ERRATA

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

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BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to a change in cost required in the economic model. The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
21 Paragraph 2	Changed "£10,288" to "£6,506" Changed "Probabilistic sensitivity analysis reduced this figure to £5,989 principally due to a lowering of the incremental cost" to "Probabilistic sensitivity analysis produced a very similar ICER of £6,068"
21 Paragraph 3	Changed "In order to use a conservative estimate for all subsequent analyses we focused on the deterministic results" to "As the deterministic results and the probabilistic results were so similar all subsequent analyses were based on the deterministic model"
21 Paragraph 4	• Changed "reduced the ICER from £10,288 to £7,691" to " reduced the ICER from £6,056 to £13,425" • Changed "reducing the time horizon to 5 years almost doubled the base case ICER to £19,549" to "reducing the time horizon to 5 years more than doubled the base case ICER to £14,261"
21 Paragraph 5	Changed "); highest cost of implant/procedure for dual pacemaker (ICER £27,242) and" to "),highest implant/procedure cost for dual-chamber pacemaker (ICER £23,010), and"
21 Paragraph 6	Changed "HF (ICER £20,948), using the risk of stroke from the TAG's meta-analysis (ICER £10,912), using spell level costs of pacemaker implantation (ICER £11,837), using monthly cost of stroke from Saka 2009 (ICER £10,901), using reprogramming/device replacement for AF of 0% (ICER £14,806), and using a discount rate of 6% (ICER £11,224)" to "HF (ICER £22,213), using the risk of stroke from the TAG's meta-analysis (ICER £6,438), using spell level costs of pacemaker implantation (ICER £7,605), using monthly cost of heart failure from TA88 (ICER £7,140), using reprogramming/device replacement for AF of 0% (ICER £10,872), and using a discount rate of 6% (ICER £6,938)"
22 Paragraph 1	• Changed "cost of stroke from Saka 2008" to "cost of heart failure from TA88" • Changed "ICER of £49,018" to "ICER of £48,738"
22 Paragraph 2	Changed "When the risk of heart failure is assessed by age, the ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively)" to "When the risk of heart failure is adjusted by age, the ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective)"
23 Paragraph 1	Changed "ICER of £10,288" to "ICER of £6,056"
23 Paragraph 2	Changed "indicates that using dual-chamber pacemakers in older patients is cost-effective, with an ICER of £4,918, while using dual-chamber pacemakers is dominated (i.e. more expensive and less effective) in younger patients compared to single-chamber atrial pacemakers" to "indicates that in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective)"
42 Table 3	• Changed Lau 1994 follow-up from "3 months" to "4 weeks per treatment" • Changed Schwaab 2001 added "per treatment"
43	Changed "patients spent 4 weeks in each pacing mode before crossing over to the other pacing mode" to "patients spent four weeks and three months, respectively, in each pacing mode"
116-117 Table 38	• Changed "Total UK direct healthcare cost of CVD" mean value from "£8,680,892" to "£8,680,892,000" • Changed "Total UK direct healthcare cost of CVD" variance from "95% CI: £6,267,529 to £13,422,948" to "95% CI: £6,267,529,000 to £13,422,948,000" • Changed "Cost of hospital admissions with principal diagnosis of AF" from "£271,600" to "£271,600,000" • Changed "Cost of hospital admissions with principal diagnosis of AF" from "95% CI: £196,093 to £419,965" to "95% CI: £196,093,000 to £419,965,000" • Added "(daily)" to the mean cost for apixaban, dabigatran and rivaroxaban • Added "(monthly)" to the mean cost for warfarin
139	• Changed "Thereafter, the 2011 UK direct healthcare costs of CVD (£9,086,227,882) and of HF (£632,586,584) were estimated. Resulting in a per person cost of HF of £4,112 per annum (£343 per cycle) at 2013 prices" to "Thereafter, the 2011 UK direct healthcare costs of CVD (£8,680,892,000) and of HF (£632,586,584) were estimated. Resulting in a per person cost of HF of £3,316 per annum (£276.34 per cycle) at 2013 prices"
142 Table 56	• Changed "Unit" to "Daily unit" • Changed "Calculated" to "Monthly unit cost calculated"

146 Paragraph 1	• Changed "£6.023.21, whereas single-chamber atrial pacemakers had a mean cost of £5,566.11, resulting in an incremental cost of £457.10" to "£9,211.41, whereas single-chamber atrial pacemakers had a mean cost of £9,480.47, resulting in an incremental cost of £269.06" • Changed "with a resultant ICER of £10,288" to "with a resultant ICER of £6,056"
146 Paragraph 2	• Changed "£8,991.02 across 1,000 simulations, whereas single-chamber atrial pacemakers accrued a mean cost of £8,720.68, thus yielding an incremental cost of £270.34" to "£9,104.81 across 1,000 simulations, whereas single-chamber atrial pacemakers accrued a mean cost of £8,828.23, thus yielding an incremental cost of £276.59" • Changed "Mean QALYs were 5.29" to "Mean QALYs were 5.30" • Changed "resultant ICER of £5,989" to "resultant ICER of £6,068"
147 Table 59	Total costs have been changed from "£5,566.11" to "£9,211.41", "£6,023.21" to "£9,480.47", "£8,720.68" to "£828.23", and "£8,991.02" to "£9,104.81", and incremental costs from "£457.10" to "£269.06", and ICERs from "£10,288" to "£6,056".
147 Paragraph 1	Changed the following percentages "63.40%" to "66.00%", "25.8%" to "24.1%", "10%" to "9%", "72.3%" to "72.9%", "76.6%" to "78.7%".
148	Figures 12 and 13 have been replaced
149 Paragraph 1	• Changed the difference in costs in the deterministic results from "£307.79" to "£224.53" • Changed the incremental costs from "£236.80" to "£228.97" • Changed the ICER from "£14,002" to "£13,837"
149 Paragraph 2	Changed the following percentages "54.2%" to "55.3%" and "63.2%" to "64.0%"
149 Table 60	Total costs have been changed from "£3,544.22" to "£4,854.82", "£3,852.01" to "£5,079.35", "£4,756.14" to "£4718.12", and "£4,992.94" to "£4947.09", and total QALYs from "3.34" to "3.35" and "3.36" to "3.37", and incremental costs from "£307.79" to "£224.53", and "£236.80" to "£228.97", and ICERs from "£19,549" to "£14,261" and "£14,002" to "£13,837"
150	Figures 14 and 15 have been replaced
151 Paragraph 1	Changed the incremental costs of dual-chamber pacemakers from "£306.37" to "£136.43" Changed the ICER from "£7,691" to "£3,425"
151 Table 61	Total costs have been changed from "£5,865.68" to "£9,488.81", and "£6,172.05" to "£9,625.25", and incremental costs from "£306.37" to "£136.43", and ICERs from "£7,691" to "£3,425".
151 Paragraph 2	"and probability of paroxysmal AF" has been deleted "In the case of HF," has been deleted
152	Figure 16 has been replaced
152 Paragraph 2	Changed "doubles the ICER, increasing it to £20,948 from a base case of £10,288" to "quadruples the ICER, increasing it to £22,213 from a base case of £6,056"
152 Paragraph 3	Changed "ICER, increasing it to £10,912" to "ICER, increasing it to £6,438"
153 Paragraph1	• Changed "£11,837 compared with £10,288" to "£7,605 compared with 6,056" • Changed "substantially lower than in the base case and reduced" to "substantially higher than in the base case and increased" • Changed "low ICER" to "slightly higher ICER" • Changed "£1,892 compared with £10,288" to "£7,140 compared with £6,056" • Changed "£8,866 compared with £10,288" to "£3,476 compared with £6,056" • Changed "£5,513 compared with £10,288" to "£5,513 compared with £6,056"
153 Paragraph 2	Changed "£14,806 and a reduction in the ICER to £1,251 in analyses assuming 0% and 100% of people, respectively, required reprogramming/replacement" to "£10,872 assuming 0% of people, required reprogramming/replacement, and dual chamber pacemakers became dominant when this was set to 100% (i.e. less costly and more effective)"
153 Paragraph 3	Changed "£9,202" to "£5,045" and "£11,224" to "£6,938"
153 Paragraph 4	Changed "to £9,174 compared with £10,288" to "£4,942 compared with £6,056"
154 and 155	Table 62 has been replaced
155 Paragraph 1	Changed "£948" to "£2,213"
155 Paragraph 2	• Changed "£49,018 compared to the base case of £10,288" to "£48,738 compared to the base case of £6,056" • Changed "ICER of £28,905 at 10 years" to "ICER of £27,918 at 10 years"
156	Table 63 has been replaced

