Radiofrequency Catheter Ablation Versus Cryoballoon Ablation in the Treatment of Paroxysmal Atrial Fibrillation: A Cost-effectiveness Analysis in China

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ABSTRACT

Purpose: The aim of this study was to evaluate the cost-effectiveness of radiofrequency catheter ablation (RFCA) compared with cryoballoon (CB) ablation in the treatment of patients with paroxysmal atrial fibrillation (PAF) from the payer's perspective in China.

Methods: We constructed a cohort model, combining a 12-month decision-tree model with a lifetime Markov state-transition model, in a hypothetical cohort of patients with drug-refractory PAF managed with either RFCA or CB ablation, to compare the cost-effectiveness of the 2 procedures. Data related to clinical outcomes and costs in this model were obtained from a retrospective 12-month follow-up study in patients in China and from related literature. The incremental cost-effectiveness ratio (ICER) over a 10-year time period was calculated and compared against the willingness-to-pay (WTP) threshold. We used a 1-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) to access the structural uncertainty and the parameter uncertainty, respectively.

Findings: Over a 10-year time horizon, the total costs per patient of RFCA and CB ablation were ¥98,164.04 (US $15,339.57; €13,058.94) and ¥107,542.37 ($16,805.07; €14,306.55), respectively, and quality-adjusted life-years (QALYs) gained were 5.47 and 5.43, respectively. The ICER ratio was −¥224,365.01 (−$35,060.32; −€29,847.68) per QALY, indicating that RFCA is associated with greater QALYs and lower costs than CB ablation. The 1-way sensitivity analysis demonstrated that the model results were most sensitive to the odds ratio of the atrial fibrillation recurrence within 12 months in the RFCA group versus the CB ablation group, the cost of RFCA, and the perioperative stroke risk with RFCA. According to the results of the PSA, RFCA was associated with a high probability of being cost-effective (99.48%) compared with CB ablation at a WTP threshold of ¥161,940 ($25,305.50; €21,543.17) per QALY.

Implications: Our analysis indicates that RFCA is cost-saving compared with CB ablation in the treatment of patients with PAF in China, based on better QALYs and lower costs over a 10-year time horizon, from the payer's perspective. (*Clin Ther.* 2019;41:78−91) © 2018 Published by Elsevier Inc.

Key words: cost-effectiveness analysis, cryoballoon ablation, paroxysmal atrial fibrillation, quality-adjusted life-years, radiofrequency catheter ablation.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in the adult population. The age-standardized (>30 years) prevalence of AF in China is 0.65%, and it increases with age.[1] Over the past

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decade, there has been a 20-fold increase in the prevalence of AF in China, which is related to the aging population. Furthermore, with the propagation of basic health care systems, people with AF are more likely to be diagnosed in China now than in previous years, especially in less-developed areas.[2] Individuals with AF typically have poorer quality of life (QOL) than age-matched controls from the general population.[3–5] Moreover, AF is associated with a significant risk for adverse events, such as stroke, heart failure (HF), and death. Given the large population of China, AF can be a substantial burden on public health.[1] Thus, a comparison of AF-management strategies is essential for decision makers in the field of public health and health care spending in China.

Catheter ablation is a well-established treatment in patients with AF. According to the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society's guideline[6] on the management of patients with AF, catheter ablation is useful in the treatment of symptomatic paroxysmal atrial fibrillation (PAF) in patients who are refractory to or intolerant of at least 1 class I or III antiarrhythmic drug (AAD), when a rhythm-control strategy is desired (IA recommendation); China's 2018 guideline on the management of AF recommends a similar strategy. Circumferential pulmonary vein isolation (PVI) remains the "gold standard" of interventional therapy for PAF.[7,8] Radiofrequency catheter ablation (RFCA) and cryoballoon (CB) ablation are the most widely used AF-ablation techniques.

Both ablation techniques can effectively maintain sinus rhythm and improve QOL in patients with PAF. The 2016 FIRE AND ICE (Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation) trial[9,10] and a recent meta-analysis of data from 16 clinical trials that compared RFCA with CB ablation[11] demonstrated that CB ablation is noninferior to RFCA of PAF in terms of efficacy and tolerability. However, some studies have raised questions about the cost-effectiveness of both therapies in clinical practice.[12,13] Whether one ablation approach is more cost-effective than the other, especially in the long term, is yet to be determined.

RFCA and CB ablation are commonly used in patients with PAF in China. However, comparative analyses that have assessed the costs and QOL of both interventions are sparse. We constructed a cohort model to compare the cost-effectiveness of RFCA and CB ablation in treating patients with PAF, from the perspective of payers in China.

MATERIALS AND METHODS

Strategy and Basic Assumptions

We developed a decision-analytic simulation model using a combination of a 12-month decision tree and a lifetime Markov cohort state-transition structure to analyze effectiveness and costs in a hypothetical cohort of patients with PAF refractory to 1 or more AADs and managed with either RFCA or CB ablation. We chose this population because the expert consensus guideline in China recommends ablation in these patients.[6]

Based on a retrospective 12-month follow-up study in the clinical-practice setting in China, patients referred for ablation were assumed to be, on average, 60 years of age, without severe structural heart disease; the percentage of male patients was assumed to be 60%; the initial mean CHA_2DS_2-VASc (Cardiac failure or dysfunction, Hypertension, Age $\geq$75[Doubled], Diabetes, Stroke[Doubled]-Vascular disease, Age 65–74 and Sex category [Female]) score in the cohort was assumed to be 3, with variations determined by age and prevalence of stroke.

