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CLINICAL RESEARCH
Cardiac pacing

Cost-effectiveness analysis of cardiac implantable electronic devices with reactive atrial-based antitachycardia pacing

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Aims Reactive atrial-based anti-tachycardia pacing (rATP) in pacemakers (PMs) and cardiac resynchronization therapy defibrillators (CRT-Ds) has been reported to prevent progression of atrial fibrillation, and this reduced progression is expected to decrease the risk of complications such as stroke and heart failure (HF). This study aimed to assess the cost-effectiveness of rATP in PMs and CRT-Ds in the Japanese public health insurance system.

Methods and results We developed a Markov model comprising five states: bradycardia, post-stroke, mild HF, severe HF, and death. For devices with rATP and control devices without rATP, we compared the incremental cost-effectiveness ratio (ICER) from the payer's perspective. Costs were estimated from healthcare resource utilisation data in a Japanese claims database. We evaluated model uncertainty by analysing two scenarios for each device. The ICER was 763 729 JPY/QALY (5616 EUR/QALY) for PMs and 1,393 280 JPY/QALY (10 245 EUR/QALY) for CRT-Ds. In all scenarios, ICERs were below 5 million JPY/QALY (36 765 EUR/QALY), supporting robustness of the results.

Conclusion According to a willingness to pay threshold of 5 million JPY/QALY, the devices with rATP were cost-effective compared with control devices without rATP, showing that the higher reimbursement price of the functional categories with rATP is justified from a healthcare economic perspective.

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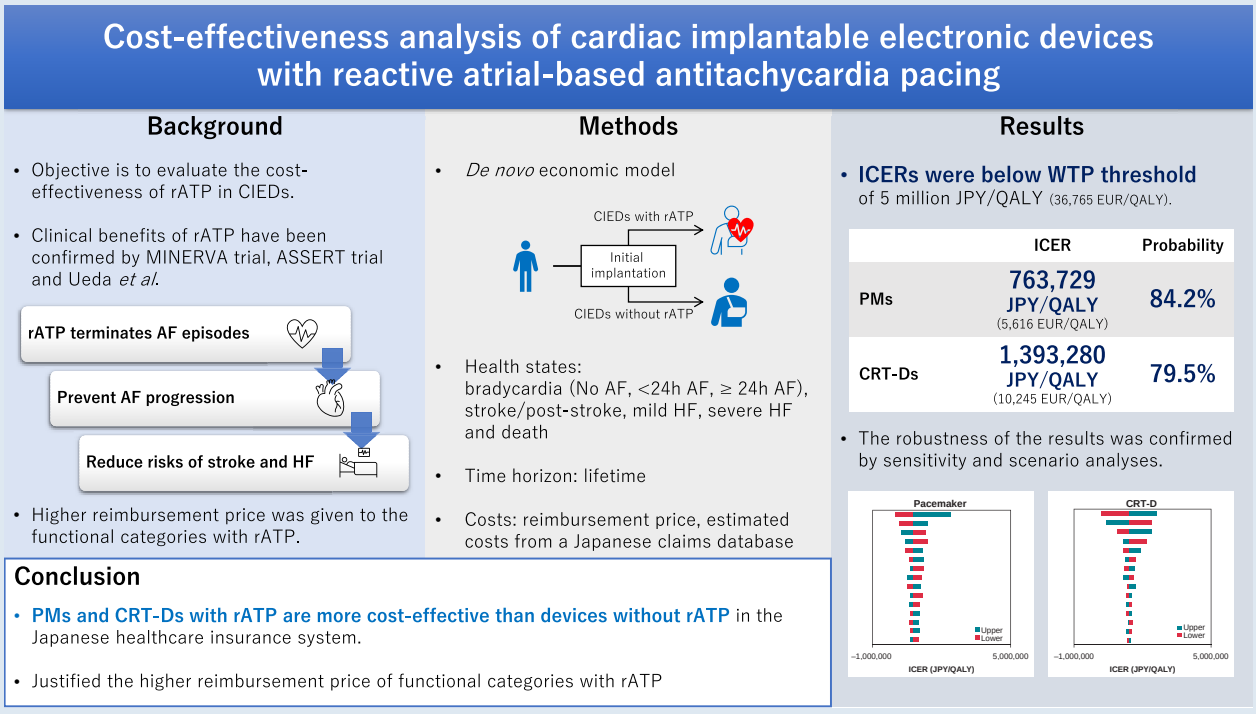
Graphical Abstract



Keywords Cost-effectiveness • Atrial fibrillation • Heart failure • Pacemaker • Cardiac resynchronization therapy • Atrial anti-tachycardia pacing

What's new?

- Cost-effectiveness of implantable devices with reactive atrial-based anti-tachycardia pacing (rATP) that can detect atrial fibrillation (AF) and prevent AF progression and subsequent events was evaluated from the Japanese payer's perspective.
- A Markov model was developed to represent pathological changes in patients with a dual-chamber pacemaker (PM) for bradycardia or a cardiac resynchronization therapy defibrillator (CRT-D) for heart failure.
- Healthcare resource utilization in patients with a dual-chamber PM or CRT-D device was estimated by using a Japanese claims database.
- According to a willingness to pay threshold of 5 million Japanese Yen/quality-adjusted life year, in the Japanese healthcare insurance system dual-chamber PMs and CRT-D devices with rATP are cost-effective compared with control devices without rATP.

Introduction

Atrial fibrillation (AF), a type of tachycardia that causes irregular heart rhythm, is one of the most frequently occurring arrhythmias and most prevalent in people aged 65 years and older; overall, the estimated prevalence in Japan in 2020 was around 0.8–0.9%. The prevalence of AF increases with age, and AF is a major problem in an ageing society.[1,2] AF can cause subjective symptoms such as palpitations and chest discomfort, but it can also be asymptomatic. Worsening AF not only reduces quality of life but also increases the risk of stroke and heart failure (HF) deterioration, which leads to a poor prognosis.[3] AF has an impact on healthcare system budgets; e.g. in January 2022, AF accounted for almost 1% of total healthcare costs in Japan.[4] The prevalence of AF is expected to increase in the future.