157	Table 64 has been replaced
157 Paragraph 3	Changed “ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively)” to “ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective)”
158 to 160	Table 65 has been replaced
161 Paragraph 1	Changed “deterministic ICER of £10,288 at 10 years” to “deterministic ICER of £6,056 at 10 years”
161 Paragraph 2	• Deleted “lowest risk of stroke (ICER £20,643);” and “lowest risk of paroxysmal AF (ICER £25,177);” • Changed “highest cost of implant/procedure for dual-chamber pacemaker (ICER £27,242);” to “highest implant/procedure cost for dual-chamber pacemaker (ICER £23,010);” • Changed “lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £31,641)” to “lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £27,409)” • Changed “While the result for the lowest risk of HF may appear to dramatically alter the direction of results, it should be borne in mind that the “dominant” ICER for single-chamber atrial pacemakers is being driven by a modest increase in cost (£391)” to “The result for the lowest risk of HF is being driven by a an increase in cost of £710”
161 Paragraph 3	Changed “highest cost associated with dual-chamber pacemakers increasing the ICER to £27,242, and the lowest cost for single-chamber atrial pacemaker resulting in an ICER in excess of £30,000 (£31,641)” to “the lowest cost for single-chamber atrial pacemaker resulting in an ICER of £27,409.”
161 Paragraph 4	Changed “The ICER from this analysis at 10 years is £5,989, which is notably lower than the deterministic result. This is predominantly due to a reduction in the incremental costs rather than a change in the incremental QALYs.” to “The ICER from this analysis at 10 years is £6,068, which is similar to the deterministic result (£6,056). This is due to a slight increase in the difference in costs and difference in QALYs (£277 and 0.05, respectively).”
161 Paragraph 5	• Changed “about a doubling of the resulting ICER” to “more than a doubling of the resulting ICER” • Changed “£10,288 at 10 years to £19,549 at 5 years” to “£6,056 at 10 years to £14,261 at 5 years”
162 Paragraph 1	Changed “£5,989 at 10 years to £14,002 at 5 years” to “£6,068 at 10 years to £13,837 at 5 years”
162 Paragraph 2	Changed “was modest. The deterministic ICER was reduced to £7,691 at 10 years due to a small reduction in incremental costs” to “almost halved the ICER. The deterministic ICER was reduced to £3,425 at 10 years due to a reduction in incremental costs”
162 Paragraph 3	• Changed “£20,948” to “£22,213” • Deleted “monthly cost for HF from TA88 (ICER £1,892);” • Changed “£14,806” to “£10,872” • Changed “ICER £1,251” to “dual-chamber pacemakers dominant” • Changed “£948” to “£2,213”
162 Paragraph 4	Changed “is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively)” to “in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective),”
166 Paragraph 3	Changed “ICER of £10,288. Probabilistic sensitivity analysis reduced this figure to £5,989 principally due to a lowering of the incremental cost. This reduction in the difference in cost is likely to be due to the non-linearity of the min-max cost of implant/implantation of a single pacemaker compared to the min-max cost of implant/implantation of a dual pacemaker” to “ICER of £6,056. Probabilistic sensitivity analysis produced a very similar ICER of £6,068”
166 Paragraph 4	Changed “In order to use a conservative estimate for all subsequent analyses we focused on the deterministic results” to “As the results for the probabilistic analysis were very similar to the deterministic results we focused on the deterministic results for all subsequent analyses”
166 Paragraph 5	Changed “£10,288” to “£6,056” and “£7,691” to “£3,425” Changed “almost doubled the base case ICER to £19,549” to “more than doubled the base case ICER to £14,261”
166 Paragraph 6	• Deleted “lowest risk of stroke (ICER £20,643);” and “lowest risk of paroxysmal AF (ICER £25,177);” • Changed “highest cost of implant/procedure for dual-chamber pacemaker (ICER £27,242);” to “highest implant/procedure cost for dual-chamber pacemaker (ICER £23,010);”

167 Paragraph 1	• Changed “lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £31,641)” to “lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £27,409)” • Changed “While the result for the lowest risk of HF may appear to dramatically alter the direction of results, it should be borne in mind that the “dominant” ICER for single-chamber atrial pacemakers is being driven by a modest increase in cost (£391)” to “The result for the lowest risk of HF is being driven by a an increase in cost of £710”
167 Paragraph 2	• Changed “£20,948” to “£22,213” • Changed “£10,912” to “£6,438” • Changed “£11,837” to “£7,605” • Changed “stroke from Saka 2009 (ICER£10,901)” to “heart failure from TA88 (ICER £7,140)” • Changed “£14,806” to “£10,872” • Changed “£11,224” to “£6,938” • Changed “£20,948” to “£22,213”
167 Paragraph 3	• Changed “stroke from Saka 2009,” to “heart failure from TA88,” • Changed “£49,018” to “£48,738”
167 Paragraph 4	Changed “assessed by age, the ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively)” to “adjusted by age, the ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective)”
168 Paragraph 2	Changed “base case ICER of £10,288” to “base case ICER of £6,056”
168 Paragraph 3	Changed “that using dual-chamber pacemakers in older patients is cost-effective, with an ICER of £4,918” to “that dual-chamber pacemakers are a dominant treatment option in older patients (i.e. less costly and more effective, with an ICER of £4,918,)”
285 to 287	Appendix 5 One way sensitivity analysis has been replaced

1.4.3 Technology Assessment Group de novo cost-effectiveness analysis

The TAG carried out a *de novo* cost-effectiveness analysis. However, due to concerns around potential clinical heterogeneity as a result of different patient populations (e.g. prior history of atrial fibrillation) and different device programming used (e.g. different % ventricular pacing) in the RCTs identified, the decision was made to base the model on DANPACE. Furthermore, this was supported by clinical expert opinion as DANPACE is the largest trial with the longest follow-up period.

The base case results of the TAG's economic model demonstrate that dual-chamber pacemakers are more expensive but also more effective than single-chamber atrial pacemakers resulting in an ICER of £6,056. Probabilistic sensitivity analysis produced a very similar ICER of £6,068. The likelihood for dual-chamber pacemakers to be cost effective was found to be over 70% at a threshold of either £20,000 or £30,000.

As the deterministic results and the probabilistic results were so similar all subsequent analyses were based on the deterministic model.

Structural sensitivity analysis, incorporating risk of reoperation using the available Kaplan–Meier data from DANPACE reduced the ICER from £6,056 to £3,425. A second structural sensitivity analysis, reducing the time horizon to 5 years more than doubled the base case ICER to £14,261. Based on feedback from our clinical experts a time horizon of 10 years would appear to be the most appropriate as the development of AV block is expected to increase steadily over time.

One-way sensitivity analysis showed the key drivers of cost-effectiveness in the economic model to be: lowest risk of HF (dual pacemakers dominated by single atrial pacemakers), highest implant/procedure cost for dual-chamber pacemaker (ICER £23,010), and lowest cost of implant/procedure for single atrial pacemaker (ICER £27,409).

A series of scenario analyses were undertaken to test the impact on the results when using alternative sources for parameter estimates or challenge assumptions in the model. The scenario analyses that raised the ICER above the base case were: assuming no difference in HF (ICER £22,213), using the risk of stroke from the TAG's meta-analysis (ICER £6,438), using spell level costs of pacemaker implantation (ICER £7,605), using monthly cost of heart failure from TA88 (ICER £7,140), using reprogramming/device replacement for AF of 0% (ICER £10,872), and using a discount rate of 6% (ICER £6,938).

A cumulative "worst case" scenario was also conducted that combined the monthly cost of heart failure from TA88, the risk of stroke from the meta-analysis conducted by the TAG, the spell level costs of implantation, reprogramming/device replacement for AF of 0%, and assuming no difference in risk of developing HF between the two types of implant. This resulted in an ICER of £48,738.

The results of the scenario analysis and the one way sensitivity analysis highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. Subgroup analysis from DANPACE identified a significant difference in HF due to age ($p=0.05$), all other subgroups assessed were non-significant ($p>0.31$). When the risk of heart failure is adjusted by age, the ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

Discussion

This MTA sought to assess the available evidence for dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block in comparison with single-chamber atrial pacemakers. It is a partial update of NICE TA88 (2005), which had a wider remit investigating dual-chamber pacemakers for the treatment of symptomatic bradycardia due to SSS and/or AV block. With regards to the subset of patients of interest to this research, TA88 recommends single-chamber atrial pacemakers for patients with SSS in whom, after full evaluation, there is no evidence of impaired AV conduction.

This MTA uses the best available evidence to explore the clinical and cost-effective implications for using dual-chamber pacemakers rather than single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. DANPACE has demonstrated a significant reduction in re-operation due to need for surgical change of mode of pacing, where it was found to be significantly higher in patients implanted with a single-chamber atrial pacemaker compared with patients implanted with a dual-chamber pacemaker (9.3% vs 0.6%, $p < 0.001$). The difference is primarily due to the development of AV block requiring upgrade to a dual-chamber device. DANPACE also demonstrated a reduced risk of paroxysmal AF with dual-chamber pacing compared to single-chamber atrial pacing (OR 0.75, 95% CI: 0.59 to 0.96). No statistically significant difference was shown between the pacing modes for mortality, heart failure, stroke or quality of life. However, the risk of developing heart failure may vary with age and device.

The *de novo* economic model developed by the TAG shows that dual-chamber pacemakers are more expensive and more effective than single-chamber atrial devices resulting in a base case ICER of £6,056. The ICER remains below £20,000 in probabilistic sensitivity analysis, structural sensitivity analysis, and most scenario analyses and one-way sensitivity analyses.

