

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block

1 Guidance

This guidance refers only to pacing for the primary indications of sick sinus syndrome and/or atrioventricular block, and does not cover more complex pacing indications.

- 1.1 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, except:
- in the management of sick sinus syndrome in patients in whom, after full evaluation, there is no evidence of impaired atrioventricular conduction; in this situation, single-chamber atrial pacing is appropriate
 - in the management of atrioventricular block in patients with continuous atrial fibrillation; in this situation, single-chamber ventricular pacing is appropriate
 - in 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.

2 Clinical need and practice

- 2.1 Abnormal heart rhythms (dysrhythmias) are caused by disturbances in electrical impulse generation or by abnormal conduction between chambers of the heart – principally within the sinus node, atrioventricular (AV) node and

the His–Purkinje network. Dysrhythmias may be fast (tachyarrhythmias) or slow (bradyarrhythmias), and regular or irregular.

- 2.2 Symptoms of bradycardia include faints, falls, dizziness and confusion (manifestations of hypotension), palpitations, fatigue on exertion, difficulty with breathing (dyspnoea) and chest pain. Common pathological conditions that cause bradycardia are sick sinus syndrome, atrioventricular block or a combination of the two.
- 2.3 Sick sinus syndrome is an irreversible dysfunction of the sinus node, a small area of the right atrium in which a small group of cells spontaneously depolarise and act as the heart's natural pacemaker. Sick sinus syndrome is characterised by impaired impulse formation, which is often the result of chronic fibrotic degeneration or calcification of the sinus node and/or the surrounding atrial tissues.
- 2.4 Atrioventricular block is a failure in the conduction of electrical impulses from the atria to the ventricles. This may be caused by conduction defects at the AV node (situated between the atria and ventricles), bundle of His and/or bundle branches. The AV node captures waves of depolarisation from the atria, which are then transferred to the ventricles via the bundles of His and the Purkinje system (branches of the conducting system). Atrioventricular block may be intermittent or permanent, and it can progress from minimal asymptomatic conduction delay to the ventricles (first-degree), to partial (second-degree) atrioventricular block, or complete (third-degree) atrioventricular block, in which there is no conduction between the atria and ventricles. Although partial atrioventricular block is usually asymptomatic, it carries a high risk of progression to complete block.
- 2.5 The diagnosis of sick sinus syndrome and atrioventricular block is based on the correlation of symptoms with electrocardiographic findings (electrocardiogram [ECG] and ambulatory ECG or Holter monitoring). The prognosis of individuals with sick sinus syndrome or atrioventricular block is variable and difficult to predict because it may depend on the presence and

severity of comorbidities (such as ischaemic heart disease) and the underlying cause of the conduction defect.

- 2.6 The prevalence of sick sinus syndrome is thought to be about 0.03% of the whole population, and increases with age. Estimates of the prevalence of atrioventricular block (based on clinical studies) range from 0.015% to 0.1%, although it is common for people to have coexisting abnormalities of both the sinus node and the AV node.
- 2.7 Pacemakers are indicated for use in the treatment of symptomatic bradycardia, and they control or replace the heart's intrinsic electrical activity. Some patients require intermittent pacing, whereas patients whose intrinsic heart rate is slow for most of the time require a pacemaker to pace most of their heartbeats.
- 2.8 Pacing systems 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 pacemaker senses whether an intrinsic depolarisation has occurred. When this has not occurred, the pacemaker generates an electrical impulse, which is delivered to the heart muscle via the pacemaker leads to initiate contraction.
- 2.9 Pacemakers may be broadly classified as single- or dual-chamber devices, depending on whether leads are applied to one or two heart chambers. A range of additional features is also available, such as rate modulation (which allows the pacing rate to increase in response to physical activity or metabolic demand).
- 2.10 The British Pacing and Electrophysiology Group (BPEG) and the North American Society of Pacing and Electrophysiology have developed nomenclature that describes the different types of pacemakers (see Appendix D).

- 2.11 Pacemaker syndrome refers to a group of symptoms that includes nausea, palpitations, chest pain, fatigue, breathlessness, pre-syncope and syncope. The underlying cause of pacemaker syndrome is not fully understood. It is thought to be caused by loss of the heart's natural AV sequence, causing simultaneous contraction of the atria and ventricles. Under these circumstances, blood in the atrial chamber is not efficiently expelled into the ventricles, which results in large reductions in systolic blood pressure and cardiac output. There are difficulties in the diagnosis of pacemaker syndrome because of the overlap of the symptoms of pacemaker syndrome with many symptoms typical of cardiac disease, and with symptoms arising from comorbidities, particularly in elderly patients. Pacemaker syndrome may develop in patients with functional atria who receive a single-chamber ventricular pacemaker. Severe pacemaker syndrome can be eradicated by an upgrade to a dual-chamber pacemaker, although this may be associated with an increased risk of perioperative complications. Patients with mild pacemaker syndrome often adapt over time to the condition and do not require a pacemaker upgrade.
- 2.12 Dual-chamber pacing and single-chamber atrial pacing (in patients with sick sinus syndrome without atrioventricular block), as opposed to single-chamber ventricular pacing, are considered to be 'physiological' pacing modes because AV synchrony is maintained and the frequency of contractions of the atria and ventricles varies with metabolic demand, mimicking the heart's natural rhythm.
- 2.13 In the UK, about 26,000 pacemakers are implanted each year. In 2003, about 60% of implants were dual-chamber pacemakers, 40% were single-chamber ventricular pacemakers, and 1% were single-chamber atrial pacemakers. Pacemakers may be implanted in patients of any age, although the average age of the recipients of pacemakers was 76 years in 2003.