AF is a progressive condition that generally increases in duration over time. It is classified according to its duration as paroxysmal, persistent, long-standing persistent or permanent.[5] Asymptomatic AF in patients with cardiac implantable electronic devices (CIEDs) and symptomatic AF have been reported to increase the risk of stroke with increasing duration of AF,[6] requiring appropriate therapeutic intervention. Recently, quality indicators (QIs) were suggested to evaluate the quality of care for cardiac pacing in CIEDs patients.[7] Furthermore, AF is a risk factor for the development of HF, and the two conditions are closely inter-related.[8] Patients with AF have been reported to have a worse prognosis when they develop HF.[9] Among patients with CIEDs, the complication rate of AF is particularly high in patients with reduced cardiac function and implantation of a cardiac resynchronization therapy defibrillator (CRT-D).[10] Deterioration of HF can be fatal, so management of AF is also important in terms of HF management.

The risk of stroke and HF deterioration was reported to increase with increasing duration of AF in patients with CIEDs for bradycardia or HF.[6,11] Recently, implantable devices with a reactive atrial-based anti-tachycardia pacing (rATP) algorithm were introduced to prevent AF progressing from paroxysmal to persistent and permanent forms by detecting AF and delivering atrial anti-tachycardia pacing to terminate AF episodes.[12] Patients with CIEDs with rATP were reported to have less progression of AF than patients with CIEDs without rATP, and this reduced progression is expected to decrease the risk of

complications such as stroke and HF.[13–17] Furthermore, in patients with a CRT-D, the risk of hospitalisation for HF is significantly lower in those with rATP device[14]; a CRT-D with rATP may also prevent deterioration of HF.[14] Because stroke and HF have a significant impact on not only patient quality of life but also healthcare costs, devices with rATP may reduce healthcare costs and improve the cost-effectiveness of bradycardia and HF treatment.[18]

To manage medical technology prices, the Japanese public health insurance system uses a functional category system in which reimbursement prices are set for each functional category instead of each brand; these functional categories are mainly decided on the basis of similarity in structure, purpose of use, and clinical efficacy. Costs for devices in functional categories, e.g. implantable devices, including CIEDs, are paid separately from the cost of the procedure, whereas less expensive or reusable devices in comprehensive categories are paid for inclusively, i.e. they are included in the cost of the procedure. For innovative new medical technologies, new categories are created with premium rates.[19] When the clinical effectiveness of rATP was approved by the Japanese regulatory authority in the challenge application programme, novel functional categories with higher reimbursement prices than CIEDs without rATP were established for pacemakers (PMs) and CRT-D devices with rATP.[20] However, to the best of our knowledge, no studies have examined the cost-effectiveness of rATP. Therefore, the aim of this study was to assess the cost-effectiveness of rATP in PMs and CRT-D devices and the functional categories of these devices in the Japanese public health insurance system.

Methods

Model structure

In this study, we developed a Markov model to represent pathological changes in patients with a dual-chamber PM for bradycardia or a CRT-D device for HF. The incremental cost-effectiveness ratio (ICER) was calculated by comparing CIEDs with and without rATP from the perspective of the Japanese public health insurance system as the payer. Because reimbursement prices are set for functional categories of devices and not individual devices, target and control devices were defined by using functional categories (*Table 1*). Reimbursement prices of cardiac resynchronisation therapy pacemakers (CRT-Ps) and implantable cardioverter-defibrillators (ICDs) are same with or without rATP in the Japanese public health insurance system, so it is obviously that CRT-Ps and ICDs with rATP are dominant to those of without rATP in the perspective of cost-effectiveness. Therefore, CRT-Ps and ICDs were not analysed in this study.

The Markov model comprised five states: bradycardia, stroke/post-stroke, mild HF [New York Heart Association (NYHA) Class II], severe HF (NYHA Class III/IV), and death. Onset of stroke and HF were assumed to be irreversible and to not occur simultaneously, so patients in the stroke/post-stroke and severe HF states could progress to death only and those in the mild HF could progress to severe HF or death. On the basis of the results of Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT),[13] a randomized controlled study on the relationship between AF progression and risk of stroke and HF, and the Minimize Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure (MINERVA) trial, the first randomized controlled trial to show the effectiveness of rATP in preventing progression of AF, we defined three substates of bradycardia: no AF, AF lasting <24 h and AF lasting 24 h or longer (*Figure 1*).[15]

We did not include adverse events in the analysis because we assumed that incidences of adverse events would be similar with rATP and control devices.[14,15]

We used a common model for the PM and CRT-D analyses. For the PM analysis, all patients were entered into the model in the state of bradycardia with no AF and assumed that the PM was not replaced with a CRT-D in case of transition to HF; for the CRT-D analysis, we entered all patients into the model in the state of mild HF (NYHA Class II).

The time horizon was set to the period until patients reached the age of 100 years and 99.9% of patients were dead (equivalent to a lifetime horizon). The model cycle was set at 1 month, and a half-cycle correction was performed. Costs and utilities were discounted at a rate of 2% per annum according to the Japanese cost-effectiveness analysis guideline of the Center for Outcomes Research and Economic Evaluation for Health (C2H), National Institute of Public Health.[21]

The present study utilized the data obtained from the ASSERT trial,[6,11,13] MINERVA trial,[15] RAFT (Resynchronization for Ambulatory Heart Failure Trial),[22] Ueda *et al.*[14] and Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial.[23,24] The ASSERT trial, MINERVA trial, RAFT, and COMPANION trial had been registered at ClinicalTrials.gov as NCT00256152, NCT00262119, NCT00251251, and NCT00180258, respectively. All trials were approved by the ethics committees of all participating centres and were performed in compliance with the Declaration of Helsinki. The study protocol of Ueda *et al.* was approved by the institutional review board of the National Cerebral and Cardiovascular Center, Japan (M26-150-6). Check list of the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) is presented in Supplementary material online, *Table S1*.[25]

Model inputs

The parameters used in the model are summarized in *Table 2*. For almost all transition probabilities, we used results of clinical trials conducted outside Japan, but we based cost and utility values on the results of clinical trials or database analyses performed in Japan.

Modelled population

The baseline patient characteristics were the same as those of users of dual-chamber PMs and CRT-Ds in the National Database (NDB) Open Data in 2019, a Japanese nationwide claims database.[26] The mean age of PM users was 79.3 years, and 47.0% of them were male and the mean age of CRT-D users was 69.1 years and 75.6% were male.