A potentially important finding of this MTA is the impact that HF may have on the decision to use dual-chamber pacemakers or single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AVB. The results from an analysis based on age (>75 years or ≤75 years) and risk of HF, indicates that in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective). However, these results are based on a subgroup analysis and should be treated with caution.

Strengths, limitations and uncertainties of the analyses

Strengths

- The evidence used to inform the decision problem that is the focus of this MTA has been identified following the general principles published by the Centre for Reviews and Dissemination (CRD).
- Economic analyses have been carried out in accordance with NICE guide to methods of technology appraisal and ISPOR guidance for decision analytic models.
- The economic model used to provide a framework for analysis is based primarily on the economic model constructed in TA88. In addition, parameter estimates have been informed by the best available evidence.
- Expert clinical input has been sought and received throughout the project, in particular with respect to assumptions made in clinical and economic analyses and the face validity of final results and conclusions.

Weaknesses

- The limited number of RCTs available to inform this decision question and the lack of reporting in a consistent manner in those trials identified.

Table 3. Summary of studies included in the review of the clinical effectiveness literature.

Study	Population	Intervention	Comparator 1	Comparator 2	Randomisation	Country	N patients	Follow up	Supplementary publications
Parallel group RCTs									
Albertsen 2008[41]	sinus arrest/sino-atrial block, BTS, sinus bradycardia	DDD(R)	AAI(R)	N/A	device	Denmark	50	12 months	None identified
DANPACE[42]	sino-atrial block/sinus-arrest, sinus bradycardia, bradycardia-tachycardia	DDDR	AAIR	N/A	device	Denmark, UK, Canada	1,415	Mean 5.4 ± 2.6 years	Andersen et al.[43] Nielsen et al.[44] Riahi et al.[45]
Nielsen 2003[46]	sinus bradycardia, sino-atrial block, BTS	DDDR-s	AAIR	DDDR-l	device	Denmark	177	Mean 2.9 ± 1.1 years	Kristensen et al.[47]
Crossover RCTs									
Gallick 1994[37]	sinus node disease	DDDR	AAIR	N/A	programming	NR	12	< 1 day	None identified
Lau 1994[38]	sick sinus syndrome	DDDR	AAIR	N/A	programming	NR	15	4 weeks per treatment	None identified
Schwaab 2001[48]	sinus bradycardia	DDDR	AAIR	N/A	programming	Germany	21	3 months per treatment	None identified

Abbreviations used in table: BTS, bradycardia-tachycardia syndrome; DDDR-s, DDDR with a short programmed atrioventricular (AV) delay; DDDR-l, DDDR with a long programmed AV delay; N/A, not applicable; RCTs, randomized controlled trials.

Six RCTs described and reported in nine publications, were included in the review. The review included one trial (Gallick 1994[37]) that was identified but excluded from the original MTA, TA88.[19] In TA88, studies of less than 48 hours duration, like Gallick 1994, were excluded, whereas no time limitation was specified for the purposes of this review. This review also includes two trials that have been completed and published since TA88; Albertsen 2008 and DANPACE.[41;42]

Information about and results from DANPACE have been published in three publications included in this review: the protocol; the primary publication; and one publication focusing on subgroup analyses of HF data.[42;43;45] One other included trial (Nielsen 2003) was reported in a main publication and an additional paper focusing on AF and thromboembolism analyses.[46;47]

Study design

Three RCTs with a parallel group design (Albertsen 2008, DANPACE, and Nielsen 2003)[41;42;46] and three crossover RCTs (Gallick 1994, Lau 1994, Schwaab 2001)[37;38;48] were identified as relevant and were included in this review.

The follow-up period varied greatly among the included studies. Of the parallel group RCTs, Albertsen 2008 had a set follow up of 12 months,[41] DANPACE had a follow up of up to 10 years with an average of 5.4 ± 2.6 years,[42] and, in Nielsen 2003 the follow up ranged from 6 days to 5.3 years (mean 2.9 ± 1.1 years).[46]

The follow up in the crossover trials was shorter than in the parallel studies. In Lau 1994 and Schwaab 2001, patients spent four weeks and three months, respectively, in each pacing mode before crossing over to the other pacing mode.[38;48] Gallick 1994 studied the immediate effects of pacing mode during exercise: haemodynamic effects were measured during bicycle exercise first in one pacing mode and after 0.5 to 1 hour rest the exercise was repeated in the other pacing mode.[37]

Intervention and comparator

The three parallel RCTs randomised patients to receive single or dual-chamber pacemakers.[41;42;46] In the crossover trials, all patients were implanted with a dual-chamber pacemaker and then randomised to a pacing programme of dual-chamber or single-chamber atrial pacing, followed by the alternate pacing mode.[37;38;48]

Most trials randomised patients before pacemaker implantation, including the trials randomising patients by device (parallel RCTs),[41;42;46] and two of the studies randomising by pacing programme

Heart failure	0.64	95% CI: 0.44 to 0.91	Lopez-Jimenez 2002[11]	5.2.10
AF & Heart failure	0.64	95% CI: 0.44 to 0.91	That values are the same as heart failure without AF[11]	5.2.10
Death	0	N/A	Assumption	5.2.10
Costs				
Unit costs				
Single chamber atrial pacing	£1,875	Estimated 95% CI: £1,191 to £2,366	Weighted average calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Dual chamber pacing	£2,438	Estimated 95% CI: £1,642, £3,040	Weighted average calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Heart failure episode	£1,228	Estimated 95% CI: £1,004 to £1,541	Weighted average calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Stroke episode	£1,427	Estimated 95% CI: £988 to £1,616	Weighted average cost calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Cardiologist Non-Admitted Non-Face to Face Attendance, Follow-up	£86	Estimated 95% CI: £40 to £107	NHS Reference Costs 2012-2013[93]	5.2.11
Total UK direct healthcare cost of CVD	£8,680,892,000	95% CI: £6,267,529,000 to £13,422,948,000[a]	Townsend 2012[94]	5.2.11
Average annual post-stroke hospitalisation cost	£1,444	95% CI: £1,043 to £2,234[a]	Calculated from average of post-first year hospitalization costs (2009 cost year US$ converted to UK£ according to conversion rate reported in study [$1 = £0.64]),Luengo-Fernandez 2012[95]	5.2.11
Total annual UK stroke medication costs	£86,172	95% CI: £62,215 to £133,245[a]	Townsend 2012[94]	5.2.11

Total UK stroke primary care costs	£40,034	95% CI: £28,904 to £61,903[a]	Townsend 2012 [94]	5.2.11
Episode cost of stroke in people with AF	£10,413	£95% CI: £215 to £53,539	Luengo-Fernandez 2013[96]	5.2.11
Average annual post-stroke hospitalisation cost in people with AF	£3,370	95% CI: £0.85 to £24,371	Annual costs for people surviving past the 90-day acute period, Luengo-Fernandez et al[96]	5.2.11
Cost of GP referrals for AF	£49,800	95% CI: £35,955 to £77,004[a]	Stewart 2004[97]	5.2.11
Cost of hospital outpatient referrals for AF	£36,400	95% CI: £26,280 to £56,284[a]	Stewart 2004[97]	5.2.11
Cost of hospital admissions with principal diagnosis of AF	£271,600,000	95% CI: £196,093,000 to £419,965,000[a]	Stewart 2004[97]	5.2.11
Cost of post-discharge outpatient visits	£31,700	95% CI: £22,887 to £49,017[a]	Stewart 2004[97]	5.2.11
Cost of anticoagualation in AF patients: - Apixaban - Dabigatran - Rivaroxaban - Warfarin	 £1.10 (daily) £1.10 (daily) £2.20 (daily) £6.08 (monthly)	N/A	 BNF 67(98) BNF 67(98) BNF 67(98) eMIT(99)	5.2.11

[a] As no measure of uncertainty was reported, a standard error of 0.25 was assumed.

Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; BNF, British National Formulary; eMIT, electronic market information tool; HR, hazard ratio; NHS, National Health Service; ONS, Office of National statistics.

5.2.7 Treatment effectiveness

The effect of dual-chamber versus single-chamber atrial device implantation on the clinical outcomes considered in the TAG economic model were predominantly informed by the results reported from the DANPACE trial. In particular, the risk of reoperation due to change of mode of pacing was

	• £4,428 (AA35B, Stroke with CC Score 13-15); • £2,433 (AA35C, Stroke with CC Score 10-12); • £1,575 (AA35D, Stroke with CC Score 7-9); • £1,060 (AA35E, Stroke with CC Score 4-6); • £1,023 (AA35F, Stroke with CC Score 0-3).	• 9,563 • 28,388 • 58,580 • 114,664 • 92,215	
Stroke following AF[b]		–	£11,275

[a] Weighted average of unit costs; weighted by activity.

[b] Based on 2008/09 cost of £10,413 reported by Luengo-Fernandez et al.[96] inflated to 2013 prices.[109]

Abbreviations used in table: CC, critical care; HRG, Healthcare Resource Group.

Long-term costs

Following the onset of HF, stroke or AF, patients are assumed to accrue costs over the long term, for example, medication, hospitalisation and primary care costs. For people with HF, these costs were determined from national prevalence and cost statistics reported in the 2012 BHF, Coronary heart disease statistics publication.[94] The following data were extracted from the BHF statistics report:

- 2009 total UK direct healthcare costs of cardiovascular disease (CVD): £8,680,892,000;
- 2011 UK prevalence of HF: 0.90% in men and 0.70% in women, total 160,719 cases;
- 2007–2010 UK prevalence of CVD (Table 53).