3 The technology

- 3.1 Dual-chamber pacemakers have pacing leads in the right atrium and ventricle. They are indicated for use in the treatment of atrioventricular block in the absence of continuous atrial fibrillation, and in sick sinus syndrome with atrioventricular block.
- 3.2 The unpublished draft report of the UKPACE cost utility analysis provided information on the aggregate acquisition (discounted) cost of pacemakers. The cost of pacemakers varied according to the type of device (see Appendix D for an explanation of pacemaker nomenclature): VVI £690, VVIR £1099, DDD £1365 and DDDR £2017, all excluding VAT. Atrial leads were £175 and ventricular leads were £172, excluding VAT.
- 3.3 The Association of British Healthcare Industries (ABHI) has advised that the average market (discounted) price of dual-chamber pacemakers is between £1265 (for DDD) and £1713 (for DDDR), excluding VAT, compared with between £658 (for VVI) and £935 (for VVIR) for single-chamber pacemakers (See Appendix D for definitions of device types). The average price of leads is £169, excluding VAT. The Institute believes that these market prices represent a substantial discount on the list prices of these devices (which have not been provided to the Institute), and these prices may change over time because of environmental factors.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 Clinical effectiveness

- 4.1.1 Outcomes against which the relative effectiveness of dual-chamber and single-chamber pacing were assessed included the incidence of pacemaker syndrome, exercise capacity, functional status, quality of life (QoL), and

incidence of atrial fibrillation, stroke, heart failure, mortality and adverse events.

Dual-chamber pacing versus single-chamber ventricular pacing

- 4.1.2 The Assessment Group searches identified 32 studies of dual-chamber pacemakers versus single-chamber ventricular pacemakers. Four parallel randomised controlled trials (RCTs) allocated a total of 7006 patients to single- or dual-pacing modes (MOST and PASE studies), or single- or dual-chamber devices (CTOPP and the unpublished UKPACE study). Populations varied among the four RCTs and included patients with sick sinus syndrome with or without atrioventricular block (MOST), those with atrioventricular block alone (UKPACE), and mixed populations of patients with sick sinus syndrome and atrioventricular block (PASE and CTOPP). The CTOPP study randomised patients with sick sinus syndrome, with or without atrioventricular block to either single-chamber ventricular pacing or 'physiological' pacing where the device used maintains the heart's natural AV synchrony (dual-chamber pacing in atrioventricular block with or without sick sinus syndrome, and single-chamber atrial pacing in sick sinus syndrome without atrioventricular block). Crossover trials (n = 28) randomised a total of 515 patients with sick sinus syndrome and/or atrioventricular block to dual-chamber pacing or single-chamber ventricular pacing.
- 4.1.3 There was no statistically significant difference in the incidence of mortality or stroke with dual-chamber pacing compared with single-chamber ventricular pacing in the four large RCTs. PASE and CTOPP were, however, conducted in a mixed population of patients with sick sinus syndrome and atrioventricular block, either alone or in combination. The results were presented for the populations as a whole and it was not possible to disaggregate the results for subgroups of patients.

- 4.1.4 The incidence of atrial fibrillation associated with dual-chamber pacing compared with single-chamber ventricular pacing varied among the four large RCTs. The cumulative incidence of atrial fibrillation was up to 21.4% in the dual-chamber pacing arm and 27.1% in the single-chamber ventricular pacing arm. The proportional reduction in the relative risk of atrial fibrillation with dual-chamber pacing reached significance in two of the studies (MOST: adjusted hazard ratio 0.77, 95% confidence interval [CI] 0.64 to 0.92; and CTOPP: reduced annual risk with dual-chamber pacing of 18%, 95% CI 5.5 to 43.6%). A meta-analysis of the results of three of the published RCTs (excluding the UKPACE study) demonstrated a statistically significant reduction in the incidence of atrial fibrillation with dual-chamber pacing (odds ratio 0.76, 95% CI 0.65 to 0.90). A meta-analysis incorporating the results of the unpublished UKPACE trial was also made available, in confidence, to the Appraisal Committee.
- 4.1.5 The MOST study had the highest power to detect differences in the incidence of atrial fibrillation with dual-chamber pacing and single-chamber ventricular pacing because it was a large trial in patients with sick sinus syndrome (thought to be one of the risk factors for atrial fibrillation) and the patients in this study had the highest incidence of prior non-chronic atrial fibrillation (up to 47%), which is also a risk factor for recurrence. The MOST study also reported a statistically significant higher incidence of atrial fibrillation with pacemaker dependency (compared with pacemaker non-dependency) of 1% with dual-chamber pacing (95% CI 0.2 to 1.8%; $p = 0.01$) and 0.7% with single-chamber ventricular pacing (95% CI 0 to 1.4%; $p = 0.04$) for every 1% increase in the proportion of ventricular beats paced.
- 4.1.6 Two published RCTs (MOST and CTOPP) reported a lower incidence of heart failure with dual-chamber pacing (which reached significance in one of the studies) compared with single-chamber ventricular pacing. Results of the meta-analysis of these two studies showed no overall difference in the rate of heart failure with dual-chamber pacing compared with single-chamber ventricular pacing (pooled odds ratio 0.83; 95% CI 0.66 to 1.05). A

meta-analysis incorporating the unpublished UKPACE trial was also made available, in confidence, to the Appraisal Committee.