The model extrapolated the total costs and QOL over a lifetime horizon, using annual cycles after an initial decision on AF management. We used data from a retrospective 12-month follow-up study in patients in China and from related literature to calculate the expected total costs and quality-adjusted life-years (QALYs) associated with each ablation approach. The analysis was conducted from the payer's perspective. We used Excel 2016 software (Microsoft Corp, Redmond, Washington) for all model programming and calculations.

Model Structure

We created a short-term decision-tree model and a long-term Markov model (Fig. 1). The short-term model captured the clinical outcomes and costs within 12 months after the initial ablation procedure, while the long-term model simulated the clinical outcomes and costs after the first 12 months and over a patient's lifetime.

The starting point for the short-term model was the initial decision: RFCA or CB ablation. Following the ablation procedure, patients had probabilities of perioperative death, no complications, and nonfatal complications, including pericardial tamponade,

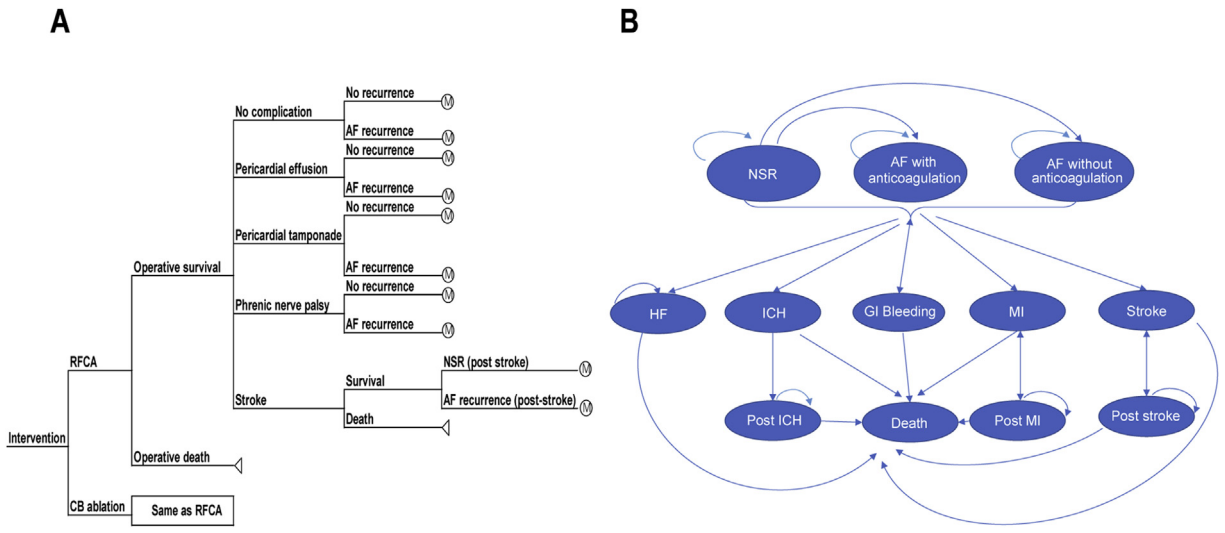

Fig. 1. Short-term (12-month; A) decision-tree model and long-term (lifetime; B) Markov model. AF = atrial fibrillation; CB ablation = cryoballoon ablation; GI bleeding = gastrointestinal bleeding; HF = heart failure; ICH = intracranial hemorrhage; MI = myocardial infarction; NSR = normal sinus rhythm; RFCA = radiofrequency catheter ablation.

pericardial effusion, phrenic nerve palsy, and perioperative stroke. Patients who died or had a nonfatal, procedure-related complication incurred an immediate cost and disutility. At the end of the 12-month period, the expected total short-term costs and QALYs were calculated by adding the costs and QALYs associated with each pathway weighted by the percentage of patients in the pathway. The short-term model also established the percentage of patients who entered the Markov process in different health states, based on the short-term AF recurrence rate, the percentage of patients with recurrent AF on anticoagulation therapy, and the perioperative stroke rate.

Fig. 1B illustrates the different health states used in the long-term Markov model and the possible transitions between them. Patients in the RFCA and CB ablation groups entered this model in 1 of 3 states: normal sinus rhythm (NSR), AF with or without anticoagulation therapy, and poststroke. The NSR state could transition to a state of AF with or without anticoagulation therapy, as shown by the annual AF recurrence rate and the percentage of patients with recurrent AF while being treated with an anticoagulant. Patients in any of these health states could transition to other health states (stroke, hemorrhagic event, HF, myocardial infarction [MI], and death), due to the risks for adverse events and mortality. Poststroke and post–MI patients could experience recurrent stroke and MI. Patients in every health state incurred an immediate cost and disutility. The cycle length for health–state transitions was set at 12 months; we used the standard half-cycle correction to remedy bias. The expected total long-term costs and QALYs were calculated by adding the costs and QALYs associated with each state weighted by the percentage of patients in the state, and subsequently adding the expected annual costs and QALYs across 10 cycles in the Markov model. We also assumed that patients could not move into a less severe state.