Table 53. Prevalence of cardiovascular disease, by sex and age, UK 2007 to 2010 (adapted from Table 2.20, Townsend et al[94]

Year	Men	Women
2007	10.9%	9.7%
2008	11.1%	9.4%
2009	11.4%	9.5%
2010	11.7%	10.1%

Based on the prevalence data presented in Table 53 above, the relative prevalence of HF as a percentage of CVD was calculated (7.53% for men and 6.39% for women, average 6.96%). Thereafter, the 2011 UK direct healthcare costs of CVD (£8,680,892,000) and of HF (£632,586,584) were estimated. Resulting in a per person cost of HF of £3,316 per annum (£276.34 per cycle) at 2013 prices.. Full calculation details are available in Appendix 6 Calculation of long-term care costs associated with heart failure. The long-term costs associated with people with HF were applied monthly to people residing in the “Heart failure” and “AF & heart failure” health states.

Warfarin	99.38%	£6.08[b]	Once daily
Monthly cost of oral anticoagulation[c]			**£6.45**

[a] Daily unit cost from BNF67.[98]

[b] Monthly unit cost calculated from a weighted average of quantity and average price, reported in eMiT.[99]

[c] Weighted average of cost, weighted by market share.

The long-term cost associated with people with AF and stroke was applied monthly to people residing in the "AF", "AF & stroke" "AF & heart failure" and health states.

5.2.12 Approach to uncertainty

Assessment of uncertainty associated with the TAG economic model is carried out probabilistically (with mean estimates of costs and QALYs used to calculate the base case results), deterministically (one-way sensitivity analysis) and through structural and scenario analyses.

Probabilistic

The TAG economic model has been constructed probabilistically; that is, to simultaneously account for the impact of parameter uncertainty on the cost-effectiveness results. Probability distributions were assigned to parameters used within the model, from which values have been simultaneously sampled 1,000 times. Table 57 summarises the type of distribution, and rationale for selection of the distribution, used to inform each group of parameters; full details of distributional specifications are provided in Table 38.

Table 57. Probability distributions used for model parameters

Parameter type	Parameter description	Distribution(s) used	Rationale
Probabilities	Probabilities of clinical outcomes with dual-chamber pacemaker and probability of re-operation due to AV block	Beta	Probabilities that are based on the proportion of observed outcomes (i.e., probability of event is 1 – probability of non-event) may be assumed to follow a binomial distribution. Therefore, the beta distribution was used as it is the conjugate of the binomial distribution and is bounded by 0 and 1.[113]
Hazard ratios	Hazard ratios of clinical outcomes with single versus dual-chamber pacemaker	LogNormal	Lognormal distribution was used in order to replicate the "real-world" confidence intervals.[113]

Other		
Alternative discount rates for costs and benefits	Discount rate for costs and benefits assumed to be 1% or 6%	As per NICE methods guides[104]
Market share change for apixaban, dabigatran, rivaroxaban, and warfarin	Assumed 15% receive each of apixaban, dabigatran, and rivaroxaban and 55% receive warfarin	To assess the potential impact of future increased uptake of apixaban, dabigatran, rivaroxaban
Abbreviations used in table: AF, atrial fibrillation; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; TA, Technology Appraisal.		

5.2.13 Base-case results

Incremental deterministic and probabilistic results are presented in Table 59. In the deterministic analysis, the mean costs associated with dual-chamber pacemakers were £9,211.41, whereas single-chamber atrial pacemakers had a mean cost of £9,480.47, resulting in an incremental cost of £269.06. Mean QALYs were 5.56 and 5.51 for dual-chamber pacemakers and single-chamber atrial pacemakers respectively, with a resultant ICER of £6,056 per QALY.

When accounting for uncertainty surrounding parameters, the mean costs associated with dual-chamber pacemakers were £9,104.81 across 1,000 simulations, whereas single-chamber atrial pacemakers accrued a mean cost of £8,828.23, thus yielding an incremental cost of £276.59. Mean QALYs were 5.30 and 5.25 for dual-chamber pacemakers and single-chamber atrial pacemakers respectively, with a resultant ICER of £6,068 per QALY.

Table 59. Base case results

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Deterministic results					
Single-chamber atrial pacemakers	£9,211.41	5.51	–	–	–
Dual-chamber pacemakers	£9,480.47	5.56	£269.06	0.04	£6,056
Probabilistic results					
Single-chamber atrial pacemakers	£8,828.23	5.25	–	–	–
Dual-chamber pacemakers	£9,104.81	5.30	£276.59	0.05	£6,068
Abbreviations used in table: QALY, quality adjusted life year.					

5.2.14 Results of the sensitivity analysis

Probabilistic sensitivity analysis

Using a time horizon of 10 years, the results of the probabilistic analysis are presented below in Figure 12 and Figure 13. Probabilistic sensitivity analysis revealed that, in the majority (66.00%) of cases, implanting patients with dual-chamber pacemakers resulted in greater costs and greater QALYs than implanting single-chamber atrial pacemakers. Furthermore, dual-chamber pacemakers produced more QALYs at a lower cost in 24.1% of cases and were dominated by single-chamber atrial pacemakers in 9% of cases. At a WTP threshold of £20,000, the probability of dual-chamber pacemakers being cost-effective is 72.9%, which increases to 78.7% at a WTP threshold of £30,000.

Figure 12. Scatter plot of cost-effectiveness results for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 10 years (dark blue line indicates threshold of £20,000 per additional QALY, light blue line indicates threshold of £30,000 per additional QALY)

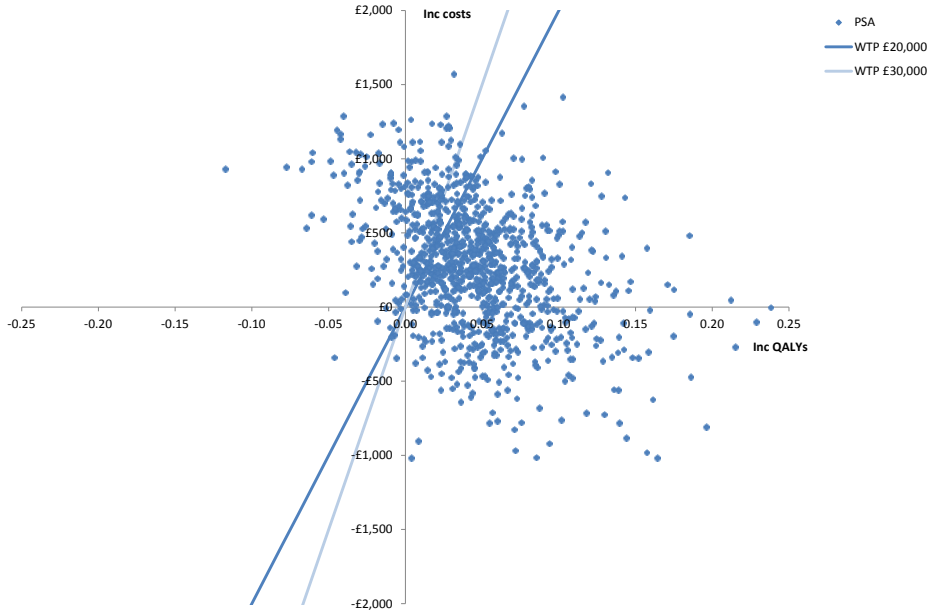
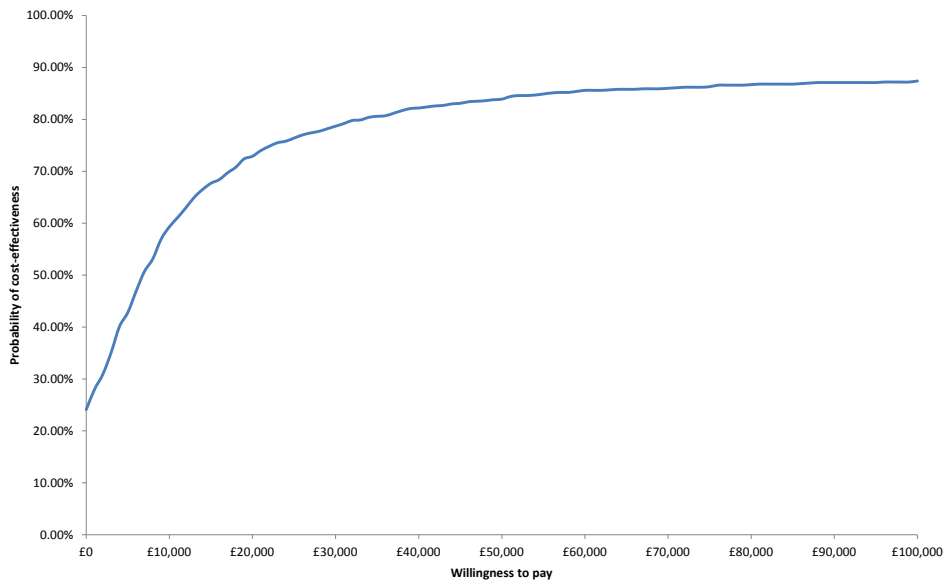


Figure 13. Cost-effectiveness acceptability curve for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 10 years



Structural sensitivity analysis

Table 60 presents the results of the structural sensitivity analysis, where the time horizon was reduced from 10 years to 5 years. The difference in costs in the deterministic results falls to £224.53 with a reduction in QALYs accrued to 0.02. This results in an increase in the deterministic ICER for the base case from £6,056 to £14,261. Similarly, the probabilistic results demonstrate a fall in the incremental costs to £228.97 and a reduction in the incremental QALYs gained to 0.02, resulting in an increased ICER to £13,837. These results are perhaps to be expected, a halving of the time horizon results in a roughly halving of the difference in incremental QALYs and roughly a doubling of the resulting ICER.

