation with a cardiologist (£86) and an ECG (£41), based on HRG codes.
- People with a single-chamber atrial device: modelled patients accrued the cost of a replacement single ventricular device (the Assessment Group assumed an equivalent cost to the single atrial pacemaker of £1,875).

The Assessment Group 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 a sensitivity analysis.

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

- **Heart failure:** the Assessment Group used national prevalence and cost statistics reported in the 2012 British Heart Foundation coronary heart disease statistics publication, calculating the relative prevalence of heart failure as a percentage of cardiovascular disease, and estimating the 2011 UK direct healthcare costs of cardiovascular disease and heart failure, resulting in annual costs of £3,316 per person. The Assessment Group applied this cost monthly (£276 per cycle) to people in the 'heart failure' and 'atrial fibrillation and heart failure' health states.
- **Stroke:** the Assessment Group used the cost of hospitalisation (£1,564 stroke alone, and £3,649 for atrial fibrillation and stroke) estimated from a population-based cohort study reported by Luengo-Fernandez et al. (2012) and the cost of medication (£81) and primary care (£31) for stroke derived from Townsend et al. (2012). The Assessment Group applied the costs monthly to people residing in the 'stroke' (£140 per cycle) and 'atrial fibrillation and stroke' (£400 per cycle) health states.
- **Atrial fibrillation:** the Assessment Group identified long-term costs of £955 per person per year for 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 Assessment Group also assumed that people with atrial fibrillation received effective anticoagulation therapy (£6.45 per cycle) with apixaban, dabigatran etexilate, rivaroxaban or warfarin in addition to the costs of primary and hospital care (because the Assessment Group stated this reflected current clinical guidance). The Assessment Group applied the costs of primary care, hospitalisation and anticoagulation as a cost per cycle of £86.01. The Assessment Group 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.

## Results of the economic analyses

- 4.39 After consultation on the Assessment Group 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 reduced the base-case ICER, and all ICERs in scenario and sensitivity analyses. The original base-case ICERs are described in detail in the [overview](#) and an Erratum has been produced to describe the corrections, both of which are available in the [committee papers](#). This document contains only the corrected ICERs.
- 4.40 The deterministic base-case ICER for dual- compared with single-chamber atrial pacemakers was £6,056 per QALY gained (incremental costs £269, incremental QALYs 0.04), and the mean probabilistic ICER across 1,000 simulations was £6,068 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 Assessment Group 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-chamber devices in 9% of cases.
- 4.41 The Assessment Group carried out one-way sensitivity analyses 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 Assessment Group presented a tornado diagram of the 10 most influential results in the deterministic sensitivity analysis, 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 Assessment Group noted that the parameters most likely to increase the deterministic ICER over £20,000 per QALY gained were:
- highest cost of implant or procedure cost for dual-chamber pacemaker (£23,010 per QALY gained)
  - lowest cost of implant or procedure cost for single-atrial pacemaker (£27,409 per QALY gained)

- lowest risk of heart failure (single-chamber atrial pacemakers dominated dual; the Assessment Group noted that this result was driven by an increase in cost of £710 and a modest reduction in benefit (-0.01).

4.42 The Assessment Group conducted structural sensitivity analyses. 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.

4.43 The Assessment Group conducted scenario analyses on the base-case results, 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 or device replacement for atrial fibrillation in 0% patients (£10,872 per QALY gained)
- reprogramming or device replacement for atrial fibrillation in 100% patients (dual-chamber pacemakers dominated single atrial)
- A cumulative ICER for all 'worst-case' scenarios that combined several assumptions taken from efficacy and cost scenarios that increased the ICER from the base case (monthly cost of heart failure from [NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block](#), the risk of stroke from the meta-analysis conducted by the Assessment Group, spell level costs of implantation, reprogramming or device replacement for atrial fibrillation of 0%, and assuming no difference in risk of developing heart failure between the 2 types of implant; £48,738 per QALY gained).

4.44 To address the uncertainty in the appraisal arising from the lack of a specific list price for pacemaker devices, the Assessment Group conducted a threshold analysis, in which the costs of dual-chamber pacemakers were increased until



the ICER reached £20,000 per QALY gained. When the price of dual-chamber pacemakers was increased by £495 to £2,933 (and the price of single-chamber atrial pacemakers remained at £1,875), the ICER was £19,992 per QALY gained (incremental costs £888.28, incremental QALYs 0.04).

## Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dual-chamber pacemakers, having considered evidence on the nature of symptomatic bradycardia due to sick sinus syndrome and no evidence of atrioventricular block, and the value placed on the benefits of dual-chamber pacemakers by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.45 The Committee considered the experience of people with bradycardia due to sick sinus syndrome and no evidence of atrioventricular block. It noted that the patient expert's personal statement outlined that before pacemaker implantation, initially the cause of ill health was unclear with non-specific symptoms such as tiredness, nausea and light-headedness, later followed by sickness, diarrhoea, exhaustion and fainting. The Committee further noted that for the patient expert, the implantation of a dual-chamber pacemaker led to an improved and more stable quality of life. The Committee heard from the clinical experts that a dual-chamber pacemaker can be programmed to be used as a single-chamber pacemaker, and that the likelihood of re-operation to upgrade from a single-chamber atrial pacemaker to a dual-chamber pacemaker because of the development of atrioventricular block was an important consideration for patients. The Committee recognised that implantation of a pacemaker device was the only effective treatment for people with this condition, and the risk of re-operation was an important consideration in its deliberations.
- 4.46 The Committee considered the treatment pathway for people with symptomatic bradycardia due to sick sinus syndrome without evidence of atrioventricular block. It noted that [NICE's technology appraisal guidance TA88 on dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block](#) had originally recommended single-chamber atrial pacemakers for treatment of the disease, however it heard from clinical experts

that clinical practice had changed since publication of the guidance. Clinical experts noted that in 2012, implantation of a single-chamber atrial pacemaker for any heart condition was rare (of around 40,000 pacemaker implants in the UK, around 165 were single-chamber atrial devices). For pure sinus node disease, dual-chamber devices were now usually implanted because the DANPACE trial had demonstrated a statistically significant reduction with dual-chamber pacemakers in the need for re-operation to surgically change pacing mode, which would be needed following the development of atrioventricular block. The Committee further heard from the clinical experts that most of the pacemaker devices implanted are rate responsive. The Committee concluded that in clinical practice, the pacemaker devices implanted were by default rate responsive, and that dual-chamber rather than single-chamber atrial devices were already being implanted for most patients with the condition.

## Clinical effectiveness

- 4.47 The Committee considered the quality of the evidence comparing dual- with single-chamber atrial pacemakers for people with sick sinus syndrome and no evidence of atrioventricular block. It noted that, although the crossover trials were small and had limited follow-up, the parallel trials were larger, and in particular DANPACE (2011) was a large, high-quality trial, which provided the best available evidence base for this appraisal. It heard from the clinical experts that, because randomisation was assigned before the pacemaker was implanted in the DANPACE trial, approximately 6.5% of those randomised to receive a single-chamber atrial device had instead received a dual-chamber device because it was more clinically suitable at the time of the intervention. The clinical experts stated that because the estimates of clinical efficacy were based on an intention-to-treat analysis, the likely impact of this was to underestimate the efficacy of dual-chamber devices. The Committee concluded that it was satisfied with the quality of the clinical evidence outlined in this appraisal, and that DANPACE and the other trials could be used as a basis for its decision-making.
- 4.48 The Committee considered the clinical-effectiveness evidence for dual- compared with single-chamber atrial pacemakers for the population in this appraisal. It noted that the clinical evidence indicated that there were no statistically significant differences shown for the whole population for several



important outcomes, including mortality, stroke, quality of life and heart failure. However, it noted that dual-chamber pacemakers were associated with a statistically significant reduction in paroxysmal atrial fibrillation, the need to change pacing mode and re-operation. It heard from the clinical experts that, whereas generally there were no differences in a number of clinical outcomes such as mortality, the key reason for preferring a dual-chamber device was a reduced need for re-operation. The Committee concluded that, although there were no statistically significant differences for a number of important outcomes, dual-chamber pacemakers had been clearly demonstrated to statistically significantly reduce the need for re-operation.