Transition probabilities

In patients with bradycardia, transition probabilities for AF progression (i.e. transitions to a more severe AF substate) were based on the results of ASSERT[13]; for the rATP device, the relative reduction in risk of AF progression was set to the value reported in the MINERVA trial.[15] The risk of HF and stroke by AF bradycardia substate was also obtained from ASSERT.[6,11,13] Any patients with bradycardia who progressed to HF were assumed to transition to the mild HF state. Because HF hospitalization indicates worsening HF, the probability of transition from mild HF to severe HF was set to the incidence of HF hospitalization reported in RAFT,[22] a randomized trial conducted in the US that compared implantable cardioverter-defibrillators with and without CRT. The relative reduction in risk of HF hospitalization with rATP was based on the result of a single-centre, retrospective study performed by Ueda *et al.*[14]

Regarding mortality in patients with bradycardia, we used the results of Gonzalez *et al.*[27] for patients without AF and those of the MINERVA trial[15] for patients with AF. Mortality in mild HF was based on the RAFT[22] results and that in severe HF on the results of the COMPANION trial,[23,24] a randomized controlled study conducted in the US that reported mortality in patients with advanced HF who were using a CRT-D. In addition, we assumed that a certain proportion of patients died in the acute phase of stroke or HF. Acute mortality of HF was obtained from Sasaki *et al.*[29] and that of stroke from Toyoda *et al.*[35] Patients in a stroke/post-stroke state were assumed to experience recurrence, and the rates were obtained from Takashima *et al.*[28] Patients with severe HF were assumed to experience HF re-hospitalization, and the rate was obtained from RAFT[22] and converted to a rate per patient-month. Acute mortality was also assumed in patients who experienced recurrence of stroke or re-hospitalization for HF. Natural mortalities were based on the 2020 Japanese life tables,[36] adjusted for sex and age. The initial value of the sex ratio was assumed to remain constant over the entire period.

Costs and utility values

The price of devices with rATP and control devices were the reimbursement prices of the corresponding functional categories as of April 2022. We estimated costs other than the device prices on the basis of healthcare resource

Table 1 Reactive atrial-based anti-tachycardia pacing devices and control devices used in the analysis and their functional categories

Arm	Functional category	Main definition	Reimbursement price (as of April 2022)
Pacemakers			
rATP	Category 112 pacemaker (3) dual-chamber (Type V)	Has the rATP algorithm	¥751 000 (€5522)
Control	Category 112 pacemaker (2) dual-chamber (Type IV)	Does not have the rATP algorithm	¥593 000 (€4360)
CRT-Ds			
rATP	Category 144 implantable cardioverter-defibrillator with biventricular pacing (2) quadripolar (c) with rATP algorithm	CRT-D meets the following definitions: – Has the algorithm that dynamically adjusts CRT pacing parameters (optimisation algorithm with automated pacing parameters and RV-synchronized, LV-only pacing): – Has the rATP algorithm	¥4 750 000 (€34 926)
Control	Category 144 implantable cardioverter-defibrillator with biventricular pacing (2) quadripolar (b) with automated optimisation algorithm	CRT-D meets the following definitions: – Has the algorithm that dynamically adjusts CRT pacing parameters (optimization algorithm with automated pacing parameters and RV-synchronized, LV-only pacing): – Does not have the rATP algorithm	¥4 410 000 (€32 426)

CRT-D, cardiac resynchronization therapy defibrillator; LV, left ventricle; rATP, reactive atrial-based anti-tachycardia pacing; RV, right ventricle; €1 = \136 (monthly exchange rate announced by Bank of Japan on 20 September 2022).

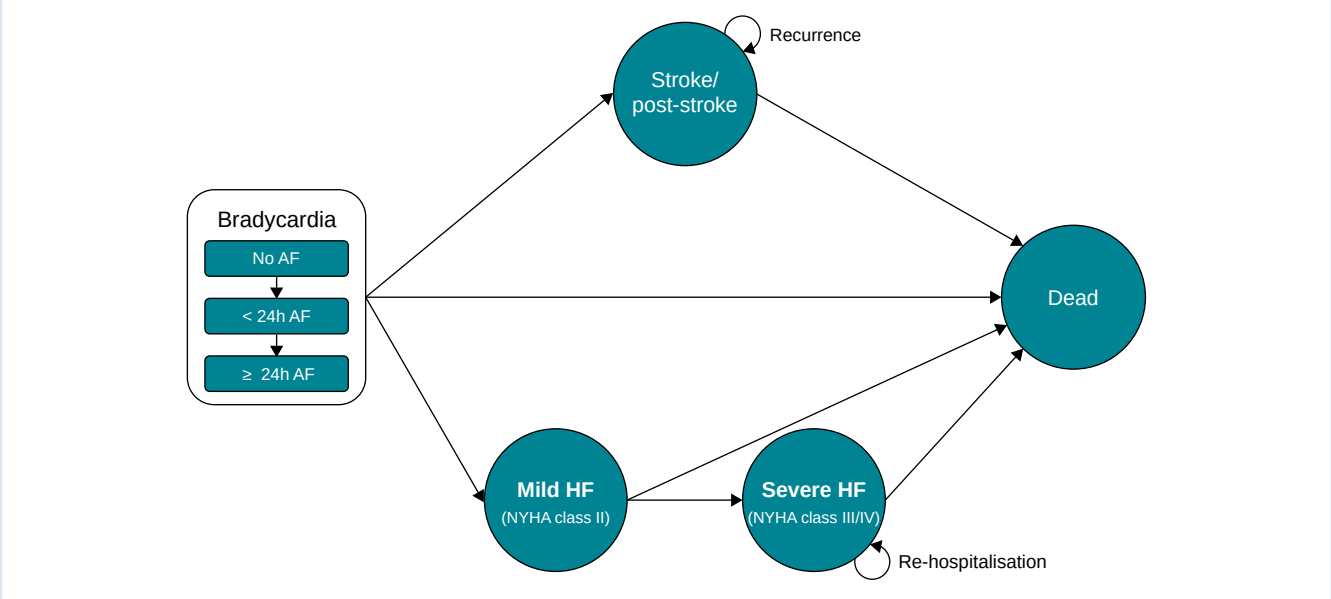


Figure 1 Markov model diagram. For the pacemaker analysis, all patients were entered into the model in the bradycardia without atrial fibrillation, and no replacement with cardiac resynchronization therapy was performed in case of transition to heart failure; for cardiac resynchronisation therapy device, all patients were entered into the model in the mild HF state. AF, atrial fibrillation; HF, heart failure.

utilisation in real clinical settings. Healthcare resource utilisation was estimated by using Medical Data Vision (MDV) database,[30] a Japanese claims database (see Supplementary material online, *Table S2* for details). Data on all patients in whom CIEDs were implanted from April 2018 to December 2020 were extracted and the following costs were estimated: (i) cost at the time of device implantation, (ii) cost at time of device replacement, (iii) cost of hospitalization for acute HF, (iv) cost of hospitalization for acute stroke, and (v) monthly cost of follow-up for HF and stroke. Hospitalization for acute HF was defined as inpatient claims for brain natriuretic peptide or N-terminal pro-brain natriuretic peptide testing after initial hospitalization and hospitalization for acute stroke as use of tissue plasminogen activator or stoke-related medical devices or both.