The results of the probabilistic sensitivity analysis when the time horizon is reduced to 5 years are presented below in Figure 14 and Figure 15. At a WTP threshold of £20,000 the probability of dual-chamber pacemakers being cost-effective is 55.3%, which increases to 64.0% at a WTP threshold of £30,000.

Table 60. Structural sensitivity analysis using a 5-year time horizon

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Deterministic results					
Single-chamber atrial pacemakers	£4,854.82	3.48	–	–	–
Dual-chamber pacemakers	£5,079.35	3.49	£224.53	0.02	£14,261
Probabilistic results					
Single-chamber atrial pacemakers	£4,718.12	3.35	–	–	–
Dual-chamber pacemakers	£4,947.09	3.37	£228.97	0.02	£13,837
Abbreviations used in table: QALY, quality adjusted life year.					

Figure 14. Scatter plot of cost-effectiveness results for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 5 years (dark blue line indicates threshold of £20,000 per additional QALY, light blue line indicates threshold of £30,000 per additional QALY)

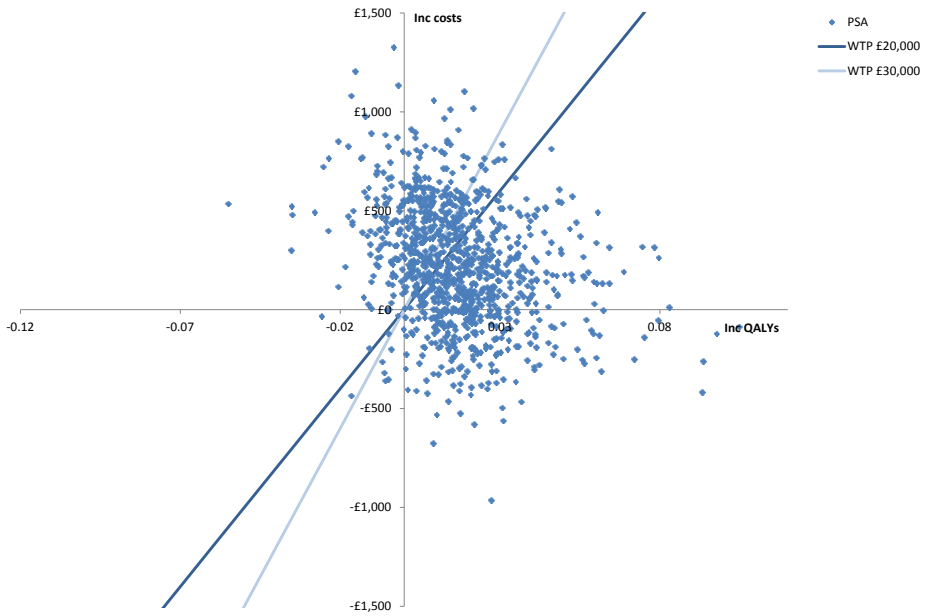


Figure 15. Cost-effectiveness acceptability curve for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 5 years

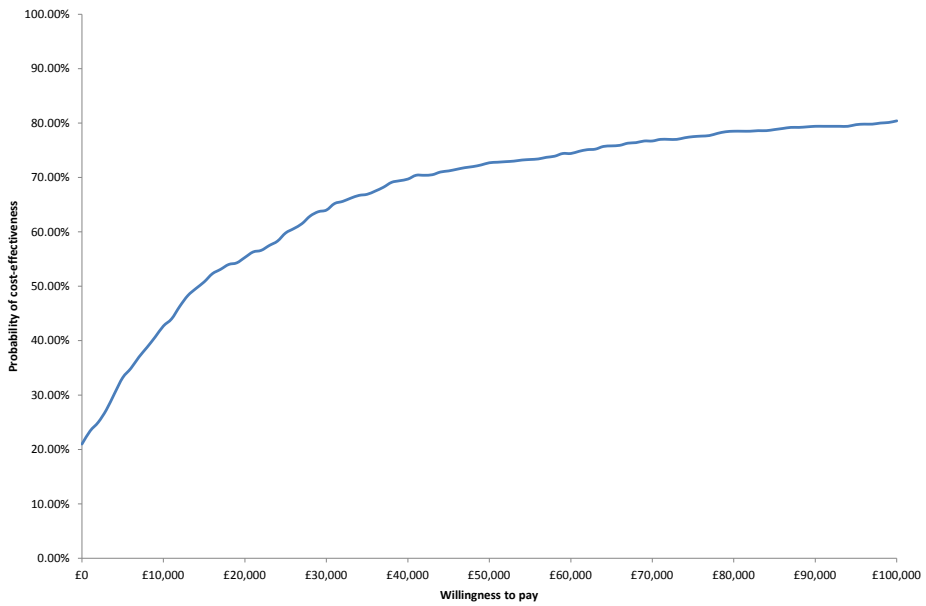


Table 61 shows the results of the structural sensitivity analysis when risk of reoperation was taken from Kaplan–Meier data instead of using a constant risk. The incremental costs of dual-chamber pacemakers decreased to £136.43 while QALYs remained the same compared with the deterministic base case. This caused the ICER to decrease to £3,425 per QALY.

Table 61. Structural sensitivity analysis using Kaplan–Meier data as the basis for reoperation

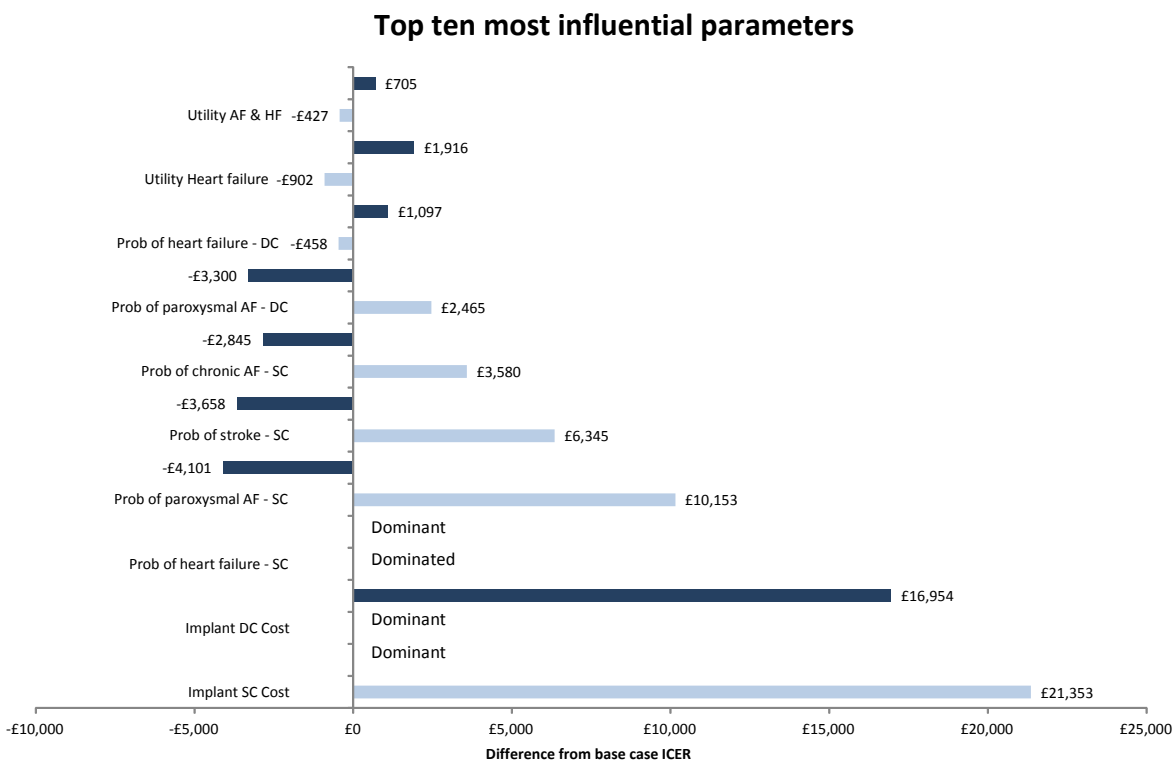
Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Single-chamber atrial pacemakers	£9,488.81	5.52	–	–	–
Dual-chamber pacemakers	£9,625.25	5.56	£136.43	0.04	£3,425
Abbreviations used in table: QALY, quality adjusted life year.					