- 4.1.7 A meta-analysis of the 20 crossover studies showed a statistically significant improvement in exercise capacity with dual-chamber pacemakers compared with single-chamber ventricular pacemakers (standardised mean difference 0.35, 95% CI 0.17 to 0.52; $p < 0.0001$). These benefits were evident when dual-chamber pacemakers were compared with non-rate-responsive single chamber ventricular pacemakers (standardised mean difference 0.49, 95% CI 0.1 to 0.89; $p < 0.01$). A meta-analysis of exercise capacity with dual-chamber pacing compared with single-chamber ventricular pacing demonstrated no difference in exercise capacity for patients older than 75 years (standardised mean difference 0.19; 95% CI -0.08 to 0.45), but there was a statistically significant improvement for patients younger than 75 years (standardised mean difference of 0.47; 95% CI 0.21 to 0.73). A meta-analysis of perceived exercise capacity reported in eight crossover studies showed a statistically significant improvement with dual-chamber pacing (standardised mean improvement 0.68; 95% CI 0.29 to 1.08).
- 4.1.8 A meta-analysis of 12 studies reporting global measures of QoL, obtained using visual analogue scales, showed a statistically significant improvement in QoL with dual-chamber pacing compared with single-chamber ventricular pacing. Three of the four RCTs evaluated QoL using the SF-36 (UKPACE data on QoL was not available for the Assessment Report). The MOST study reported statistically significant improvements in QoL with dual-chamber pacing in some of the QoL domains (improvement in physical function, physical role, social function, energy and emotional role, but not in mental health, pain and general health). The PASE study showed an improvement in QoL for domains of social function, physical role, emotional role, mental health and energy in the short-term at 9-month but not at 18-month follow-up. The CTOPP study did not provide a separate analysis of dual-chamber versus single-chamber ventricular pacing.

4.1.9 The four large RCTs reported large variations in the incidence of pacemaker syndrome with single-chamber ventricular pacing. The incidence reported in trials comparing pacing modes ranged from 18.3% to 26.1%, whereas trials comparing pacing devices reported a 4% rate of upgrade from single-chamber ventricular pacing to dual-chamber pacing as a result of pacemaker syndrome. A meta-analysis (based on the assumption that pacemaker syndrome does not occur in dual-chamber pacing) of the three published RCTs showed a statistically significant reduction in the incidence of pacemaker syndrome with dual-chamber pacing compared with single-chamber ventricular pacing. This was confirmed by the pooled analysis of 14 crossover studies, which reported a statistically significant improvement in the symptoms of pacemaker syndrome with dual-chamber pacing (standardised mean difference -0.88 ; 95% CI -1.13 to -0.62). A meta-analysis incorporating the results of the UKPACE trial was also made available, in confidence, to the Appraisal Committee.

Dual-chamber pacing versus single-chamber atrial pacing

4.1.10 Literature searches identified one small parallel RCT and two crossover RCTs that randomised a total of 211 patients with sick sinus syndrome to dual-chamber pacing or single-chamber atrial pacing. The parallel RCT was a pilot study for a larger trial and was underpowered because recruitment was suspended before the target number of patients was reached.

4.1.11 The parallel RCT reported a statistically significant lower incidence of atrial fibrillation with single-chamber atrial pacing compared with dual-chamber pacing (7.4% for single-chamber atrial pacing; 20% for dual-chamber pacing; $p = 0.03$), but no statistically significant difference in mortality (all-cause or cardiovascular mortality), the incidence of heart failure or stroke, functional status (based on specific activity scale scores) or QoL.

4.1.12 One crossover study in 19 patients showed a statistically significant improvement in exercise tolerance based on bicycle ergometer tests with single-chamber atrial pacing compared with dual-chamber pacing

(single-chamber atrial pacing 103 watts, SD 31, compared with dual-chamber pacing 96 watts, SD 27; $p < 0.05$).

- 4.1.13 The incidence of development of atrioventricular block in patients who received single-chamber atrial pacing was variable, ranging from an annual incidence figure of 1.9% in the parallel RCT to a prevalence of 37% found during follow-up in one of the crossover studies.
- 4.1.14 The crossover studies reported no difference in the presence of symptoms of cardiac dysfunction (palpitations, dizziness, chest pain) with dual-chamber pacing compared with single-chamber atrial pacing.