Cost of acute hospitalization and monthly costs of follow-up were assumed to be common to rATP and control devices. For rATP devices, costs

Table 2 Values and distributions of model parameters

Parameter	Base case value		Distribution	Source
	rATP arm	Control arm		
(a) Pacemakers				
Background				
Age (years)	79.3	—	Log-normal	NDB Open Data[26]
Male (%)	47.0%	—	None	NDB Open Data[26]
Initial distribution		—		
No AF	100.00%	—	None	Assumption
<24 h AF	0.00%	—	None	Assumption
≥24 h AF	0.00%	—	None	Assumption
Mild HF	0.00%	—	None	Assumption
Severe HF	0.00%	—	None	Assumption
Transition rate (/month)				
No AF to no AF	97.59%	—	Beta	Assumption
No AF to <24 h AF	1.58%	—	Beta	Wong et al. [13]
No AF to ≥24 h AF	0.46%	—	Beta	Wong et al.[13]
No AF to stroke	0.05%	—	Beta	Van Gelder et al. [6]
No AF to mild HF	0.19%	—	Beta	Healey et al.[11]
No AF to death	0.13%	—	Beta	Gonzalez et al.[27]
<24 h AF to <24 h AF	98.68%	98.20%	Beta	Assumption
<24 h AF to ≥24 h AF	0.85%	1.29%	Beta	Wong et al.[13] Borian *et al.*[15]
<24 h AF to stroke	0.08%	—	Beta	Van Gelder et al. [6]
<24 h AF to mild HF	0.21%	—	Beta	Wong et al.[13]
<24 h AF to death	0.18%	0.22%	Beta	Borian et al.[15]
≥24 h AF to ≥24 h AF	98.81%	98.77%	Beta	Assumption
≥24 h AF to stroke	0.24%	—	Beta	Van Gelder et al.[6]
≥24 h AF to mild HF	0.77%	—	Beta	Wong et al. 2018[13]
≥24 h AF to death	0.18%	0.22%	Beta	Borian et al.[15]
Stroke to stroke	99.82%	99.78%	Beta	Assumption
Stroke to death	0.18%	0.22%	Beta	Borian et al.[15]
Mild HF to mild HF	99.15%	98.80%	Beta	Assumption
Mild HF to severe HF	0.26%	0.61%	Beta	Tang et al.[22] Ueda et al.[14]
Mild HF to death	0.59%	—	Beta	Tang et al.[22]
Severe HF to severe HF	98.07%	—	Beta	Assumption
Severe HF to death	1.93%	—	Beta	Carson et al. [23]
Re-hospitalization rate (/month)				
Mild HF	0.00%	—	None	Assumption
Severe HF	0.62%	1.45%	Beta	Tang *et al.*[22] Ueda *et al.*[14]
Recurrent rate (/month)				
Stroke	0.27%	—	Beta	Takashima *et al.*[28]
Acute death (/month)				
HF	8.70%	—	Beta	Sasaki *et al.*[29]
Stroke	4.92%	—	Beta	Toyoda *et al.*[27]
Acute phase cost (/month)				
Initial implantation[a]	¥2 265 928 (€16 661)	¥2 107 928 (€15 499)	Gamma	MDV database[30]

Continued

Table 2 *Continued*

Parameter	Base case value		Distribution	Source
	rATP arm	Control arm		
Stroke	¥2 038 484 (€14 989)	—	Gamma	MDV database[30]
HF	¥1 016 617 (€7475)	—	Gamma	MDV database[30]
Device replacement[a]	¥1 685 386 (€12 393)	¥1 527 386 (€11 231)	Gamma	MDV database[30]
Follow-up cost (/month)				
Mild/severe HF	¥47 188 (€347)	—	Gamma	MDV database[30]
Stroke	¥18 998 (€140)	—	Gamma	MDV database[30]
Utility		—		
NoAF/<24 h AF/≥24 h AF	0.897	—	Beta	Shiroiwa *et al.*[31]
Stroke	0.632	—	Beta	Shiroiwa et al.[31]
Mild HF	0.878	—	Beta	Göhler *et al.*[32]
Severe HF	0.768	—	Beta	Göhler *et al.*[32]
Device replacement (year/time)				
PM	13.70	—	Gamma	Product catalogue[33]
Effect ratio—rATP				
AF extension	0.659	NA	Beta	Borian *et al.*[15]
AF mortality	0.818	NA	Beta	Gonzalez et al.[27]
Stroke mortality	0.818	NA	Beta	Gonzalez *et al.*[27]
HF deterioration	0.426	NA	Beta	Ueda *et al.*[14]
Discount rate	2.00%	—	None	C2H guideline[21]
(b) Cardiac resynchronization therapy defibrillators				
Background				
Age (years)	69.1	—	Log-normal	NDB Open Data[26]
Male (%)	75.6%	—	None	NDB Open Data[26]
Initial distribution				
Mild HF	100.00%	—	None	Assumption
Severe HF	0.00%	—	None	Assumption
Transition rate (/month)				
Mild HF to mild HF	99.39%	99.14%	Beta	Assumption
Mild HF to severe HF	0.19%	0.44%	Beta	Tang *et al.*[22] Ueda *et al.*[14]
Mild HF to death	0.42%	—	Beta	Tang *et al.*[22]
Severe HF to severe HF	98.79%	—	Beta	Assumption
Severe HF to death	1.21%	—	Beta	Carson *et al.*[23]
Re-hospitalisation rate (/month)				
Mild HF	0.00%	—	None	Assumption
Severe HF	0.41%	0.95%	Beta	Tang *et al.*[22] Ueda *et al.*[14]
Acute death (/month)				
HF	8.70%	—	Beta	Sasaki *et al.*[29]
Acute phase cost (/month)		—		
Initial implantation[a]	¥7 610 493 (€55 960)	¥7 950 493 (€58 460)	Gamma	MDV database[30]