One-way sensitivity analysis

As discussed in Section 5.2.12, in addition to probabilistic sensitivity analysis, OWSA has been carried out on the following parameters; age; clinical outcomes; health state utility values; and all-cause mortality. The full results of these analyses are presented in Appendix 5 One way sensitivity analysis. The TAG notes that many of the parameters tested in sensitivity analysis had minimal impact on the deterministic cost-effectiveness results and therefore the parameters that the ICER is most sensitive to are presented in Figure 16 below.

The ICER of dual-chamber pacemakers versus single-chamber atrial pacemakers was most sensitive to probability of HF in patients implanted with single-chamber atrial pacemakers. Dual-chamber pacemakers become dominated when the minimal probability is applied to single-chamber atrial pacemakers (i.e. when risk of HF was less likely to occur in patients with single-chamber atrial pacemakers than dual-chamber pacemakers). The ICER was also sensitive to implant/implantation costs for both dual-chamber and single-chamber atrial pacemakers.

Figure 16. Tornado diagram of parameters to which the cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial pacemakers is most sensitive (upper/lower parameter estimate, respectively)



Scenario analysis

As discussed in Section 5.2.12, a series of scenario analyses was conducted to test the robustness of the results to alternative sources for parameter estimates or testing broader assumptions (e.g., reprogramming/device replacement in patients developing AF) within the model. The results of the scenario analyses are depicted in Table 62.

Assuming no difference in the risk of developing HF with the two types of implant almost quadruples the ICER, increasing it to £22,213 from a base case of £6,056.

The only outcome from the meta-analyses conducted in Section 4.2 that could be implemented in the economic model was stroke. However, utilising the risk of stroke from the TAG's meta-analysis (Section 4.2.2) had only a modest impact on the ICER, increasing it to £6,438.

Using spell level costs for pacemaker implantation increased the costs of dual-chamber pacemaker implantation more than single-chamber atrial pacemaker. This resulted in a modest increase in the incremental costs of dual-chamber pacemakers, resulting in a slightly higher ICER (£7,605 compared with £6,056). The alternative cost of HF was higher than in the base case and increased the incremental difference in costs between interventions. This resulted in a slightly higher ICER compared with the base case (£7,140 compared with £6,056). The lower alternative cost of stroke from TA88 had a more modest effect on the incremental cost of interventions and a relatively modest change in ICER compared with the base case (£3,476 compared with £6,056). Similarly, the alternative cost per episode of stroke from Saka 2009 had little impact on the incremental cost or the resulting ICER compared with the base case (£5,513 compared with £6,056).

The proportion of patients experiencing AF resulting in either reprogramming or replacement of their pacemaker was estimated as one-third of patients in the base case, based on advice from clinical experts. This was tested in two extreme scenario analyses in which it was assumed either no one required reprogramming/replacement or that 100% of patients required reprogramming/replacement. These two scenarios had a pronounced impact on the resulting ICERs compared with the base case, with an increase in the ICER to £10,872 assuming 0% of people required reprogramming/replacement, and dual chamber pacemakers became dominant when this was set to 100% (i.e. less costly and more effective).

Varying the discount rate from 3.5% in the base case to either 0% or 6% had a modest impact on the ICER. While costs and benefits increased overall at a discount rate of 0%, the ICER was reduced to £5,045. Similarly, while increasing the discount rate to 6% decreased the cost and benefits overall, the impact on the ICER was an increase to £6,938.

The final individual scenario analysis undertaken was to increase the proportion of prescribing of the novel oral anticoagulants (NOACs) to a more even level with warfarin. This was achieved by setting the market share for warfarin to 55% and the NOAC market share to 45% (evenly distributed in three blocks of 15% to apixaban, dabigatran, and rivaroxaban). This resulted in an overall increase in costs but a reduction in the incremental cost between the two interventions and a modest reduction in the ICER to £4,942 compared with £6,056 in the base case.

Table 62. Scenario analyses using alternative sources for parameter estimates or testing assumptions used within the base case

Analysis	Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**£9,211.41**	**5.51**	**–**	**–**	**–**
	Dual	**£9,480.47**	**5.56**	**£269.06**	**0.04**	**£6,056**
Efficacy						
Assuming no impact on heart failure (i.e., HR set to 1)	Single	£9,025.43	5.54	–	–	–
	Dual	£9,480.47	5.56	£455.05	0.02	£22,213
Stroke used from meta-analysis (Section 4.2.2)	Single	£9,205.51	5.51	–	–	–
	Dual	£9,480.47	5.56	£274.96	0.04	£6,438
Cost scenarios						
Spell level costs of pacemaker implantation from NHS Reference costs 2012–2013	Single	£11,416.24	5.51	–	–	–
	Dual	£11,754.15	5.56	525.94£337.90	0.04	£7,605
Cycle cost for heart failure from TA88	Single	£8,277.74	5.51	–	–	–
	Dual	£8,594.96	5.56	£317.22	0.04	£7,140
Cycle cost for stroke from TA88	Single	£11,150.63	5.51	–	–	–
	Dual	£11,305.08	5.56	£154.44	0.04	£3,476
Cycle cost for stroke from Saka 2009	Single	£9,619.42	5.51	–	–	–
	Dual	£9,864.37	5.56	£244.95	0.04	£5,513
Reprogramming/device replacement for AF in 0% patients	Single	£8,997.42	5.51	–	–	–
	Dual	£9,480.47	5.56	£483.05	0.04	£10,872
Reprogramming/device replacement for AF in 100% patients	Single	£9,639.40	5.51	–	–	–
	Dual	£9,480.47	5.56	£55.60-	0.04	£1,251Domin

				£158.92		ant
Other						
Discount rate 0%	Single	£10,664.51	6.27	–	–	–
	Dual	£10,936.09	6.33	£271.58	0.05	£5,045
Discount rate 6%	Single	£8,380.45	5.07	–	–	–
	Dual	£8,651.45	5.11	£271.00	0.04	£6,938
Market share 55% warfarin 45% NOAC[a]	Single	£9,683.98	5.51	–	–	–
	Dual	£9,903.55	5.56	£219.57	0.04	£4,942

[a] novel oral anticoagulant have equal market share of 15%

Abbreviations used in table: AF, atrial fibrillation; HR, heart rate; NOAC, novel anticoagulant; QALY, quality adjusted life year; TA, technology appraisal.

The results of the individual scenario analyses suggest that the base case ICER is robust to changes in costs of pacemaker implantation, stroke, discount rate and market share of NOACs. In addition, while varying the costs of HF and the proportion of patients requiring reprogramming or replacing their pacemaker due to developing AF to extreme values had a more pronounced impact on the resulting ICER, it was still well below the NICE threshold value of £20,000. In only one scenario, where it was assumed that there is no difference in the development of HF, did the ICER exceed £20,000, and only by £2,213.

A cumulative "worst case" scenario is depicted in Table 63, where each efficacy and cost scenario analyses found to increase the ICER beyond the base case has been combined. This results in an ICER £48,738 compared to the base case of £6,056 at 10 years. However, if the assumption that reprogramming/device replacement due to AF is reinstated as one-third (as in the base case) the cumulative impact of the other adjustments result in an ICER of £27,918 at 10 years.

Overall, the ICER increases beyond £20,000 but remains below £30,000 with the inclusion of an assumption of reprogramming/device replacement for AF in 0% patients or the inclusion of an assumption of no impact on HF in the cumulative "worst case" scenario. It only exceeds £30,000 when both are included in the cumulative "worst case" scenario.

Table 63. Summary of cumulative effect of all sensitivity analyses found to increase the ICER from the base case

Analysis	Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**£9,211.41**	**5.51**	**–**	**–**	**–**
	Dual	**£9,480.47**	**5.56**	**£269.06**	**0.04**	**£6,056**
Stroke used from meta-analysis (Section 4.2.2)	Single	£9,205.51	5.51	–	–	–
	Dual	£9,480.47	5.56	£274.96	0.04	£6,438
Cycle cost for heart failure from TA88	Single	£8,271.06	5.51	–	–	–
	Dual	£8,594.96	5.56	£323.90	0.04	£7,584
Spell level costs of pacemaker implantation from NHS Reference costs 2012–2013	Single	£10,476.27	5.51	–	–	–
	Dual	£10,868.64	5.56	£392.37	0.04	£9,187
Reprogramming/device replacement for AF in 0% patients	Single	£10,092.06	5.51	–	–	–
	Dual	£10,868.64	5.56	£776.58	0.04	£18,183
Assuming no impact on heart failure (i.e., HR set to 1)[a]	Single	£9,956.17	5.54	–	–	–
	Dual	£10,868.64	5.56	£912.47	0.02	£48,738

[a] As assumed in Oddershede et al.[59]

Abbreviations used in table: AF, atrial fibrillation; HF, HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality adjusted life year.

The overall adjusted hazard ratio for risk of developing HF used in the base case indicates a non-significant increase in risk with single-chamber atrial pacemakers compared with dual-chamber pacemakers (HR 1.09, 95% CI: 0.88 to 1.35).[45] Based on feedback from our clinical experts, and as was assumed in Oddershede et al.,[59] we conducted a scenario analysis assuming that there was no difference in risk of HF based on implanted device (i.e. HR 1.00).