Model Inputs

Data regarding clinical outcomes, including AF recurrence rate, likelihood of procedure-related complications, adverse events, mortality, utility, and utility adjustment, were obtained from a retrospective 12-month follow-up study and related literature review. All data related to resource use and associated costs were provided by a local tertiary hospital in China.

AF Recurrence Rate Within 12 Months and Cost of Ablation Procedures

A retrospective, nonrandomized, single-center study was conducted in a clinical practice setting in China to obtain the AF recurrence rate within 12 months and the costs of ablation procedures. All therapies were provided according to guideline recommendations.[6] The study protocol was approved by the ethics committee at Beijing Chao-Yang Hospital (Beijing, China). We recruited patients with PAF who underwent RFCA or CB ablation between March 2014 and December 2016 at Beijing Chao-Yang Hospital. Eligible patients had PAF, had undergone catheter ablation, were aged 18−80 years, were successfully followed up for 12 months, and signed an informed-consent form. Patients with any of the following conditions were excluded: valvular AF, previous RFCA or CB ablation of AF, recent cardiac events (including MI, pacemaker therapy, percutaneous coronary intervention, valve replacement, or coronary artery bypass grafting in the preceding 3 months), symptomatic HF (New York Heart Association class III or IV), uncontrolled hypertension, severe hepatic disease, and renal dysfunction.

According to different ablation procedures, participants were stratified into 1 of 2 groups: RFCA or CB ablation. Circumferential PVI was performed in both groups of patients. All patients in the RFCA group underwent ablation with the ThermoCool SmartTouch (ST) catheter (Biosense Webster Inc., Irvine, California), which provided real-time contact force data in combination with the Carto 3-dimensional electroanatomic mapping system. In the CB ablation group, the first-generation cryoballoon (CBG-1) Medtronic Inc., Minneapolis, Minnesota was used in some patients, while others underwent ablation with the second-generation cryoballoon (CBG-2), which can record pulmonary vein potentials during ablation and has reengineered cryogen ports that ensure more homogeneous cooling at its frontal surface.[14]

After the RFCA or CB ablation procedure, patients received anticoagulation therapy and AAD therapy for 3 months. All patients were followed up by a nurse assigned to their case. They underwent 12-lead ECG and 24-h Holter monitoring at 1, 3, 6, and 12 months after the ablation procedure or when presenting with discomfort.

AF recurrence was defined as a recording of AF/atrial flutter/atrial tachycardia by ECG or AF/atrial flutter/atrial tachycardia lasting >30 s on 24-h ambulatory blood pressure monitoring after a 3-month blanking period. Data on demographic characteristics were collected. The end points were the rates of AF recurrence within 12 months and the costs associated with the ablation procedures. In the existing literature, data on patients with PAF in China were sparse and played a crucial role as input parameters in our cohort model.

Annual AF Recurrence Rate After the First Year of Ablation Procedures

The annual AF recurrence rate after the first year of ablation procedures was obtained from a previously published study by Roland et al, Ten-year Clinical Outcome After Circumferential PVI in Patients With Symptomatic Drug-Refractory PAF.[15] We calculated the mean annual AF recurrence rate after the first 12 months of PVI using RFCA (5.28%) based on the recurrence rates within 12 months and after 10 years of ablation reported by Roland et al. However, data on such long-term clinical outcomes after CB ablation were not reported. Jürgen et al[16] found long-term (over several years) AF success rates after CB ablation comparable to those with RFCA. Thus, we assumed that the annual AF recurrence rate after the first 12 months of CB ablation was the same as recurrence after RFCA.

Probability of Procedural Complications and Adverse Events

Because head-to-head clinical trials comparing RFCA and CB ablation are lacking, the probability of procedural complications such as perioperative death, perioperative stroke, pericardial effusion, pericardial tamponade, and phrenic nerve palsy was based on a meta-analysis that compared the hazard ratios in the RFCA (ST catheter; 78.2%) and CB ablation (CBG-2; 78.1%) groups and those from other published studies.[9,17,18]

The annual probability of ischemic stroke in patients on anticoagulation therapy while in the AF health state was based on the clinical risk stratification using the CHA_2DS_2-VASc score from a clinical trial in anticoagulated patients with AF (n = 7329).[18] A meta-analysis of data on anticoagulation therapies for stroke

prevention in patients with nonvalvular AF showed that anticoagulation reduced the risk for stroke by 64%.[19] The AFFIRM (Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management) study[20] reported an ischemic stroke hazard ratio of 1.6 in patients with AF recurrence on anticoagulation therapy compared with patients in NSR. Additionally, the annual probability of hemorrhagic events, including gastrointestinal bleeding (GI) and intracranial hemorrhage (ICH); the annual probability of HF; and the annual recurrence rates of stroke and MI in poststroke and post−MI patients, respectively, were obtained from other published studies.[21−25] The annual probability of MI was obtained from the 2013 Report on Cardiovascular Diseases in China.[26] In the 12-month follow-up study we conducted at Beijing Chao-Yang Hospital, the rate of AF recurrence with anticoagulation therapy was 54% in both groups, and the ratio of patients with AF recurrence while on warfarin versus those with AF recurrence while taking novel oral anticoagulants was 3:2; the rate of AF recurrence with AAD therapy was 48%, and the ratio of patients with AF recurrence while taking amiodarone versus those with AF recurrence while taking propafenone was 2:3. However, we did not consider the adverse effects of AADs in our analysis.