Continued

Table 2 *Continued*

Parameter	Base case value		Distribution	Source
	rATP arm	Control arm		
HF	¥1 090 732 (€8020)	—	Gamma	MDV database[30]
Device replacement[a]	¥5 764 311 (€42 385)	¥6 104 311 (€44 885)	Gamma	MDV database[30]
Follow-up cost (/month)				
Mild/severe HF	¥43 154 (€317)	—	Gamma	MDV database[30]
Utility				
Mild HF	0.884	—	Beta	Göhler *et al.*[32]
Severe HF	0.768	—	Beta	Göhler *et al.*[32]
Device replacement (year/time)				
CRT-D	9.20	—	Gamma	Product catalogue[34]
Effect ratio—rATP				
HF deterioration	0.432	NA	Beta	Ueda *et al.*[14]
Discount rate	2.00%	—	None	C2H guideline[21]

AF, atrial fibrillation; HF, heart failure; rATP; reactive atrial-based anti-tachycardia pacing; —, same value as rATP arm.
[a]Device reimbursement price is included; €1 = 136 (monthly exchange rate announced by Bank of Japan on 20 September 2022).

Table 3 Values for scenario analysis

	No AF	<24 h AF	≥24 h AF	Source
(a) Pacemakers				
Base case	100.0%	0.0%	0.0%	Assumption
Scenario 1	79.1%	9.3%	11.6%	Connolly *et al.*[37] Botto *et al.*[38]
Scenario 2	53.0%	20.9%	26.1%	Botto *et al.*[38] Lamas *et al.*[39]
	NYHA II	**NYHA III**	**NYHA IV**	**Source**
(b) Cardiac resynchronization therapy defibrillators				
Base case	100.0%	0.0%	0.0%	Assumption
Scenario 1	47.5%	46.9%	5.6%	Tang *et al.*[22] Carson *et al.*[23]
Scenario 2	26.0%	61.9%	12.1%	Yokoshiki *et al.*[40]

at the time of device implantation and device replacement were calculated by adding the difference in reimbursement price between rATP devices and control devices to the costs for control devices because there should be no difference in costs for implantation procedures, treatments for controlling adverse events or device replacement between devices with and without rATP. For battery longevity, we used the product specification values for the PMs and CRTs with rATP.[33,34] We assumed the same battery longevity for devices with and without rATP because rATP has only a minor impact on battery longevity.[14]

The utility values for patients with bradycardia were assumed to be equivalent to those of healthy individuals corrected for age at baseline, as estimated by Shiroiwa *et al.*[31] In stroke patients, the utility values were calculated by subtracting their disutility values, which were also estimated by Shiroiwa *et al.*,[31] from the utility values of healthy individuals. The utility values for patients with HF were obtained from Göhler *et al.*[32] who examined the utility values according to NYHA class with a regression model that considered patient background. In the present model the utility values for each NYHA class were calculated by using coefficients reported in Göhler *et al.*,[32] i.e. the age and sex ratio at baseline in the present study, as described above. For the ratio of NYHA III to NYHA IV in patients with severe HF, we used the values from the COMPANION trial.[23,24] We did not consider disutility according to the progression of AF because of a lack of published studies.

Table 4 Base case results

	Total costs	Total QALYs	ΔCosts	ΔQALYs	ICER (/QALY)
(a) Pacemaker					
rATP	¥3 826 939 (€28 139)	7.22	50 028 (€1103)	0.20	763 729 (€5616)
Control	¥3 676 911 (€27 036)	7.03			
(b) Cardiac resynchronization therapy device					
rATP	¥15 923 150 (€117 082)	7.69	956 973 (€7037)	0.69	1 393 280 (€10 245)
Control	¥14 966 178 (€110 045)	7.01			

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; rATP; reactive atrial-based anti-tachycardia pacing; €1 = 136.

Sensitivity and scenario analyses

We performed deterministic sensitivity analyses (DSAs) and probabilistic sensitivity analyses (PSAs) to assess the uncertainty of base case results and selected parameters to cover the uncertainty. To avoid devices with rATP being less effective than control devices, we varied the ratio of transition probabilities rather than the transition probabilities themselves. Similarly, for the cost of rATP devices, we varied the difference with respect to control devices. In DSA, sufficiently large variation was considered to be plus or minus 5 years for age and 20% for other parameters, and the discount rate was varied from 0% to 4% in accordance with the C2H guideline.[21] PSA were performed with a Monte Carlo simulation with 3000 samples. The distributions were chosen by the nature of the parameters and are shown in *Table 2*. The results of the DSA were plotted as Tornado diagrams and that of the PSA as a cost-effectiveness plane and acceptability curve.

To evaluate the uncertainty introduced by the assumption that all patients entered the model in the bradycardia substate without AF for the PM analysis and in the mild HF state for the CRT-D analysis, we performed an analysis of two scenarios for each category in which we used a modified initial distribution of AF substates for the PMs and an initial distribution of NYHA class for the CRT-Ds (*Table 3*).

Results

The ICER for PMs with rATP was 763 729 Japanese Yen (JPY)/QALY (5616 EUR/QALY) and for CRT-Ds with rATP was 1 393 280 JPY/QALY (10 245EUR/QALY). Both values were below the willingness to pay threshold of 5 million JPY/QALY (36 765 EUR/QALY) (*Table 4*).[41] The results of the DSA showed that for PMs the variables with a significant impact on ICER were the device costs, chronic monthly healthcare costs for mild HF and the risk of developing HF from an AF state lasting more than 24 h; for CRT-Ds the variables were the device costs and chronic monthly healthcare costs for mild HF, device costs and utility values for patients with mild HF. However, the maximum ICER for all of these variables was below 5 million JPY/QALY (*Figure 2*).

The results from the PSA are shown in *Figures 3* and *4*. The analyses found that the probability of ICER being below the willingness to pay threshold was 84.2% for PMs and 79.5% for CRT-Ds.

For PMs the ICERs in the scenario analysis were 712 412 JPY/QALY for scenario 1 and 660 698 JPY/QALY for scenario 2 and for CRT-Ds they were 1 454 653 JPY/QALY for Scenario 1 and 1 521 943 JPY/QALY for Scenario 2. The ICERs were below 5 million JPY/QALY in all scenarios.

Discussion

To our knowledge, this study was the first to assess the cost-effectiveness of PMs and CRT-Ds with rATP.