4.2 Cost effectiveness

- 4.2.1 Literature searches identified one systematic review of the cost effectiveness of dual-chamber pacing in patients with sick sinus syndrome, sick sinus syndrome with atrioventricular block or unspecified bradycardia, who were eligible for dual-chamber or single-chamber pacing. The studies included in this review were of limited relevance because they did not incorporate effectiveness data from the recent large parallel-group RCTs, because results were not presented as cost per quality-adjusted life year (QALY), and because of the technological developments in dual-chamber pacing.
- 4.2.2 Three models were submitted to the Institute by consultees, and the Assessment Group also developed two separate Markov models that compared dual-chamber with single-chamber pacing according to whether the underlying cause of bradycardia was sick sinus syndrome or atrioventricular block.
- 4.2.3 The ABHI submitted a discrete event simulation model of the costs and outcomes of DDDR compared with VVIR pacemakers in patients with sick sinus syndrome or atrioventricular block over a 5-year time horizon. Dual-chamber pacing was associated with an incremental cost of £42 and incremental benefits of 0.09 QALYs, giving an incremental cost effectiveness

ratio (ICER) of £477 per QALY. Sensitivity analysis demonstrated that the incidence of severe pacemaker syndrome was the key driver of the cost effectiveness of dual-chamber pacing: assumptions of 0% severe pacemaker syndrome with single-chamber pacing increased the ICER of dual-chamber pacing to £10,444 per QALY.

- 4.2.4 Guidant submitted a Markov model of the costs and outcomes of dual-chamber pacing compared with single-chamber ventricular pacing in a population of patients with sick sinus syndrome and atrioventricular block over a 10-year time horizon. Dual-chamber pacing was associated with an incremental cost of £742 and incremental benefits of 0.399 QALYs over 10 years compared with single-chamber ventricular pacing, giving an ICER of about £1800 per QALY. Sensitivity analysis of the cost effectiveness of dual-chamber pacing in younger patients (50 years of age, over a 30-year time horizon) showed the dominance of dual-chamber pacing, which was less costly and generated more QALYs than did single-chamber pacing.
- 4.2.5 St Jude Medical submitted a model that compared the costs and outcomes of dual-chamber with single-chamber pacing in patients with atrioventricular block and sick sinus syndrome, or sick sinus syndrome alone, over a 7.5-year time horizon. Dual-chamber pacing was associated with an incremental cost of £438, which was offset by a reduction in the cost of adverse events (severe pacemaker syndrome, stroke, heart failure and atrial fibrillation) demonstrating a cost saving of £182 for a mixed population of patients with sick sinus syndrome and atrioventricular block (or the avoidance of 101 adverse events), or a cost saving of £265 for a population of patients with sick sinus syndrome alone (or the avoidance of 56 adverse events). Sensitivity analysis demonstrated that the incidence of pacemaker syndrome had a major effect on the cost effectiveness of dual-chamber pacing.
- 4.2.6 The Assessment Group developed separate models that compared the cost and outcomes of dual-chamber compared with single-chamber pacing in populations of patients with sick sinus syndrome and atrioventricular block

over a 10-year time horizon. The atrioventricular block model compared dual-chamber with single-chamber ventricular pacing, and the sick sinus syndrome model compared dual-chamber with single-chamber atrial pacing. The models were similar in structure. A hypothetical cohort of 2000 75-year-old patients entered each model immediately before pacemaker implantation, during which they could develop perioperative complications. After successful pacemaker implantation, patients progressed through the model in 1-monthly cycles between the following health states: postoperative complications; well with pacemaker; health states associated with complications (atrial fibrillation, heart failure, stroke), which could occur in any arm of the model; mild and severe pacemaker syndrome (which occurred only in the single-chamber ventricular pacing arm); generator expiry; upgrade to a dual-chamber pacemaker; and death. Patients progressed to death from any health state, although the transition probability was specific to the previous health state (for example, risk of death from stroke) where possible.

4.2.7 Baseline estimates of the effectiveness of single-chamber pacing were based on trials identified in the systematic review. The relative effectiveness of dual-chamber pacing was incorporated into the model by applying the relative risk estimates from the meta-analysis or from individual trials to the baseline parameters.

4.2.8 The cost of pacemakers was based on a survey of the annual hardware cost of all pacemakers implanted from 10 hospitals that were involved in the UKPACE study. These costs represent the aggregate acquisition cost of pacemakers contained in the draft report of the unpublished UKPACE cost–utility analysis (see Section 3.2). The proportion of rate-responsive single- and dual-chamber pacemakers used in the model was based on the proportion of rate-responsive and non-rate-responsive devices reported in the clinical trials. In the ventricular pacing arm of the model, 24% of devices were VVI and 76% of devices were VVIR, and in the dual-chamber arm, there was an equal proportion of DDD and DDDR pacemakers. The cost of the implantation procedure was estimated using cost data from the Resource

Cost Initiative and incorporated differences in the costs of dual- and single-chamber devices.