Mortality

In the model, death occurred in relation to stroke, ICH, GI, HF, MI, and other related events. Mortality caused by other related events was based on age- and sex-specific mortality rates of the general population, which were obtained from the sixth national population census conducted in China.[27] Various adverse events increased mortality in patients with AF compared with the general population, not only when death occurred immediately following the adverse events, but also when it occurred later. The relative risk for mortality associated with stroke, poststroke (12 months after stroke), ICH, post-ICH (12 months after ICH), GI, HF, MI, and post−MI (12 months after MI) in patients with AF as compared with the general population was obtained from previously published studies.[28−31]

Utility and Utility Adjustments

General population−based utilities in relation to age and sex were obtained from a study that assessed health status in the population in China.[32] Utilities were adjusted each time a patient in the cohort experienced an AF recurrence, a procedural complication, or an adverse event. The different utility decrements or multipliers applied to the loss of QOL due to procedural complications and adverse events were also obtained from previously published studies.[33−36]

Resource Use and Costs

Resource use and total costs in each ablation group were calculated using the decision-tree model and the Markov model. The short-term costs included those related to the ablation procedures and the management of procedural complications; the long-term costs included those related to various adverse events, anticoagulation therapy, and AAD therapy. Information on the resource use and associated costs was obtained from a local tertiary hospital by chart review and follow-up. We assumed that the annual poststroke, post-ICH, and post−MI treatment costs were 1/10 of the cost of immediate treatment of stroke, ICH, and MI, respectively.

Analytical Methods

We generated the cohort model with all necessary input parameters. The total costs and QALYs in the RFCA group and the CB ablation group were obtained from this model over the 10-year time period of the Markov model plus the 12-month period of the decision-tree model. The future costs and QALYs were discounted at a rate of 3.5% per year. Incremental cost-effectiveness ratios (ICERs) over a 10-year time period were calculated and compared against the willingness-to-pay (WTP) threshold.

Structural uncertainty was assessed using a 1-way sensitivity analysis, which was conducted by varying all parameters of ±20% within 95% CIs to examine the impact of important input variables on the ICER calculations. Parameter uncertainty was evaluated using a probabilistic sensitivity analysis, which was run using Monte Carlo simulation with 5000 iterations by varying the parameters following their distributions, to measure the probability of the cost-effective treatment with a given threshold. The results of the probabilistic sensitivity analysis (PSA) were presented in the form of a cost-effectiveness scatterplot.

RESULTS

Retrospective 12-month Follow-up Study Analysis

A total of 250 patients were enrolled in the retrospective study: 207 in the RFCA group (ST catheter,100%) and 43 in the CB ablation group (CBG-1, 72%). We collected the data on patients' baseline characteristics, presented in Table I. The mean age, sex distribution, and CHA_2DS_2-VASc score in the patients enrolled in this study did not differ significantly between the RFCA and CB ablation groups.

The rates of AF recurrence within 12 months of ablation were 14.49% (30/207) after RFCA and 30.23% (13/43) after CB ablation, and the odds ratio of the AF recurrence within 12 months in the RFCA group versus the CB ablation group was calculated to be 0.391. The mean (SD) costs of the ablation procedures were ¥83,203.44 (¥5706.60) ($13,001.76 [$891.74]; €11,068.70 [€759.16]) and ¥89,505.34 (¥2824.70) ($13,986.52 [$441.40]; €11,907.06 [€375.77]), respectively (Table II).

Base-case Analysis

All of the input parameters applied in the cohort model are presented in Table II. The deterministic results of the cost-effectiveness analysis included total cost, total QALYs, and ICERs over a 10-year time horizon. The total costs per patient were ¥98,164.04 ($15,339.57; €13,058.94) with RFCA and ¥107,542.37 ($16,0805.07; €14,306.55) with CB ablation; the total QALY values per person were 5.47 in the RFCA group and 5.43 in the CB ablation group. The ICER was −¥224,365.01 (−$35,060.32; −€29,847.68) per QALY, indicating that RFCA is associated with better QALYs and lower costs than CB ablation over a 10-year time horizon. These results suggest that RFCA is more cost-effective compared with CB ablation in the treatment of patients with PAF in China.