The results of the scenario analysis and the OWSA highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber

atrial pacemakers depending on the data used. These results warranted further investigation into HF for which we assessed the subgroups analysed from DANPACE.[45]

The subgroups identified as statistically significant in an analysis of risk of HF from DANPACE were due to age (p=0.05), all other subgroups assessed were found to be statistically non-significant (p>0.31).[45] As additional scenario analyses we explored the impact of using the HRs for the subgroups based on age (patients >75 years or patients ≤75 years). The results are depicted in Table 64.

Table 64. Additional scenario analyses investigating the impact of heart failure compared to the base case results

Analysis	Intervention	Heart failure HR[a]	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**1.09 (95% CI: 0.88 to 1.35)[b]**	**£9,211.41**	**5.51**	**–**	**–**	**–**
	Dual		**£9,480.47**	**5.56**	**£269.06**	**0.04**	**£6,056**
Assuming no impact on heart failure	Single	1.00 (N/A)	£9,025.43	5.54	–	–	–
	Dual		£9,480.47	5.56	£455.05	0.02	£22,213
Patients >75 years[45]	Single	1.34 (95% CI: 1.00 to 1.80)[c]	£9,706.42	5.45	–	–	–
	Dual		£9,480.47	5.56	-£225.94	0.11	Dominant
Patients ≤75 years[45]	Single	0.72 (95% CI: 0.53 to 1.00)[c]	£8,418.67	5.61	–	–	–
	Dual		£9,480.47	5.56	£1,061.81	-0.06	Dominated

[a] HR for single-chamber atrial pacemaker vs dual-chamber pacemaker

[b] HR adjusted for age, sex, hypertension, diuretic treatment, LVEF, prior myocardial infarction, PQ interval, and NYHA class.

[c] p = 0.05

Abbreviations used in table: HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QALY, quality adjusted life year.

The additional scenario analyses highlight the impact that risk of heart failure has on the results. When the risk of heart failure is adjusted by age, the ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective),

whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

5.2.15 Summary of the Technology Assessment Group *de novo* economic evaluation

An overall summary of the results from the TAG's economic model is presented in Table 65.

Table 65. Summary of results comparing the cost-effectiveness of dual-chamber pacemakers with single-chamber atrial pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block

Analysis	Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**£9,211.41**	**5.51**	**–**	**–**	**–**
	Dual	**£9,480.47**	**5.56**	**£269.06**	**0.04**	**£6,056**
Structural sensitivity analyses						
Time horizon reduced to 5 years	Single	£4,854.82	3.48	–	–	–
	Dual	£5,079.35	3.49	£224.53	0.02	£14,261
Utilising Kaplan–Meier data as the basis for reoperation	Single	£9,488.81	5.52	–	–	–
	Dual	£9,625.25	5.56	£136.43	0.04	£3,425
Probabilistic sensitivity analyses						
Base case	Single	£8,828.23	5.25	–	–	–
	Dual	£9,104.81	5.30	£276.59	0.05	£6,068
Time horizon reduced 5 years	Single	£4,718.12	3.35	–	–	–
	Dual	£4,947.09	3.37	£228.97	0.02	£13,837
Efficacy scenarios						
Stroke used from meta-analysis (Section 4.2.2)	Single	£9,205.51	5.51	–	–	–
	Dual	£9,480.47	5.56	£274.96	0.04	£6,438
Assuming no impact on heart failure (i.e., HR set to 1)[a]	Single	£9,025.43	5.54	–	–	–
	Dual	£9,480.47	5.56	£455.05	0.02	£22,213
Cost scenarios						
Spell level costs of pacemaker implantation from NHS Reference costs 2012–2013	Single	£11,416.24	5.51	–	–	–
	Dual	£11,754.15	5.56	525.94£3 37.90	0.04	£7,605
Cycle cost for heart failure from TA88	Single	£8,277.74	5.51	–	–	–
	Dual	£8,594.96	5.56	£317.22	0.04	£7,140

Cycle cost for stroke from TA88	Single	£11,150.63	5.51	–	–	–
	Dual	£11,305.08	5.56	£154.44	0.04	£3,476

Cycle cost for stroke from Saka 2009	Single	£9,619.42	5.51	–	–	–
	Dual	£9,864.37	5.56	£244.95	0.04	£5,513
Reprogramming/device replacement for AF in 0% patients	Single	£8,997.42	5.51	–	–	–
	Dual	£9,480.47	5.56	£483.05	0.04	£10,872
Reprogramming/device replacement for AF in 100% patients	Single	£9,639.40	5.51	–	–	–
	Dual	£9,480.47	5.56	£55.60-£158.92	0.04	£1,251Dominant
Other scenarios						
Discount rate 0%	Single	£10,664.51	6.27	–	–	–
	Dual	£10,936.09	6.33	£271.58	0.05	£5,045
Discount rate 6%	Single	£8,380.45	5.07	–	–	–
	Dual	£8,651.45	5.11	£271.00	0.04	£6,938
Market share: 55% warfarin and 45% NOAC[b]	Single	£9,683.98	5.51	–	–	–
	Dual	£9,903.55	5.56	£219.57	0.04	£4,942
"Worst case" scenario						
All efficacy and cost scenarios where the ICER increases above the base case	Single	£9,956.17	5.54	–	–	–
	Dual	£10,868.64	5.56	£912.47	0.02	£48,738
Additional scenarios for heart failure						
Patients >75 years (i.e., HR set to 1.34) from Riahi 2012	Single	£9,706.42	5.45	–	–	–
	Dual	£9,480.47	5.56	£531.86-£225.94	0.11	£4,918Dominant
Patients ≤75 years (i.e., HR set to 0.72) from Riahi 2012	Single	£8,418.67	5.61	–	–	–
	Dual	£9,480.47	5.56	£1,061.81	-0.06	Dominated

[a] As assumed in Oddershede et al.[59]

[b] Novel oral anticoagulants (NOACs)have equal market share of 15% per NOAC.

Abbreviations used in table: AF, atrial fibrillation; HF, HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality adjusted life year.

5.2.16 Discussion of the Technology Assessment Group *de novo* economic evaluation

The economic evaluation conducted by the TAG of dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block is an update of TA88. The previous assessment found dual-chamber pacemakers to be dominated by single-chamber atrial pacemakers (i.e., they are more expensive and less effective). Our own evaluation is based on more up to date

estimates employed within an economic model based on TA88. The findings are quite different in that, while dual-chamber pacemakers are more expensive, they are more clinically effective. Analyses resulted in a deterministic ICER of £6,056 at 10 years.

OWSA was undertaken to identify the key drivers of cost-effectiveness in the economic model. Those likely to increase the deterministic ICER over £20,000 were:

- lowest risk of HF (dual pacemakers dominated by single atrial pacemakers);
- highest implant/procedure cost for dual-chamber pacemaker (ICER £23,010);
- lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £27,409).

The result for the lowest risk of HF is being driven by an increase in cost of £710 and a modest reduction in benefit (–0.01) compared with dual-chamber pacemakers.

Using the extreme values for cost of implant/implantation increased the ICER substantially with the lowest cost for single-chamber atrial pacemaker resulting in an ICER of £27,409.

One-way sensitivity analysis can be misleading in that it may under represent the impact of parameter uncertainty in the results of the economic model. The results from the probabilistic sensitivity analysis capture the joint uncertainty across parameter estimates. The ICER from this analysis at 10 years is £6,068, which is similar to the deterministic result (£6,056). This is due to a slight increase in the difference in costs and difference in QALYs (£277 and 0.05, respectively).

Parameter uncertainty is not the only form of uncertainty found within an economic model. Structural uncertainty also needs to be accounted for. Two structural sensitivity analyses were undertaken in the current evaluation: reducing the time horizon from 10 to 5 years; and utilising the risk of reoperation from Kaplan–Meier data presented in DANPACE in contrast to implementing risk of reoperation as a constant risk.

Reducing the time horizon from 10 years to 5 years was undertaken to assess the impact of extrapolating the results from DANPACE beyond the typical duration of a trial participant. The results are perhaps as might be expected, a halving of the time horizon results in about a halving of the difference in incremental QALYs and more than a doubling of the resulting ICER. The deterministic result changes from £6,056 at 10 years to £14,261 at 5 years, while the results from the

probabilistic sensitivity analysis go from £6,068 at 10 years to £13,837 at 5 years. Based on feedback from our clinical experts a time horizon of 10 years would appear to be the most appropriate as the development of AV block is expected to increase steadily over time.

In the structural sensitivity analysis, the risk of reoperation was implemented as a time-dependent parameter and all patients requiring reoperation were assumed to be implanted with a dual-chamber device, regardless of the reason for reoperation or which pacemaker was originally implanted. The impact of undertaking this more granular approach to reoperation within the model almost halved the ICER. The deterministic ICER was reduced to £3,425 at 10 years due to a reduction in incremental costs. This is likely to be due to the risk being reoperated occurring slightly early than when a constant rate is assumed and indicates that the base case may be considered a conservative assumption.