In this study, any other treatment for AF performed as part of standard clinical practice, such as catheter ablation, antiarrhythmic drug administration or electrical cardioversion, was not included. Rate control and rhythm control are both used for the treatment of AF, but recent studies have reported some clinical advantages of the latter.[42,43] Catheter ablation is the leading rhythm control treatment for AF and its effectiveness is well established.[44,45] However, in some cases catheter ablation cannot completely control AF,[46] and its complications are of concern in older patients[47] and patients who subsequently develop atrial tachycardia.[48] Therefore, rATP is expected to be effective as an additional or alternative treatment to catheter ablation. Indeed, the efficacy of rATP has been reported in preventing persistent AF in PM[15,49] and HF in CRT[14] so improvement of the treatment and prognosis in patients with CIED is expected. The effectiveness of rATP has been demonstrated irrespective of AF duration and device model,[49] making it highly versatile. Also, rATP is safer than catheter ablation or drug therapy because there are no complications or concerns about adverse effects.[14,15] Therefore, the use of rATP as an alternative treatment in patients in whom catheter ablation should be carefully considered, such as older adults, is also expected to reduce the cost of catheter ablation treatment. Recently, AF was also reported to be associated with a risk of cognitive impairment and dementia,[50,51] and catheter ablation was reported to potentially reduce those risks[52]; suppression of AF progression with rATP is also expected to reduce these risks.

Although the cost-effectiveness of PM is well studied,[53–55] the effect of AF prolongation has rarely been considered. In their cost-effectiveness analysis of PM, Rinfret *et al.*[53] adopted the non-fatal cardiac incident rate, a composite parameter including AF, new HF and stroke. Edwards *et al.*[54] performed a cost-effectiveness analysis with a Markov model in patients with symptomatic bradycardia to compare single-chamber PM with dual-chamber PM. Like ours, their model incorporated AF (paroxysmal and chronic AF), stroke/post-stroke and HF as states in the model; the additional benefit of dual-chamber PM was implemented in the model by using the result of the DANPACE trial,[54] which showed that the odds ratio for paroxysmal AF is lower in patients with a dual-chamber PM than in those with a single-chamber PM. However, the incidence of HF, stroke and chronic AF were not significantly different between single-chamber PM and dual-chamber PM.[54] The results of the DSA by Edwards *et al.* showed that the variable that affected ICER most was the price of PM. The cost-effectiveness of CRT has also been extensively studied,[56,57] and some of the studies developed models to classify HF by severity. However, none of them examined the deterioration of HF due to the AF progression.

This is the first study to model the effect of rATP on prevention of AF progress and show that the ICERs for PM and CRT-D with rATP were below the Japanese willingness to pay threshold of 5 million

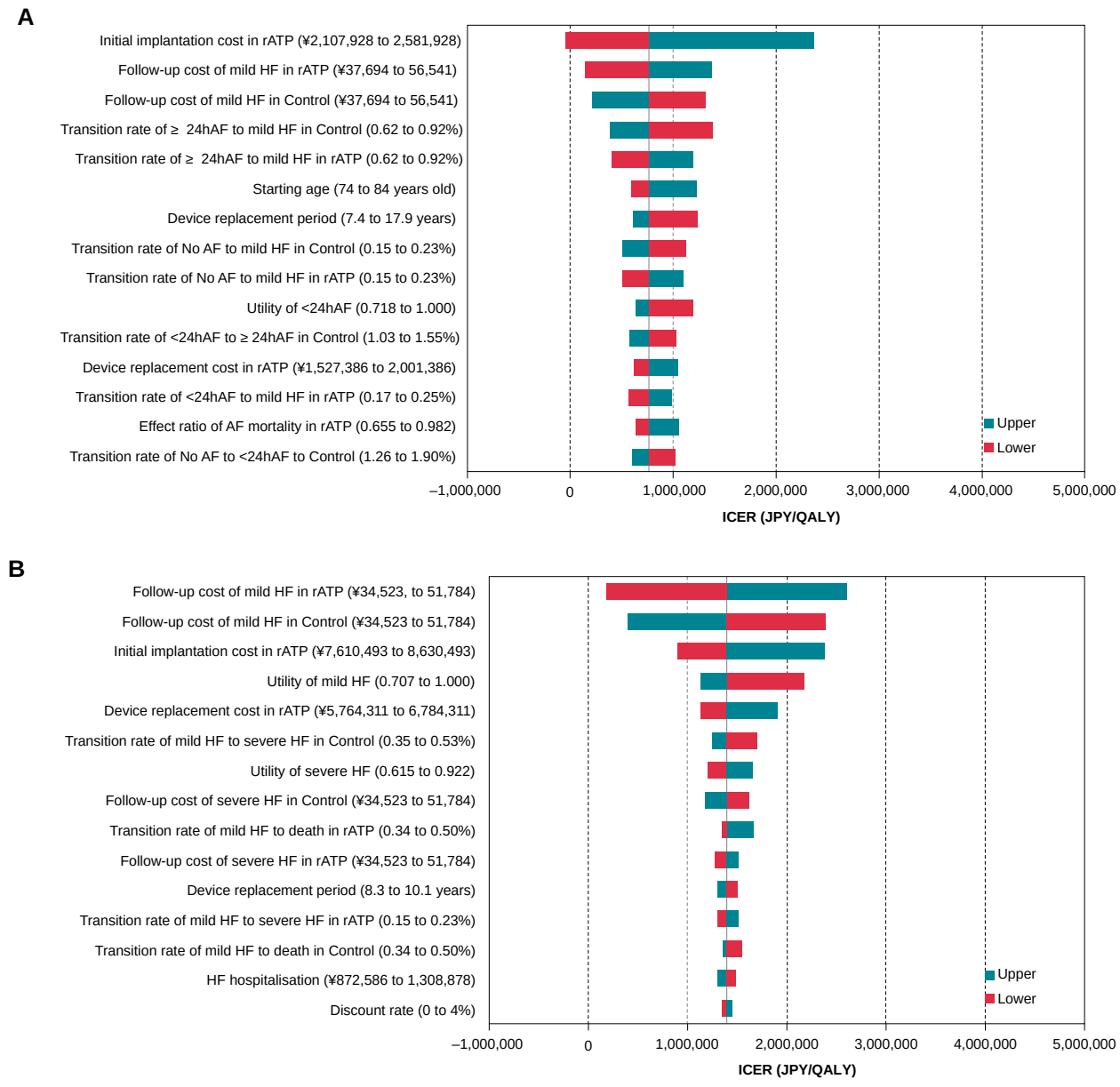


Figure 2 Tornado diagram. (*A*) Pacemaker. AF, atrial fibrillation; HF, heart failure; ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; QALY, quality-adjusted life year; rATP, reactive atrial-based anti-tachycardia pacing. (*B*) Cardiac resynchronisation therapy device. AF, atrial fibrillation; HF, heart failure; ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; QALY, quality-adjusted life year; rATP, reactive atrial-based anti-tachycardia pacing.