- 4.49 The Committee considered the importance of re-operation as an outcome for the population in this appraisal. It heard from the clinical experts that if a single atrial pacemaker is implanted in people with sinus node disease without atrioventricular block, some will need re-operation because of the development of atrioventricular block. However, there was no reliable way to predict who would be affected. The clinical experts stated complications occurred in up to 20% of re-operations, and the risks associated with re-operation should not be underestimated, because they could be unpleasant and severe. This was particularly the case if the subclavian vein had become occluded (that is, the vein used during the placement of pacemaker leads had become blocked), which would make it difficult to explant the existing leads and implant the new leads needed for a dual-chamber pacemaker. The Committee concluded that the reduced need for re-operation was a significant benefit for patients of dual-chamber pacemakers.
- 4.50 The Committee discussed the importance of the degree of ventricular pacing as an outcome for the population in this appraisal. It heard from the clinical experts that in DANPACE (2011), ventricular pacing occurred in around 65% of patients, despite using pacemaker algorithms that were designed to minimise ventricular pacing. It heard from the clinical experts about the adverse effects of unnecessary ventricular pacing, which interferes with the timing of the pacing of the upper and lower chambers of the heart, making it beat more or less efficiently. The long-term effects of this were unpredictable and potentially very harmful, possibly leading to additional morbidities and increased risk of mortality. The clinical experts were in agreement that dual-chamber pacemakers implanted for the treatment of symptomatic bradycardia as a result of sick sinus syndrome

without atrioventricular block should use algorithms that minimise unnecessary ventricular pacing. However, they noted that the dual-chamber pacemakers that have come to market since the publication of DANPACE have been developed to reduce the risk of unnecessary ventricular pacing, and a typical dual-chamber pacemaker used in clinical practice in England would now be expected to unnecessarily pace only around 10% of ventricular beats. The Committee concluded that although the consequences of unnecessary ventricular pacing could be harmful, the capabilities of modern dual-chamber pacemakers had evolved to substantially reduce levels of unnecessary pacing.

- 4.51 The Committee discussed the results of the predefined subgroup analysis in DANPACE (2011) for heart failure, which stratified patients by age. It noted that this analysis demonstrated statistically significant reductions in heart failure with dual-chamber pacemakers compared with single atrial pacemakers for people aged over 75, but higher rates of heart failure for those aged under 75. The Committee noted that the results for this subgroup analysis in DANPACE were only marginally statistically significant (for both groups  $p=0.05$ ) and that the results for the whole population had not shown a statistically significant difference. It heard from the clinical experts that the age-stratified result was unexpected and counterintuitive because the risk of heart failure increases with age, and that they could identify no biologically plausible clinical reason that could explain the result. It heard from the clinical experts that the algorithm for dual-chamber pacemakers in the DANPACE trial had an unusually long atrioventricular delay (which is also longer than used in dual-chamber pacemakers in clinical practice), which is likely to have contributed to a higher rate of ventricular pacing and may have accelerated the onset of heart failure. The clinical experts also noted that since the publication of DANPACE, modern dual-chamber devices had further reduced the level of unnecessary ventricular pacing, which had helped to improve heart outcomes for this population. The Committee therefore concluded that it was likely that the results of the age-stratified subgroup analysis would not be seen in current clinical practice, particularly with the use of newer pacemakers that reduce levels of ventricular pacing.
- 4.52 The Committee considered whether there were any situations in which it would be more appropriate for a person with sick sinus syndrome and no evidence of atrioventricular block to receive a single atrial rather than a dual-chamber

pacemaker. It heard from the clinical experts that this would only occur in very rare and more complex circumstances. One example given was for people who were particularly young with isolated sinus node disease (for example, because of surgical sino-atrial node ablation) and less likely to develop atrioventricular block (because the incidence of atrioventricular block is much higher in older people). The clinical experts explained that in these circumstances, the consequences of vein occlusion in 20 or 30 years' time would be a more important consideration for patients than the need for re-operation as a result of atrioventricular block. The Committee acknowledged that there may be rare and complex circumstances in which, for a small minority of patients with isolated sinus node disease who are at particularly low risk of developing atrioventricular block, the risks and benefits on balance would favour implantation of a single-chamber atrial pacemaker. However, it was not aware of any clinical characteristics or data that could be used to robustly identify these populations. The Committee concluded that, for most people with symptomatic bradycardia due to sick sinus syndrome without atrioventricular block, dual-chamber pacing was associated with clinical benefits compared with single-chamber atrial pacing.