A variety of scenario analyses were undertaken where an alternative source for a parameter estimate was used. Most had a minor impact on the resulting ICER with the exception of:

- assuming no difference in risk of developing HF (ICER £22,213);
- reprogramming/device replacement for AF in 0% patients (ICER £10,872);
- reprogramming/device replacement for AF in 100% patients (dual-chamber pacemakers dominant).

In only one instance did a scenario analysis result in an ICER above £20,000, and then it was by only £2,213.

The results of the scenario analysis and the OWSA highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. Subgroup analysis from DANPACE identified a significant difference in HF due to age (p=0.05), all other subgroups assessed were non-significant (p>0.31).[45] When the risk of heart failure is adjusted by age, the ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

myocardial infarction, and history of AF. The researchers were also able to categorise patients as low risk, high risk, and the remainder patients as moderate risk of a subsequent event. For each of the risk categories, and for an evaluation based on all patients, Oddershede et al. found that the probability of dual-chamber pacemakers being cost effective compared with single-chamber atrial pacemakers was > 50% at a WTP threshold of £20,000. This fell to > 40% at a WTP threshold of £30,000. This is likely to be due to the incremental QALY decrement associated dual chamber pacemakers in their analysis. However, the model developed by Oddershede et al. focused primarily on the occurrence of stroke and death, which may have restricted the comprehensiveness of the analysis to fully assess costs and benefits.

As no pre-existing economic evaluation adequately represents the cost effectiveness of dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block in comparison with single-chamber atrial pacemakers in a UK setting, the TAG developed a *de novo*, economic model to help inform this important question.

As there were concerns around potential clinical heterogeneity as a result of different patient populations (e.g. prior history of atrial fibrillation) and different device programming used (e.g. different % ventricular pacing) in the RCTs identified, the decision was made to base the model on DANPACE. The base case results of the TAG's economic model demonstrate that dual-chamber pacemakers are more expensive but also more effective than single-chamber atrial pacemakers resulting in an ICER of £6,056. Probabilistic sensitivity analysis produced a very similar ICER of £6,068. The likelihood for dual-chamber pacemakers to be cost effective was found to be over 70% at a threshold of either £20,000 or £30,000.

As the results for the probabilistic analysis were very similar to the deterministic results we focused on the deterministic results for all subsequent analyses.

Structural sensitivity analysis looking at a more granular approach to incorporating risk of re-operation using the available Kaplan–Meier data from DANPACE reduced the ICER from £6,056 to £3,425. A second structural sensitivity analysis reducing the time horizon to 5 years more than doubled the base case ICER to £14,261. In essence, halving the time horizon halved the incremental benefit.

One-way sensitivity analysis highlighted the key drivers of cost-effectiveness in the economic model. Those likely to increase the deterministic ICER over £20,000 were:

- lowest risk of HF (dual-chamber pacemakers dominated by single-chamber atrial pacemakers);
- highest implant/procedure cost for dual-chamber pacemaker (ICER £23,010);

- lowest cost of implant/procedure for single atrial pacemaker (ICER £27,409).

The result for the lowest risk of HF is being driven by an increase in cost of £710 and a modest reduction in benefit (–0.01) compared with dual-chamber pacemakers.

A series of scenario analyses were undertaken to test the impact on the results when using alternative sources for parameter estimates or challenge assumptions in the model. The scenario analyses that raised the ICER above the base case were:

- assuming no difference in HF (ICER £22,213);
- using the risk of stroke from the TAG's meta-analysis (ICER £6,438);
- using spell level costs of pacemaker implantation (ICER £7,605);
- using monthly cost of heart failure from TA88 (ICER £7,140);
- using reprogramming/device replacement for AF of 0% (ICER £10,872);
- using a discount rate of 6% (ICER £6,938).

Only when we assume the risk of developing HF is the same regardless of implanted device does the ICER increase beyond £20,000; albeit a modest increase to £22,213.

A cumulative "worst case" scenario was also conducted that combined the monthly cost of heart failure from TA88, the risk of stroke from the meta-analysis conducted by the TAG, the spell level costs of implantation, reprogramming/device replacement for AF of 0%, and assuming no difference in risk of developing HF between the two types of implant. This resulted in an ICER of £48,738.

The results of the scenario analysis and the one way sensitivity analysis highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. Subgroup analysis from DANPACE identified a significant difference in HF due to age (p=0.05), all other subgroups assessed were non-significant (p>0.31).[45] When the risk of heart failure is adjusted by age, the ICER in patients aged >75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

7.1 Statement of principal findings

This MTA uses the best available evidence to explore the clinical and cost-effective implications for using dual-chamber pacemakers rather than single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. DANPACE has demonstrated a significant reduction in re-operation due to need for surgical change of mode of pacing, where it was found to be significantly higher in patients implanted with a single-chamber atrial pacemaker compared with patients implanted with a dual-chamber pacemaker (9.3% vs 0.6%, p < 0.001).[42] The difference is

primarily due to the development of AV block requiring upgrade to a dual-chamber device. DANPACE also demonstrated a reduced risk of paroxysmal AF with dual-chamber pacing compared to single-chamber atrial pacing (OR 0.75, 95% CI: 0.59 to 0.96). No statistically significant difference was shown between the pacing modes for mortality, heart failure, stroke or quality of life. However, the risk of developing heart failure may vary with age and device.

The *de novo* economic model developed by the TAG shows that dual-chamber pacemakers are more expensive and more effective than single-chamber atrial devices resulting in a base case ICER of £6,056. The ICER remains below £20,000 in probabilistic sensitivity analysis, structural sensitivity analysis, and most scenario analyses and one-way sensitivity analyses.

A potentially important finding of this MTA is the impact that HF may have on the decision to use dual-chamber pacemakers or single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. The results from an analysis based on age (>75 years or ≤75 years) and risk of HF, indicates that dual-chamber pacemakers are a dominant treatment option in older patients (i.e. less costly and more effective) while using dual-chamber pacemakers is dominated (i.e. more expensive and less effective) in younger patients compared to single-chamber atrial pacemakers. However, these results are based on a subgroup analysis and should be treated with caution.

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Wilkoff BL, Kudenchuk PJ, Buxton AE, et al. The DAVID (Dual Chamber and VVI Implantable Defibrillator) II trial. Journal of the American College of Cardiology. 2009;53:872-880.	Not pacing
Abbreviations used in table: QoL, quality of life	

Appendix 5 One way sensitivity analysis

Parameter	Difference from ICER when using lower 95% CI	Difference from ICER when using upper 95% CI
Baseline age	£76	£1,584
Prob of paroxysmal AF - DC	£2,465	-£3,300
Prob of chronic AF - DC	£174	-£343
Prob of heart failure - DC	-£458	£1,097
Prob of stroke - DC	£574	-£1034
Prob of paroxysmal AF - SC	£10,153	-£4101
Prob of chronic AF - SC	£3,580	-£2,845
Prob of heart failure - SC	Dominated	Dominant
Prob of stroke - SC	£6,345	-£3,658
Proportion of new heart failure events leading to hospitalisation - DC	-£80	£152
Proportion of new heart failure	£314	-£597

events leading to hospitalisation - SC		
Prob of AV block	£567	-£1,095
HR death AF (versus general population)	£75	-£82
HR death Stroke - males (versus general population)	£48	-£63
HR death Stroke - females (versus general population)	£44	-£55
HR death Heart failure (versus general population)	£42	-£43
HR death AF & stroke (versus stroke population)	-£6	£7
HR death AF & HF (versus HF population)	-£2	£3
Implant SC Cost	£21,353	Dominant
Implant DC Cost	Dominant	£16,954
HF hospitalisation cost	-£1,043	£1,137
Stroke episode costs	£356	-£153
Monitoring cost	-£333	£154
Total UK direct health care cost of CVD	£0	£0
Average annual post-stroke hospitalisation cost	£97	-£191
Total annual UK Stroke medication costs	£7	-£13
Total UK Stroke primary care costs	£3	-£6
Episode cost of stroke in people with AF	£309	-£1,305
Average annual post-stroke hospitalisation cost in people with AF	£0	£0
Cost of GP referrals for AF	£120	-£236
Cost of hospital outpatient referrals for AF	£88	-£173
Cost of hospital admissions with principal diagnosis of AF	£656	-£1,289
Cost of post-discharge outpatient visits	£77	-£150
Utility Change from implant to heart	£306	-£531

failure		
Utility Heart failure	-£902	£1,916
Utility Stroke (month 1)	£0	£0
Utility Stroke (> month 1)	-£522	£434
Utility Change from with pacemaker to AF	£106	-£197
Utility AF & stroke (month 1)	-£209	£163
Utility AF & stroke (> month 1)	£0	£0
Utility AF & HF	-£426	£705

Appendix 6 Calculation of long-term care costs associated with heart failure

In 2011, the UK prevalence of heart failure was 0.90% in men and 0.70% in women.[94] No UK CVD prevalence data were identified for 2011; however data are reported for 1988-2010 (Figure 17). By extrapolation of the 4 most recent data points, it is possible to estimate the UK CVD prevalence for 2011 (Figure 18). These extrapolations provide UK CVD prevalence estimates for 2011 of 11.95% for men and 10.95% for women, which give a relative prevalence of HF as a percentage of CVD of 7.53% for men and 6.39% for women; average 6.96%.