JPY/QALY when using the reimbursement prices as of April 2022. Sensitivity and scenario analyses confirmed the robustness of the results. In DSA (*Figure 2*), the variable that most affected the ICER was the price of the device, which is consistent with Edwards *et al.*[54] The impact of the uncertainty of variables that represent an additional benefit of rATP (i.e. the risk of AF progression, HF deterioration, and HF re-hospitalization) was relatively small. We varied the additional cost of devices with rATP with respect to control devices from 0 JPY to 474 000 JPY in PM and from 0 JPY to 1 020 000 JPY in CRT-D, which is large enough in view of the variation expected in the Japanese public healthcare system, and found that the ICER of devices with rATP was lower than 5 million JPY/QALY.

Limitations

First, although we evaluated the cost-effectiveness of rATP devices implanted in Japanese patients, for some parameters we used the results of trials performed outside Japan because of a lack of data from Japanese studies. For example, we used the mortality in patients with HF from RAFT and the COMPANION trial, which were conducted in US patients, who have different backgrounds from Japanese patients on CRT: Japanese patients receiving CRT have a higher left ventricle ejection fraction, so preserved cardiac function is more common among patients in Japan than among those in the US. In addition, the proportion of patients with

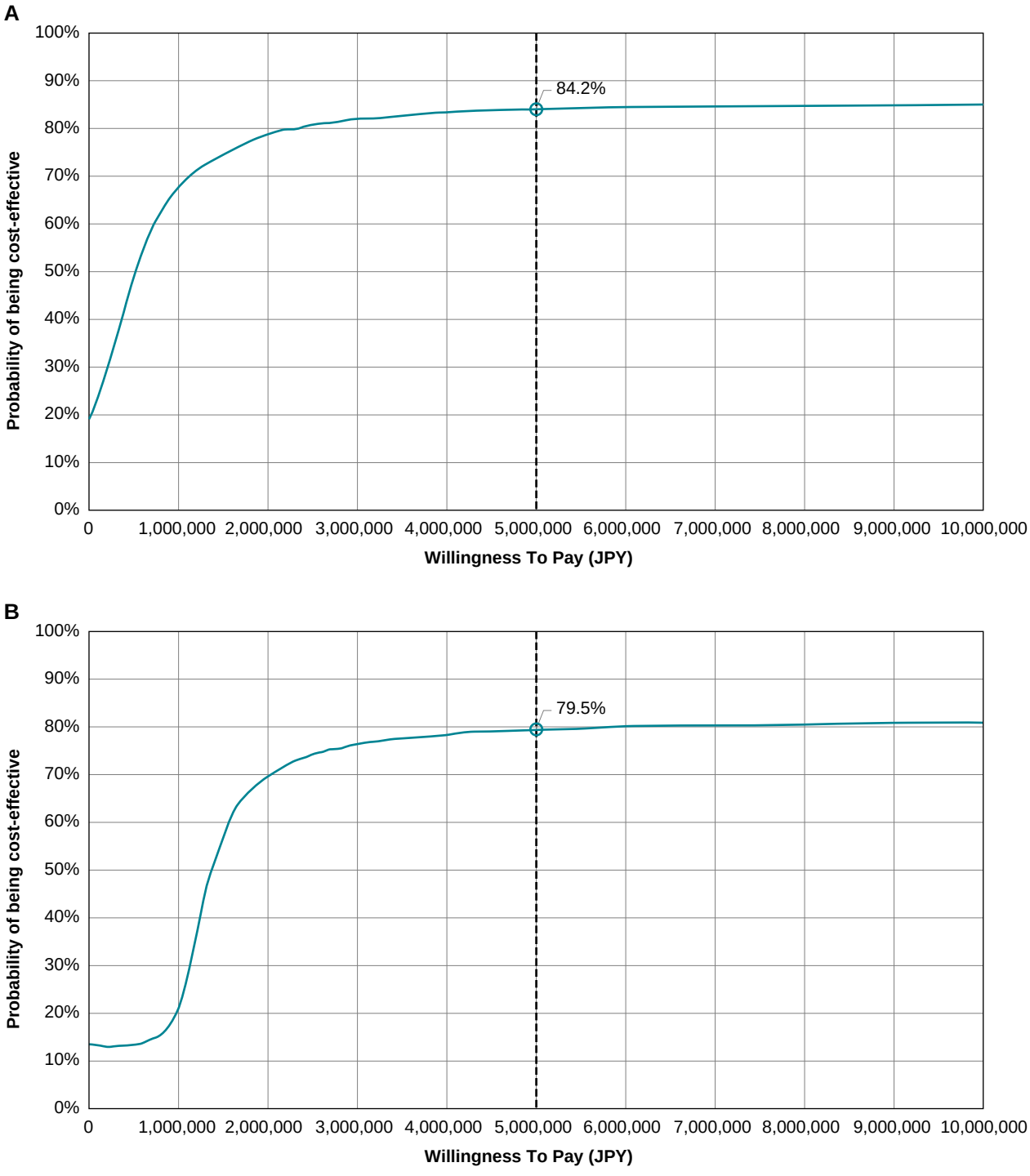


Figure 3 Cost-effectiveness acceptability curve. (*A*) Pacemaker. JPY, Japanese yen. (*B*) Cardiac resynchronization therapy device. JPY, Japanese yen.

ischaemic heart disease is lower in Japan than in the populations studied in the above-mentioned trials.[22–24] Furthermore, the present study may have overestimated mortality rates because it analysed data from 2020 by using mortality rates from RAFT and the COMPANION trial, which were published in 2010 and 2004, respectively, and the performance of CRT and drugs has improved since the publication of those trials. However, according to the results of sensitivity analysis, these is no significant impact of transition probabilities from non-Japanese clinical trials on ICERs, the extrapolation of non-Japanese clinical trials would not have a significant impact on the conclusion.