Sensitivity Analysis

The 1-way sensitivity analysis showed that the model results were most sensitive to the odds ratio of the AF recurrence within 12 months in the RFCA group versus the CB ablation group, the cost of the RFCA procedure, and the perioperative stroke risk with RFCA. The results of the 1-way sensitivity analysis are illustrated on the tornado diagram in Fig. 2A. The results of the PSA are shown on the scatterplot in Fig. 2B. RFCA had a high probability of being cost-effective (99.48%) compared with CB ablation, based on a WTP threshold of ¥161,940 ($25,305.50; €21,543.17) per QALY. The WTP threshold is assumed to be 3-fold the value of the per capita gross domestic product in China.[37–39]

DISCUSSION

Management of AF is aimed at reducing symptoms and at preventing severe complications associated with AF. These therapeutic goals need to be pursued in parallel by rhythm-control therapy, rate-control therapy, antithrombotic therapy, and adequate therapy for concomitant cardiac diseases.[40] As for long-term rhythm- and rate-control therapies, there are 2 main

Table I. Baseline characteristics of patients with paroxysmal atrial fibrillation during radiofrequency catheter ablation (RFCA) or cryoballoon ablation (CBA).

Characteristic	RFCA (n = 207)	CBA (n = 43)	All Patients (n = 250)	*P*
Male, no. (%)	122 (58.9)	26 (60.5)	148 (59.2)	1.000
Age, mean (SD), y	64.6 (11.0)	61.3 (9.6)	64.0 (10.8)	0.069
CHA_2DS_2—VASc score, mean (SD)	2.7 (1.6)	2.4 (1.8)	2.7 (1.6)	0.243
HT, no. (%)	129 (62.3)	28 (65.1)	157 (62.8)	0.863
CAD, no. (%)	61 (29.5)	11 (25.6)	72 (28.8)	0.713
LA, mean (SD), mm	37.4 (4.4)	38.0 (3.5)	37.5 (4.2)	0.366
LVEF, mean (SD), %	67.2 (6.0)	67.4 (5.6)	67.2 (6.0)	0.793

CAD = coronary artery disease; CHA2DS2-VASc = Cardiac failure or dysfunction, Hypertension, Age ≥75(Doubled), Diabetes, Stroke(Doubled)-Vascular disease, Age 65 -74 and Sex category (Female); HT = hypertension; LA = left atrium; LVEF = left ventricular ejection fraction.

Table II. Input parameters used in the base-case model.

Input Parameter	Value	95% CI		Distribution	Reference
		Low	High		
Age, y*	60	55	65	—	Assumption
Initial CHA_2DS_2—VASc score*	3	2	4	—	Assumption
Male, %	60	50.06	65.25	Beta	Assumption
Discount rate for costs, %	3.50	2.80	4.20	Triangular	Assumption
Discount rate for QALYs, %	3.50	2.80	4.20	Triangular	Assumption
AF recurrence rate at 12 mo: RFCA, %	14.49	10.05	19.59	Beta	Local hospital
OR of AF recurrence at 12 mo: RFCA vs CB	0.391	0.199	0.769	Lognormal	Local hospital
Annual AF recurrence rate after 12 mo: RFCA, %	5.28	3.90	6.86	Beta	15, 16
Annual AF recurrence rate after 12 mo: CB, %	5.28	3.90	6.86	Beta	Assumption
Probability of procedural complications, %					
Perioperative death: RFCA/CB	0.05	—	—	—	17
Perioperative stroke: RFCA	0.53	0.06	1.48	Beta	9
Perioperative stroke: CB	0.53	0.07	1.48	Beta	9
Pericardial effusion: RFCA	2.10	1.68	2.56	Beta	18
Pericardial effusion: CB	0.80	0.52	1.15	Beta	18
Pericardial tamponade: RFCA	1.38	1.00	1.81	Beta	18
Pericardial tamponade: CB	0.36	0.15	0.68	Beta	18
Phrenic nerve palsy: RFCA	0.00	—	—	—	18
Phrenic nerve palsy: CB	1.67	1.16	2.26	Beta	18
Annual probability of adverse events					
Stroke risk stratification: AF—anticoagulation, %					
CHA_2DS_2—VASc score = 3	3.20	3.20	3.20	Constant	21
CHA_2DS_2—VASc score = 4	4.00	4.00	4.00	Constant	21
CHA_2DS_2—VASc score = 5	6.70	6.70	6.70	Constant	21
CHA_2DS_2—VASc score = 6	9.80	9.80	9.80	Constant	21
CHA_2DS_2—VASc score = 7	9.60	9.60	9.60	Constant	21
CHA_2DS_2—VASc score = 8	12.50	12.50	12.50	Constant	21
CHA_2DS_2—VASc score = 9	15.20	15.20	15.20	Constant	21
RR stroke: AF—anticoagulation vs AF—non	2.78	2.78	2.78	Constant	21
RR stroke: AF—anticoagulation vs NSR	1.6	1.11	2.30	Lognormal	20
Patients requiring anticoagulation treatment, %	53.9	43.1	64.6	Uniform	Local hospital
Patients requiring AAD treatment, %	48.2	38.4	57.6	Uniform	Local hospital
ICH: AF—anticoagulation, %	0.80	0.60	1.01	Beta	23
ICH: AF—non/NSR, %	0.50	0.36	0.65	Beta	23
GI bleeding: AF—anticoagulation, %	0.91	0.73	1.09	Triangular	19