- 4.2.9 Utility estimates were based on the PASE trial (in which a time trade-off method elicited patient preferences for different health states) or reports of studies in the Harvard Catalogue of Preference Scores. Utility for the cycle of pacemaker implantation was 0.76, and the utility of 'well with pacemaker' was 0.925. All complications (including pacemaker upgrade or replacement) were associated, on the basis of clinician's estimates, with a utility decrement of 0.01.
- 4.2.10 The Assessment Group model contained a number of assumptions related to the incidence of complications with different pacing modes. Pacemaker syndrome (4% severe pacemaker syndrome and 22% mild pacemaker syndrome) occurred only in the single-chamber ventricular pacing arm. Patients with severe pacemaker syndrome were upgraded to a dual-chamber pacemaker. Mild pacemaker syndrome was chronic. The progression of atrioventricular block in sick sinus syndrome was modelled only in the single-chamber atrial pacing arm; these patients were upgraded to a dual-chamber device. When atrial fibrillation occurred with dual-chamber pacing, devices were reprogrammed to single-chamber ventricular pacing and patients assumed the same risk of atrial fibrillation, stroke and heart failure as with single-chamber ventricular pacing.
- 4.2.11 The base-case scenario of the atrioventricular block model was based on the UKPACE survey of the market price of pacemakers, and the assumption that mild pacemaker syndrome did not resolve (these patients had a utility of 0.80 for the remainder of their lifetime). Dual-chamber pacing was associated with an increased cost of £700 and an additional 0.082 QALYs at 5 years, giving an ICER of £8500 per QALY. The ICER of dual-chamber pacing decreases as benefits are accrued over a 10-year time horizon, giving an ICER of £5500 per QALY.

4.2.12 One-way sensitivity analysis demonstrated that the variations in implantation cost, and rates of background mortality, perioperative complications, atrial fibrillation, heart failure, stroke and generator replacement had little effect on the cost effectiveness of dual-chamber pacing in atrioventricular block. However, the cost effectiveness of dual-chamber pacing is sensitive to variations in price difference between dual- and single-chamber pacemakers and assumptions about the incidence and resolution of mild pacemaker syndrome. A sensitivity analysis that evaluated the cost effectiveness of dual-chamber pacing based on the market price of devices supplied by the ABHI (Section 3.3) resulted in ICERs of £7000 per QALY (over a 5-year time horizon) and £4600 per QALY (over a 10-year time horizon). Another sensitivity analysis varied the price of pacemakers to approximate the minimum (dual-chamber £5200, single-chamber atrial and ventricular pacemaker £4600), average (dual-chamber £6500, single-chamber atrial and ventricular pacemaker £4900) and maximum (dual-chamber £8400 and single-chamber atrial and ventricular pacemaker £5300) list prices of pacemakers. At the minimum and average assumed list prices of pacemakers, dual-chamber pacing was associated with an ICER of less than £16,000 per QALY at 5 years. However, the ICER rose to £34,000 per QALY when the assumed maximum cost of devices was used. Another sensitivity analysis assumed that 50% of cases of mild pacemaker syndrome resolve per cycle into a controlled state (compared with 0% in the base case). In this scenario, 90% of cases of mild pacemaker syndrome resolve within 4 months, and the ICER is increased to £36,000 per QALY at 5 years and £18,000 per QALY at 10 years.

4.2.13 The results of the model of dual-chamber pacing in sick sinus syndrome demonstrated that dual-chamber pacing is dominated by single-chamber atrial pacing, because atrial pacing generates more QALYs and is less costly than dual-chamber pacing. Sensitivity analysis showed that single-chamber atrial pacing dominates dual-chamber pacing in all scenarios.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of dual-chamber pacing, having considered evidence on the nature of the condition and the value placed on the benefits of dual-chamber pacing by users, those who represent them, and clinical experts. The discussions were also informed by consideration of the clinical appropriateness of pacing for different underlying causes of bradycardia and therefore the need to consider comparisons with single-chamber ventricular pacing separately from those with single-chamber atrial pacing. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee considered evidence on the benefits and risks of dual-chamber pacing compared with single-chamber ventricular pacing. It discussed the difficulties in interpreting the evidence from analyses in mixed populations and acknowledged that some of the large RCTs used pacing modes that may not be clinically appropriate (for example, single-chamber ventricular pacing for sick sinus syndrome without atrioventricular block). The Committee was also aware that RCT evidence from patients with a mean age of 73–80 years may not be applicable to younger patients. The Committee heard from experts that dual-chamber pacemakers are associated with a higher incidence of perioperative complications and that the lifetime of a dual-chamber pacemaker is likely to be 1 year less than a single-chamber ventricular pacemaker. The Committee accepted expert testimony of the significant quality of life and clinical benefits associated with dual-chamber pacing (reduction in the rate of atrial fibrillation, improved exercise capacity and a reduction in the incidence of pacemaker syndrome). Overall the Committee concluded that these benefits outweighed the evidence from the experts on the increased risk of perioperative complications with dual-chamber pacemakers and potential need to replace dual-chamber pacemakers up to 1 year earlier than single-chamber ventricular pacemakers.