## Cost effectiveness

- 4.53 The Committee considered the cost-effectiveness results generated by the Assessment Group's health economic model. It noted that the estimated probabilistic and deterministic ICERs of approximately £6,000 per QALY gained were very low. However, it agreed that there were high levels of uncertainty in these ICERs, as they were not based on the list price of the devices.
- 4.54 The Committee considered the estimated costs of follow-up with a consultant after pacemaker implantation within the model. It heard from the clinical experts that the costs and frequency of follow-up for single-chamber atrial pacemakers had been underestimated in the model, because in clinical practice the implantation of a single-chamber atrial device includes electrophysiological testing to assess the integrity of atrioventricular conduction and the Wenckebach phenomenon, which had not been included in the modelled costs of a single-chamber atrial pacemaker. The Committee concluded it was plausible that the costs of single-chamber pacemakers may have been slightly underestimated in the economic model; however, this was unlikely to have a significant impact on

the results of the cost-effectiveness analysis.

- 4.55 The Committee considered the estimated costs of pacemaker implantation in the model. It was aware that, when costing devices, the Assessment Group had used a weighted average of HRG codes (which included device and procedure costs), rather than using the list price of the technologies as specified in the [technology appraisals methods guide](#). The Committee heard from the Assessment Group that there were a range of devices with different costs associated, and therefore there was not a specific list price for a dual- or single-chamber atrial device. It further heard from the Assessment Group, the company and the clinical experts that the HRG codes were the most appropriate source to calculate the real-world price paid by commissioners and healthcare resource utilisation for pacemaker implantation, because they took into account the costs of the whole procedure rather than the device alone. The Committee concluded that although a cost-effectiveness analysis based on the list price of pacemakers would have been useful, the use of HRG codes is likely to approximate the real-world costs and resource utilisation of dual-chamber pacemaker implantation.
- 4.56 The Committee discussed the extent of uncertainty that had been generated by the lack of specific list price of devices in the model. It noted that the approach taken by the Assessment Group to use a weighted average of costs instead of list prices could potentially disguise the true cost of more expensive devices, for example, dual-chamber devices with additional capabilities. However, it heard from the clinical experts that, although some devices were more expensive than others and a small minority of patients did need more expensive devices with more complex algorithms, there was no incentive for clinicians to use unnecessarily expensive dual-chamber devices, because the additional pacing algorithms conferred would not be of clinical benefit. The Committee heard from the Assessment Group that in the absence of a single list price, it had conducted an additional exploratory analysis on the impact of device costs on the ICER. This indicated that the price difference between dual- and single-chamber atrial pacemakers had to be increased substantially, and to a level unlikely to be seen in clinical practice, before dual-chamber pacemakers would not be cost effective at a maximum acceptable ICER of £20,000 per QALY gained (see section 4.44). The Committee was therefore sufficiently reassured by the threshold analysis to conclude that the risk of the ICER increasing to a level that would not be considered cost-effective was acceptable for their decision-making.

4.57 The Committee summarised its discussions and reflected on the most plausible ICER for dual- compared with single-chamber atrial pacemakers for people with sick sinus syndrome and no evidence of atrioventricular block. It noted that, in clinical practice, most people were already receiving dual-chamber pacemakers, because the results of DANPACE (2011) had demonstrated a reduced need for re-operation. It further noted that this was a significant benefit of dual-chamber pacemakers, because re-operation was associated with unpleasant and severe complications affecting up to 20% of people having re-operation. The Committee was persuaded that, although the list price of pacemakers had not been incorporated into the model and instead a weighted average of HRG codes for dual- and single-chamber pacemakers had been used, this was acceptable for approximating the costs of the procedures, and the ICERs generated were acceptable for the purpose of decision-making. It concluded that the true ICER was likely to be higher than the estimated probabilistic and deterministic ICERs of approximately £6,000 per QALY gained, because there is no difference in the effectiveness of dual-chamber pacing for outcomes including heart failure, and also because of the higher acquisition cost of dual-chamber pacemakers. However, the higher acquisition costs of dual-chamber pacemakers were likely to be at least partially offset by a reduced need for re-operation. The Committee was further reassured by the threshold analysis that there was a low risk of the ICER increasing to a level that would not be considered cost effective (see section 4.44) when assuming a maximum acceptable ICER of £20,000 per QALY gained. On balance, the Committee concluded that the clinical effectiveness evidence had demonstrated the clinical superiority of dual-chamber devices because of the statistically-significantly-reduced need for re-operation (a significant benefit for patients), and that the cost-effectiveness evidence had shown that the most plausible ICER was likely to be under £20,000 per QALY gained. Therefore dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome with no evidence of atrioventricular block were recommended as a cost-effective use of NHS resources.