Table II. (*Continued*)

Input Parameter	Value	95% CI		Distribution	Reference
		Low	High		
GI bleeding: AF—non/NSR, %	0.96	0.77	1.15	Triangular	19
HF: NSR, %	0.07	0.07	0.07	Constant	24
RR HF: AF vs NSR	4.62	3.70	5.54	Lognormal	25
MI: NSR, %	0.17	0.17	0.17	Constant	26
RR MI: AF vs NSR	1.54	1.21	1.96	Lognormal	25
Recurrence rate of MI, %	5.46	4.37	6.55	Triangular	22
Annual mortality in the general population in China, %					
Age 60—64 y: men	1.30	1.30	1.30	Constant	27
Age 60—64 y: women	0.75	0.75	0.75	Constant	27
Age 65—69 y: men	2.13	2.13	2.13	Constant	27
Age 65—69 y: women	1.31	1.31	1.31	Constant	27
Age 70—74 y: men	3.70	3.70	3.70	Constant	27
Age 70—74 y: women	2.44	2.44	2.44	Constant	27
Age 75—79 y: men	5.91	5.91	5.91	Constant	27
Age 75—79 y: women	4.09	4.09	4.09	Constant	27
Age 80—84 y: men	9.86	9.86	9.86	Constant	27
Age 80—84 y: women	7.40	7.40	7.40	Constant	27
Age 85—89 y: men	14.65	14.65	14.65	Constant	27
Age 85—89 y: women	11.53	11.53	11.53	Constant	27
RR of mortality of adverse events					
Stroke	7.4	6.48	8.46	Lognormal	28
Poststroke	2.3	1.98	2.67	Lognormal	28
ICH	7.4	6.48	8.46	Triangular	Assumption
Post-ICH	2.3	1.98	2.67	Triangular	Assumption
GI bleeding	3.5	2.80	4.20	Triangular	29
HF	1.74	1.39	2.09	Triangular	30
MI	5.84	3.99	8.55	Lognormal	31
Post—MI	2.21	0.46	10.68	Lognormal	31
Utility of the general population in China					
Age 60—64 y: men	0.751	0.6008	0.9012	Triangular	32
Age 60—64 y: women	0.728	0.5800	0.8700	Triangular	32
Age 65—69 y: men	0.725	0.5608	0.8412	Triangular	32
Age 65—69 y: women	0.702	0.5472	0.8208	Triangular	32
Age 70—74 y: men	0.701	0.5296	0.7944	Triangular	32
Age 70—74 y: women	0.685	0.5288	0.7932	Triangular	32
Age 75—79 y: men	0.684	0.5824	0.8736	Triangular	32
Age 75—79 y: women	0.669	0.5616	0.8424	Triangular	32
Age 80—84 y: men	0.662	0.5480	0.8220	Triangular	32
Age 80—84 y: women	0.655	0.5352	0.8028	Triangular	32
Age 85—89 y: men	0.661	0.5240	0.7860	Triangular	32
Age 85—89 y: women	0.643	0.5144	0.7716	Triangular	32

(*continued on next page*)

Table II. (*Continued*)

Input Parameter	Value	95% CI		Distribution	Reference
		Low	High		
Utility adjustment					
Decrement					
NSR	0	—			Assumption
AF recurrence	0.0034	0.00272	0.00408	Triangular	28
Procedural complications	0.10	0.08	0.12	Triangular	33
GI bleeding	0.151	0.1208	0.1812	Triangular	34
HF	0.0175	0.352	0.528	Triangular	35
Multiplier, %					
Stroke	50	40	60	Triangular	36
Poststroke	63	50	75.6	Triangular	36
ICH	50	40	60	Triangular	Assumption
Post-ICH	63	50	75.6	Triangular	Assumption
MI	70	64	96	Triangular	36
Post—MI	80	56	84	Triangular	36
Costs of treatment, US $					
RFCA procedure	13,001.76	11,341.51	14,835.26	Lognormal	Local hospital
CBA procedure	13,986.52	13,141.26	14,871.33	Lognormal	Local hospital
Anticoagulation, per year	583.33	466.66	699.99	Triangular	Local hospital
AADs, per year	141.27	113.02	169.52	Triangular	Local hospital
Pericardial effusion treatment	121.11	96.88	145.33	Triangular	Local hospital
Pericardial tamponade treatment	340.85	272.68	409.02	Triangular	Local hospital
Phrenic nerve palsy treatment	23.44	18.75	28.13	Triangular	Local hospital
Stroke treatment	3656.94	2925.55	4388.33	Triangular	Local hospital
Poststroke treatment, per year	365.69	292.56	438.83	Triangular	Local hospital
ICH treatment	5804.57	4643.66	6965.49	Triangular	Local hospital
Post-ICH treatment, per year	580.46	464.37	696.55	Triangular	Local hospital
MI treatment	8817.64	7240.33	12307.84	Triangular	Local hospital
Post—MI treatment, per year	881.76	724.03	1230.78	Triangular	Local hospital
HF treatment, per year	452.76	362.21	543.31	Triangular	Local hospital
GI bleeding treatment	1652.82	1322.26	1983.39	Triangular	Local hospital
Death	0	0	0	Constant	Assumption

AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary heart disease; CB = cryoballoon; CHA2DS2-VASc = Cardiac failure or dysfunction, Hypertension, Age ≥75(Doubled), Diabetes, Stroke(Doubled)-Vascular disease, Age 65 -74 and Sex category (Female); GI = gastrointestinal; HF = heart failure; ICH = intracranial hemorrhage; MI = myocardial infarction; NSR = normal sinus rhythm; PAF = paroxysmal atrial fibrillation; QALY = quality-adjusted life-year; RFCA = radiofrequency catheter ablation; RR = rate ratio.