- 4.3.3 The Committee reviewed all the data and economic models on the cost effectiveness of dual-chamber pacing compared with single-chamber ventricular pacing in atrioventricular block. The Committee discussed the Assessment Group models, particularly the incidence of and utilities associated with mild and severe pacemaker syndrome, which were key drivers of the cost effectiveness estimates. The Committee heard from experts that the 4% incidence of severe pacemaker syndrome was appropriate, but the model may overestimate the incidence of mild pacemaker syndrome in single-chamber ventricular pacing, and pacemaker syndrome-like symptoms may also occur with dual-chamber pacing, albeit infrequently. The Committee also considered that the disutility associated with mild pacemaker syndrome, and therefore the cost effectiveness of dual-chamber pacing, (utility of 0.80 compared with 0.62 for severe pacemaker syndrome, and 0.925 for 'well with pacemaker') may have been overestimated in the Assessment Group model. Although the Assessment Group model may have overestimated the cost effectiveness of dual-chamber pacing, the Committee concluded that dual-chamber pacing is cost effective even when conservative assumptions around the effects of pacemaker syndrome are considered (see sensitivity analysis discussion, section 4.2.12).
- 4.3.4 The Committee considered the cost effectiveness of dual-chamber pacing compared with single-chamber ventricular pacing based on the market price of devices supplied by the ABHI, and the likely list price of devices. It considered that although the ICER for dual-chamber pacing over single-chamber ventricular pacing (based on the list price of devices) in atrioventricular block is likely to be significantly higher than identified in the Assessment Group model's central estimates, dual-chamber pacing is still likely to be a cost-effective alternative to single-chamber ventricular pacing.
- 4.3.5 The Committee agreed with expert opinion that dual-chamber pacing is clinically inappropriate for the treatment of patients with impaired atrioventricular conduction (atrioventricular block alone, or in combination with sick sinus syndrome) who also present with continuous atrial fibrillation. If

they receive a dual-chamber pacemaker, these patients are at risk of inappropriate atrial capture, which could lead to ventricular tachycardia. Single-chamber ventricular pacing is the clinically appropriate pacing mode for these patients.

- 4.3.6 The Committee considered the evidence on the clinical effectiveness of dual-chamber pacing compared with single-chamber atrial pacing for sick sinus syndrome. The Committee also acknowledged expert testimony indicating that in this population, single-chamber ventricular pacing is not clinically appropriate because of the risk of pacemaker syndrome. The available evidence indicated that single-chamber atrial pacing is likely to be more clinically effective than dual-chamber pacing in the treatment of sick sinus syndrome with normal AV conduction because it is associated with a lower rate of atrial fibrillation and with improved exercise tolerance. This was supported by other evidence from published studies that indicated the superiority of single-chamber atrial pacing over single-chamber ventricular pacing in sick sinus syndrome.
- 4.3.7 Although the evidence indicated the benefits of single-chamber atrial pacing, the Committee was aware that some people with sick sinus syndrome who receive a single-chamber atrial pacemaker may subsequently develop atrioventricular block, and would then require an upgrade to a dual-chamber pacemaker. The Committee recognised that this may mean patients need a second operation, but heard from experts that although the risk of late development of atrioventricular block in patients with sick sinus syndrome is difficult to predict, there were risk factors that could be identified by a thorough evaluation of atrioventricular conduction. The Committee was advised that this evaluation would usually include, as a minimum, the assessment of the standard ECG for the presence of conduction abnormalities. Additionally it may also involve, during pacemaker insertion, pacing of the atrium at different rates (usually between 100 and 130 beats per minute) in order to assess the onset of the Wenckebach phenomenon as a predictor of failure in atrioventricular conduction. The Committee was advised

that, provided a patient receiving a single chamber atrial device undergoes such an evaluation and exhibits none of the risk factors, the incidence of subsequent development of atrioventricular block in patients with sick sinus syndrome is likely to be as low as 1–2% per annum. Experts advised that up to 20% of patients with sick sinus syndrome do not have any evidence of atrioventricular block (after evaluation with provocation testing), and the Committee therefore concluded that single-chamber atrial pacing is suitable for these patients.

- 4.3.8 The Committee appreciated that rate-responsive dual- and single-chamber pacemakers are more costly but may confer additional benefits compared with non-rate-modulating devices. However, based on the evidence presented and the cost-effectiveness analysis, the Committee concluded that decisions about whether to implant a rate-responsive or a non-rate-responsive device should be made using clinical judgement on an individual patient basis.
- 4.3.9 In summary, the Committee concluded that, for most people who have sick sinus syndrome with atrioventricular block, and for those with atrioventricular block without continuous atrial fibrillation, dual-chamber pacing is preferred to single-chamber pacing. The Committee, however, recognised that in certain specific circumstances, single-chamber pacemakers were more clinically appropriate. Single-chamber atrial pacing is the clinically appropriate pacing mode for people with sick sinus syndrome without atrioventricular block in people who had been fully assessed (for example, using Wenckebach rate testing) for the presence of, and risk factors related to, the development of atrioventricular block. In this group, single-chamber ventricular pacing is contraindicated and dual-chamber pacing is associated with an increased incidence of atrial fibrillation. Similarly, single-chamber ventricular pacing is the clinically appropriate pacing mode for people with atrioventricular block with continuous atrial fibrillation (dual-chamber pacing is contraindicated in this group).

4.3.10 The Committee also concluded that, in the management of patients with atrioventricular block (atrioventricular block alone, or in combination with sick sinus syndrome), the presence of additional factors (such as frailty and comorbidities) may need to be taken into account in decision making. Under some circumstances these factors may affect the decision about the clinical appropriateness of dual- or single-chamber ventricular pacing, which should then be made on an individual patient basis, taking into consideration the risks and benefits associated with each pacing mode.