Second, we assumed that patient mortality after stroke is the same as that of patients with bradycardia even though it might be higher. We also assumed that there is no disutility for AF progression. We performed

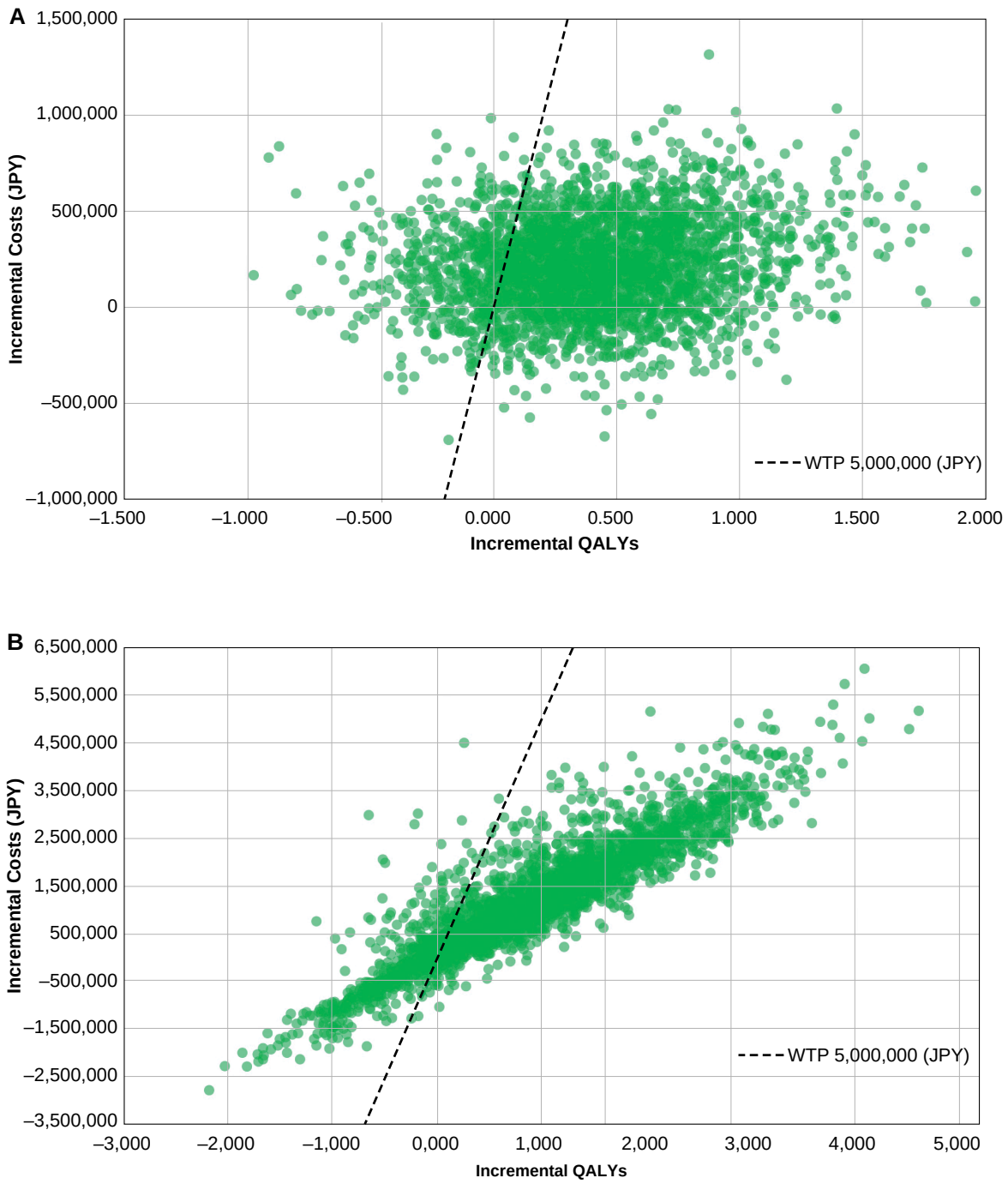


Figure 4 Incremental cost-effectiveness ratio scatter. (*A*) Pacemaker. ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; QALYs, quality-adjusted life years; WTP, willingness to pay. (*B*) Cardiac resynchronisation therapy device. ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; QALYs, quality-adjusted life years; WTP, willingness to pay.

DSA and PSA to assess the impact of uncertainty on the results and found that the uncertainty had a negligible impact on the conclusions.

Third, we did not consider whether any treatment for AF performed as part of standard clinical practice, such as catheter ablation, antiarrhythmic drug administration or electrical cardioversion, may be different between patients with devices with and without rATP.

Fourth, in real clinical practice, treatment for AF is not limited to rATP so rATP may actually have a smaller effect on preventing AF progression. However, the results of the DSA indicated that the uncertainty in the ratio of transition probability for devices with rATP to those for control devices was small.

Fifth, although tachycardiomyopathy (TCT) is partially or completely reversible after treatment of the triggering arrhythmia,[58,59] as far as we

know, no clinical evidence has shown the relation between prevention of AF progression by rATP and TCT. Therefore, we considered that it is difficult to include the reversibility in this study at this time.

Last, although battery longevity can vary depending on individual patient conditions, we used the standard value from the product specifications.

Conclusion

PMs and CRT-Ds with rATP are more cost-effective than devices without rATP in the Japanese healthcare insurance system, which justifies the higher reimbursement price of these functional categories with rATP from the perspective of healthcare economics.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: Y.T., Y.I., and T.M. are employees of Medtronic Japan, and J.-E.M. is an employee of Medtronic Korea. T.U., H.Y., and A.S. are employees of Medilead, which was commissioned by Medtronic Japan. K.K., T.N., and N.U. have received compensation for advisory services for this study from Medtronic Japan and other payments, including honoraria, for lectures which were not directly associated with this study from Medtronic Japan. K.K. has received speaker honoraria from Medtronic Japan, Biotronik Japan and Boston Scientific and research grants from Medtronic Japan and Biotronik Japan. The authors have no other conflicts of interest to disclose.

Data availability

The claims database that supports the findings of this study are available from Medical Data Vision Co., Ltd. but were used under licence for the current study; therefore, restrictions apply, and the data are not publicly available. For inquiries about access to the data set used in this study, please contact MDV (https://www.mdv.co.jp/; email address, ebm_sales@mdv.co.jp).

Other data underlying this article are available in the article and in its online *Supplementary material*.

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