* Age and initial CHA_2DS_2—VASc score vary in a reasonable range, defined by the authors instead of within 95% CIs.

management strategies: ablation therapy and AAD therapy. Catheter ablation, including RFCA and CB ablation, can effectively restore and maintain NSR.[9] Compared with AAD therapy, catheter ablation has been associated with greater efficacy and fewer serious adverse events. In addition, a number of studies have demonstrated that catheter ablation appears to be reasonably cost-effective in the long term compared with AAD therapy in patients with PAF, whether it is RFCA or CB ablation.[28,33] However, as for both

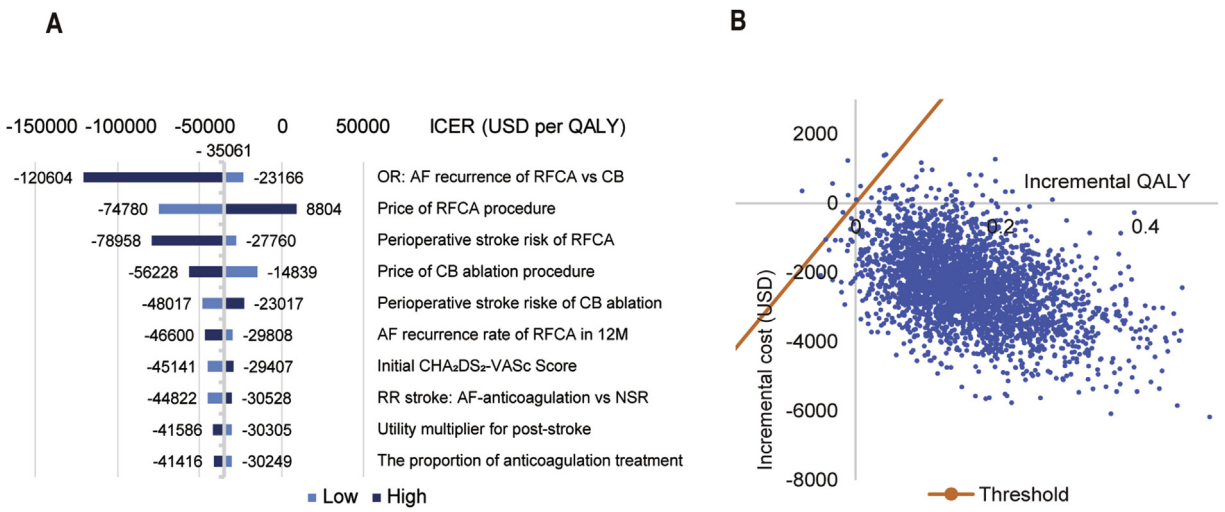

Fig. 2. One-way sensitivity analysis (tornado diagram; A) and probabilistic sensitivity analysis (scatterplot; B). AF = atrial fibrillation; CB = cryoballoon; ICER = incremental cost-effectiveness ratio; NSR = normal sinus rhythm; OR = odds ratio; QALY = quality-adjusted life year; RFCA = radiofrequency catheter ablation; RR = rate ratio.

ablation techniques, whether one ablation approach is more cost-effective than the other, especially in the long term, is not clear. In our analysis, we compared the cost-effectiveness of RFCA with that of CB ablation.

We constructed the first cohort model to compare the cost-effectiveness of RFCA and CB ablation in the treatment of patients with PAF, which combined a 12-month decision tree and a lifetime Markov state-transition structure to quantify the potential QOL reduction associated with major clinical events. Over a 10-year horizon, the ICER of −¥224,365.01 (−$35,060.32; −€29,847.68) per QALY calculated in the base-case analysis showed that RFCA maintains cost-savings compared with CB ablation. Using a WTP threshold of ¥161,940 ($25,305.50; €21,543.17) per QALY, we obtained a 99.48% probability that RFCA is cost-saving compared with CB ablation in the treatment of patients with PAF in China.