5 Recommendations for further research

- 5.1 The publication of the UKPACE trial will provide additional data on a number of outcomes including quality of life with dual-chamber pacemakers compared with single-chamber ventricular pacemakers.
- 5.2 The ongoing DANPACE trial will provide additional information on the effectiveness of dual-chamber pacing compared with single-chamber atrial pacing in patients with sick sinus syndrome without atrioventricular block.
- 5.3 The Institute recommends that further studies evaluate the incidence of mild pacemaker syndrome, and utilities associated with health states of mild and severe pacemaker syndrome.
- 5.4 Future studies should evaluate the effectiveness of rate-responsive compared with non-rate-responsive pacemakers.
- 5.5 Further research is also recommended into the predictors for the development of atrioventricular block in sick sinus syndrome, to enable clinicians to determine people for whom single-chamber atrial pacing is appropriate.
- 5.6 Further studies should evaluate the effectiveness of dual- and single-chamber pacing at follow-up beyond 5 years (where possible, up to 10 years) for outcomes of mortality, stroke, heart failure, atrial fibrillation and pacemaker syndrome.

6 Implications for the NHS

- 6.1 About 25,000 pacemakers are implanted every year in the UK; three quarters of these are first implants, and one quarter are replacements.
- 6.2 The current hardware cost of pacemaker implantation based on the market cost of pacemakers and leads (see Section 3.2) and the proportion of pacemaker types implanted is about £43 million per year. This may underestimate the annual cost of pacemakers because the market price represents a substantial discount on the list price of pacemakers. However, the Institute does not have access to information on the list price of pacemakers.
- 6.3 Dual-chamber pacemakers accounted for nearly 60% of the pacemakers implanted in 2003. The anticipated additional cost of implementing this guidance is dependent on the increased acquisition cost of dual-chamber pacemakers, the number of patients with continuous atrial fibrillation who are not suitable for dual-chamber pacing, and the likely uptake of dual-chamber pacing. The uptake of dual-chamber pacing is likely to vary between 70% and a theoretical maximum of 90%, for which the implementation cost varies between about £8 million and £10 million per year, based on the current implantation rate of pacemakers. This does not take into consideration potential differences in the staff and theatre costs between procedures for implanting dual- and single-chamber pacemakers. The Institute was made aware that dual-chamber pacing may be associated with slightly more follow-up, which may have implications for the workload of staff in some trusts. However, the Institute does not have sufficient information to estimate the national impact of this guidance on human resources.

7 Implementation and audit

- 7.1 Clinicians who care for people who have symptomatic bradycardia associated with sick sinus syndrome and/or atrioventricular block should review their

current practice and policies to take account of the guidance set out in Section 1.

7.2 Local guidelines, protocols or care pathways that refer to the care of people with symptomatic bradycardia associated with sick sinus syndrome and/or atrioventricular block should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

7.3.1 Dual-chamber pacing is used for the management of symptomatic bradycardia due to sick sinus syndrome, atrioventricular block, or a combination of sick sinus syndrome and atrioventricular block, except in the following circumstances:

- in the management of sick sinus syndrome in a patient for whom, after full evaluation, there is no evidence of impaired atrioventricular conduction; in this situation, single-chamber atrial pacing is used
- in the management of atrioventricular block in a patient with continuous atrial fibrillation; in this situation, single-chamber ventricular pacing is used
- in the management of atrioventricular block (atrioventricular block alone or in combination with sick sinus syndrome), when patient-specific factors influence the balance of risks and benefits in favour of single-chamber ventricular pacing.

7.4 The Central Cardiac Audit Database, which is part of the National Clinical Audit Support Programme, includes the collection of data on the use of cardiac pacemakers.

8 Related guidance

8.1 The Institute has two ongoing related Technology Appraisals:

- Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias – review of NICE Technology Appraisal No 11
- Biventricular pacing (cardiac resynchronisation) for the treatment of heart failure.

8.2 The Institute has one related ongoing Clinical Guideline:

- Atrial fibrillation: risk assessment, diagnosis, treatment and review.
(Publication expected in Summer 2006.)

9 Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators

9.2 The guidance on this technology will be considered for review in January 2007.

David Barnett

Chair, Appraisal Committee

October 2004

Appendix A. Appraisal Committee members and NICE project team.

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches. In order to ensure consistency, the chair of each branch is also a member of a branch of which they are not chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor Ron Akehurst

Dean of School of Health and Related Research, University of Sheffield

Dr Sunil Angris

General Practitioner, Waterhouses Medical Practice, Staffordshire

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor John Cairns

Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Dr Trevor Gibbs

Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Greenford

Mr Sanjay Gupta

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

Professor Philip Home (Vice-Chair)

Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, Molecular and Clinical Pharmacology, University of Sheffield

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle-Upon-Tyne

Dr George Levvy

Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England, Solihull,
West Midlands

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology,
University of Birmingham

Professor John Lumley

Honorary Consultant, The Ernest Cooke Clinic Microvascular Unit, Great Ormond
Street, Bart's and the Royal London NHS Trust, Barbican, London

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, Westlake Surgery, Somerset

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Norman Waugh

Department of Public Health, University of Aberdeen

Mrs Miranda Wheatley-Price

Director of Service Development, Colon Cancer Concern, London

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Eleanor Donegan

Technical Lead, NICE project team

Nina Pinwill

Project Manager, NICE project team

Appendix B Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group.