## 5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has symptomatic bradycardia due to sick sinus syndrome without atrioventricular block and the healthcare professional responsible for their care thinks that a dual-chamber pacemaker is the right treatment, it should be available for use, in line with NICE's recommendations.

# 6 Appraisal Committee members, guideline representatives and NICE project team

## Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

### **Professor Eugene Milne**

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

### **Professor Kathryn Abel**

Director of Centre for Women's Mental Health, University of Manchester

### **Dr David Black**

Medical Director, NHS South Yorkshire and Bassetlaw



**David Chandler**

Lay Member

**Gail Coster**

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

**Professor Peter Crome**

Honorary Professor, Department of Primary Care and Population Health, University College London

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Greg Fell**

Consultant in Public Health, Bradford Metropolitan Borough Council

**Dr Alan Haycox**

Reader in Health Economics, University of Liverpool Management School

**Emily Lam**

Lay Member

**Dr Nigel Langford**

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

**Dr Allyson Lipp**

Principal Lecturer, University of South Wales

**Dr Claire McKenna**

Research Fellow in Health Economics, University of York

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

**Dr Andrea Manca**

Health Economist and Senior Research Fellow, University of York



**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Dr Anna O'Neill**

Deputy Head of Nursing & Healthcare School and Senior Clinical University Teacher, University of Glasgow

**Alan Rigby**

Academic Reader, University of Hull

**Professor Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Professor Matt Stevenson**

Technical Director, School of Health and Related Research, University of Sheffield

**Dr Paul Tappenden**

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

**Professor Robert Walton**

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

**Dr Judith Wardle**

Lay Member

**Dr Paul Miller**

Director, Payer Evidence, AstraZeneca UK Ltd

## **NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Carl Prescott**

Technical Lead

**Eleanor Donegan**

Technical Adviser

**Nicole Fisher**

Project Manager

## 7 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by BMJ Technology Assessment Group:

- Edwards, S. et al. Dual-chamber pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block, part review of Technology Appraisal 88, July 2014.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope and assessment report. Companies, professional or expert and patient or carer groups, and other consultees, were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Companies:

- BIOTRONIK UK Ltd
- Boston Scientific
- Medtronic
- Sorin Group UK
- St Jude Medical Ltd

Professional or expert and patient or carer groups:

- Arrhythmia Alliance
- South Asian Health Foundation
- STARS (Syncope trust and reflex anoxic seizures)
- British Cardiovascular Society
- Royal College of Nursing

- Royal College of Physicians

Other consultees:

- Department of Health
- Welsh Government
- NHS England
- NHS Harrogate and Rural District CCG

Commentator organisations (without the right of appeal):

- Association of British Healthcare Industries (ABHI)
- Department of Health, Social Services and Public Safety-Northern Ireland (DHSSPSNI)
- Health Improvement Scotland

The following individuals were selected from clinical experts and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on dual-chamber pacemakers by attending the initial Committee discussion and/or providing written evidence to the Committee.

- Dr Chris Plummer, Consultant Cardiologist and Electrophysiologist, nominated by the Association of British Healthcare Industries – clinical expert
- Dr Christopher Lang, Consultant Cardiologist and Electrophysiologist, nominated by Health Improvement Scotland – clinical expert
- Dr Simon Sporton, Consultant Cardiologist, nominated by the British Cardiovascular Society – clinical expert
- Michele Turner, nominated by STARS (Syncope trust and reflex anoxic seizures) – patient expert

Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Medtronic
- Sorin Group UK
- St Jude Medical UK Ltd

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