Our economic analysis was based on a lifetime cohort model that showed that RFCA was more cost-effective than was CB ablation in the treatment of patients with PAF. However, another study that used a trial-based economic analysis demonstrated that CB ablation was more cost-effective compared with RFCA.[13] Four major differences between the 2 analyses may have led to different results. First, ~75% of patients in the RFCA group in the trial-based economic analysis underwent RFCA without an ST catheter, whereas an ST catheter was used in 100% of patients undergoing RFCA in our study; CBG-2 was used in 100% of patients in the CB ablation group of the trial-based analysis, whereas ~72% of patients in our study underwent CB ablation with CBG-1. RFCA with ST catheterization provides an accurate quantitative real-time estimation of catheter tip−myocardial tissue contact force data. Compared with the standard non−contact force guided ablation, RFCA with ST is reliable, easy to use, and well predictive of lesion transmurality, which results in a significant reduction in the prevalence of dormant conduction with improved long-term freedom from recurrent arrhythmias.[41] CBG-2 provides more homogeneous cooling at its frontal surface, achieving colder temperatures within less time, and a larger cooling surface area, improving contact with the pulmonary vein antrum. A meta-analysis of data on the tolerability and efficacy of CBG-2 versus CBG-1 in the treatment of AF showed that arrhythmia recurrence is significant lower with CBG-2 than with CBG-1.[42] Thus, the techniques of RFCA and CB ablation greatly affect the recurrence rate of catheter ablation. Second, in some countries, advanced technologies in AF ablation are widely used. For

example, intracardiac echocardiography is widely used in the United States because it provides real-time anatomic information on relevant atrial structures and facilitates precise guidance of AF ablation, which contribute to the safety and effectiveness of the procedure.[43] However, intracardiac echocardiography is rarely used in China because it is expensive and excluded from health insurance coverage. This fact could be relevant to the different results. Third, in the trial-based analysis, follow-up was 18 months, whereas our study used a lifetime cohort model and evaluated QALYs and costs over a 10-year time horizon. Fourth, in the trial-based study, the costs were based on 3 Western health care systems (those in Germany [€], the United Kingdom [£], and the United States [$]); the costs in our study, which were based on the health care system in China (¥), were significantly different. Thus, the difference in results between the trial-based analysis and our model-based analysis is reasonable.

RFCA using ST catheter and CB ablation have been widely performed in China. However, the efficacy and tolerability of these ablation approaches in the management of patients with PAF in China remain unclear. Evaluations of resource use and costs in the clinical setting in China are lacking. In conducting this health economic analysis, we adopted the data regarding clinical outcomes, QOL, and costs mostly from a study in clinical practice conducted in China and from related published studies reflecting the clinical setting in China. Therefore, our results likely mirror the current clinical realities of treating patients with PAF who require ablation therapy in China. In this study, cost-effectiveness was evaluated using the perspective of payers in China. The results may guide decision making when RFCA and CB ablation are both valid options for the treatment of patients in China. Nonetheless, CBG-1 ablation is a novel technology that has been used in China for only 4 years. CBG-2 ablation has been adopted widely because it is easier for surgeons to master.[44] Thus, the effectiveness and costs associated with CB ablation in China are expected to be improved in the near future.

Limitation

To date, no head-to-head clinical trials or meta-analyses have compared the efficacy of RFCA and CB ablation in the clinical setting in China. Because rates of AF recurrence within 12 months after RFCA and CB ablation in patients in China could not be obtained from published studies, we constructed a retrospective 12-month follow-up study at Beijing Chao-Yang Hospital to obtain the comparative data. In China, there is no public database to provide information on resource use and related costs. Instead, we derived the data using chart review and follow-up from Beijing Chao-Yang Hospital, a tertiary hospital with a well-maintained electronic database and systematic follow-up. Although our method of data collection was less than ideal, it affords an accurate reflection of clinical practice in China.

The cohort model we used in our economic analysis could not simulate all clinical scenarios of patients with PAF who undergo ablation procedures. We did not include repeated ablation procedures. Repeated ablation is effective in restoring NSR in patients with AF recurrence [both pulmonary vein (PV)-mediated and non-PV arrhythmia by PV reconnection] through conventional ablation or linear ablation.[45,46] RFCA is performed using a point-by-point method, while CB ablation is performed in a single step.[7,8] Considering the different mechanisms of AF recurrence and the different ablation techniques, patients with AF recurrence can benefit from the RFCA approach. Since we excluded repeated ablation procedures from our Markov model, long-term clinical outcomes in patients who initially underwent CB ablation were not influenced by subsequent RFCA.

CONCLUSION

The findings from our analysis, conducted from the payer's perspective, suggest that RFCA is more cost-saving compared with CB ablation in the treatment of patients with PAF in China, based on greater QALYs and lower costs over a 10-year time horizon.

AUTHOR CONTRIBUTION STATEMENT

Xue-Rong Sun: Methodology, Validation, Resources, Investigation, Formal Analysis, Data Curation, Writing-Original Draft. Shu-Nan He: Validation, Data Curation, Visualization. Zi-Yi Lin: Software, Formal Analysis, Visualization. Lei Zhang: Methodology, Software, Formal Analysis. Yan-Jiang Wang: Investigation, Data Curation. Li-Jun Zeng: Investigation, Data Curation. Liang Shi: Investigation, Visualization. Jian-Wei Xuan: Conceptualization, Methodology. Ying-Tian: Validation, Visualization, Funding Acquisition. Xin-Chun Yang: Resources, Supervision, Project Administration. Xing-Peng Liu: Conceptualization,

Writing – Review and Editing, Supervision, Project Administration, Funding Acquisition.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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