Castelnuovo E, Stein K, Pitt M et al. *The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome; systematic review and economic evaluation*, May 2004.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and Assessment Report and the Appraisal Consultation Document. Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Biotronik UK Ltd
- ELA Medical UK
- Guidant Ltd
- Medtronic Ltd
- Sorin Biomedica UK Ltd
- St Jude Medical UK Ltd

II Professional/specialist and patient/carer groups:

- British Association for Nursing in Cardiac Care
- British Cardiac Society
- British Geriatrics Society
- Department of Health
- Havering PCT

- Royal College of Physicians
- Royal College of Physicians' Cardiology Committee
- Action Heart
- British Heart Foundation
- Cardiac Risk in the Young
- Long-Term Medical Conditions Alliance
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- National Collaborating Centre for Chronic Conditions
- National Public Health Service for Wales
- NHS Quality Improvement Scotland
- NHS Purchasing and Supplies
- British Society for Cardiovascular Research
- Central Cardiac Audit Database
- Cochrane Heart Group

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. 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 for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the Appraisal Consultation Document.

- Dr Janet McComb, President, British Pacing and Electrophysiology Group
- Ms Jenny Tagney, Cardiology Nurse Consultant, British Association for Nursing in Cardiac Care
- Dr William D Toff, Senior Lecturer in Cardiology, University Hospitals of Leicester NHS Trust

- Dr Gerald Kaye, Consultant Cardiologist, Cochrane Heart Group.
- Mr Anthony Roth, Havering PCT
- Mrs Eddie Farrow, Cardiac Risk in the Young

Appendix C Detail on criteria for audit of the use of dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block

Possible objectives for an audit

An audit could be carried out to ensure that dual-chamber pacing is used appropriately for the management of symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block.

Possible patients to be included in the audit

An audit could be carried out on people with symptomatic bradycardia associated with sick sinus syndrome, atrioventricular block, or a combination of sick sinus syndrome and atrioventricular block who are seen in a reasonable period for audit, for example 3 or 6 months. People with more complex pacing indications should be excluded from this audit.

Measures that could be used as a basis for an audit

The measure that could be used in an audit of the management of symptomatic bradycardia to ensure that dual-chamber pacing is used appropriately as follows.

Criterion	Standard	Exception	Definition of terms
1. Dual-chamber pacing is used for the management of symptomatic bradycardia associated with any of the following:	100% of people with symptomatic bradycardia associated with SSS, AVB or a combination of SSS and AVB	A. The patient has SSS with no evidence of impaired atrioventricular conduction and single-chamber atrial pacing is	Sick sinus syndrome is also known as sinus node dysfunction. See Appendix D for pacemaker nomenclature. Patients who meet

<p>a. sick sinus syndrome (SSS)</p> <p>b. atrioventricular block (AVB)</p> <p>c. a combination of SSS and AVB</p>		<p>used <i>or</i></p> <p>B. The patient has AVB with continuous atrial fibrillation and the risk of inappropriate atrial capture is high and single-chamber ventricular pacing is used</p> <p>C. The patient has AVB (alone or in combination with SSS) and single-chamber ventricular pacing is preferred by the clinician on the basis of consideration of the risks and benefits for the patient-specific factors</p>	<p>exception A must have had a full evaluation, which clinicians will need to define locally for audit purposes.</p> <p>Clinicians will need to agree locally on how consideration of dual- or single-chamber pacing is documented for audit purposes, for example, for exception C with reference to patient factors such as frailty or the presence of comorbidities that may influence the balance of risks and benefits.</p>
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Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **excep**tion listed}{\text{Number of patients to whom the **meas**ure applies}} \times 100$$

Clinicians should review preliminary compliance with each measure and the patients whose care was not consistent with the audit measure. Clinicians may use their clinical judgement and conclude that some patients whose care is not consistent with

the audit measure nevertheless were provided with the most appropriate care for their conditions. Clinicians should then decide whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Appendix D Pacemaker nomenclature

In 1987, the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) set up the NBG (NASPE/BPEG Generic) code to describe different pacing modes. To incorporate new technologies such as dual-chamber pacing, this code was updated in 2002.

- The first letter of the code signifies the chamber being paced:
 - O = none
 - A = atrium
 - V = ventricle
 - D = dual (A + V)
 - (Manufacturers' designation only: S = single [A or V])
- The second letter signifies the chamber being sensed:
 - O = none
 - A = atrium
 - V = ventricle
 - D = dual (A + V)
 - (Manufacturers' designation only: S = single [A or V])
- The third letter signifies the response to sensing:
 - O = none
 - I = inhibited
 - T = triggered
 - D = dual (T + I)
- The fourth letter signifies rate modulation:
 - O (or no letter) = none
 - R = rate modulation
- The fifth letter signifies multi-site pacing:
 - O (or no letter) = none
 - A = atrium
 - V = ventricle
 - D = dual (A + V)

For example, 'DDD' indicates dual-chamber pacing with no rate modulation or multi-site pacing. 'AAI' indicates atrial pacing inhibited by sensed spontaneous atrial depolarisations; no rate modulation or multi-site pacing.