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ORIGINAL ARTICLE

Economic and Health Value of Delaying Atrial Fibrillation Progression Using Radiofrequency Catheter Ablation

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BACKGROUND: Radiofrequency catheter ablation (RFCA) is an established treatment for atrial fibrillation (AF) refractory to antiarrhythmic drugs. The economic value of RFCA in delaying disease progression has not been quantified.

METHODS: An individual-level, state-transition health economic model estimated the impact of delayed AF progression using RFCA versus antiarrhythmic drug treatment for a hypothetical sample of patients with paroxysmal AF. The model incorporated the lifetime risk of progression from paroxysmal AF to persistent AF, informed by data from the ATTEST (Atrial Fibrillation Progression Trial). The incremental effect of RFCA on disease progression was modeled over a 5-year duration. Annual crossover rates were also included for patients in the antiarrhythmic drug group to mirror clinical practice. Estimates of discounted costs and quality-adjusted life years asssociated with health care utilization, clinical outcomes, and complications were projected over patients' lifetimes.

RESULTS: From the payer's perspective, RFCA was superior to antiarrhythmic drug treatment with an estimated mean net monetary benefit per patient of $8516 ($148–$16681), driven by reduced health care utilization, cost, and improved quality-adjusted life years. RFCA reduced mean (95% CI) per-patient costs by $73 (−$2700 to $2200), increased mean quality-adjusted life years by 0.084 (0.0–0.17) and decreased the mean number of cardiovascular-related health care encounters by 24%.

CONCLUSIONS: RFCA is a dominant (less costly and more effective) treatment strategy for patients with AF, especially those with early AF for whom RFCA could delay progression to advanced AF. Increased utilization of RFCA—particularly among patients earlier in their disease progression—may provide clinical and economic benefits.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ catheter ablation ■ disease progression ■ humans ■ quality of life

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of heart failure, stroke, and cardiovascular mortality.[1] Patients with AF also experience significantly lower quality of life compared with the general population.[2] AF currently affects 5 to 9 million individuals in the United States, and its prevalence is expected to increase to as high as 12.1 million by 2030.[3] Direct and indirect costs associated with AF in the United States are estimated to be $30.5 billion (2015 USD) and are predicted to increase to $65.7 billion by the year 2035.[4]

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WHAT IS KNOWN?

- Atrial fibrillation (AF) is a progressive disease; more progressive forms of AF increase patient morbidity and health resource utilization.
- Radiofrequency catheter ablation is more effective than antiarrhythmic drug treatment in preventing AF progression.

WHAT THE STUDY ADDS

- This study is the first to quantify the health economic impact of reducing AF progression from early AF to advanced AF from the perspective of a US health care payer.
- Radiofrequency catheter ablation is associated with several clinical and economic advantages as compared with antiarrhythmic drug-only treatment and is the dominant cost-effective treatment for AF from a US health care payer perspective.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drugs
AF	atrial fibrillation
AT	atrial tachycardia
ATTEST	Atrial Fibrillation Progression Trial
ICER	incremental cost-effectiveness ratio
PAF	paroxysmal atrial fibrillation
PsAF	persistent atrial fibrillation
QALY	quality adjusted life year
RFCA	radiofrequency catheter ablation

Randomized clinical trials have shown that radiofrequency catheter ablation (RFCA) is safe and effective at reducing long-term AF recurrence in patients with paroxysmal AF (PAF) compared with treatment with antiarrhythmic drugs (AADs) alone.[5,6] Moreover, RFCA has been associated with greater improvements in patient-reported QoL and with similarly low complication rates relative to AAD treatment.[6,7]

AF is a progressive disease and can be clinically categorized as early AF (paroxysmal AF) or advanced AF (persistent or long-standing persistent AF).[8,9] Progression from early AF to advanced AF is associated with increased morbidity and worse clinical outcomes.[10] Prior observational evidence has suggested that patients with AF treated with medical therapy have more rapid rates of AF progression versus those treated with RFCA,[11] and the recent ATTEST (Atrial Fibrillation Progression Trial, https://www.clinicaltrials.gov; Unique identifier: NCT01570361) was the first randomized clinical study to demonstrate that patients with PAF treated with RFCA were significantly less likely to progress to persistent atrial fibrillation (PsAF) than those with AAD treatment over a 3-year period.[12] The ATTEST trial reported that at 3 years, the Kaplan-Meier estimate of progression to persistent AF/AT was ≈10× lower in the radiofrequency cohort (hazard ratio, 0.107 [95% CI, 0.024–0.47]). Rate of recurrent AF/AT at 3 years was also significantly lower in the radiofrequency ablation group compared with the AAD group (49.2% versus 84.8%, $P<0.0001$).

Previous economic analyses have demonstrated RFCA to be cost effective compared with the use of AADs alone[13,14]; however, these studies have primarily focused on cohorts of PAF-only patients or a heterogeneous mix of patients with symptomatic AF and do not explicitly consider the health and economic impact of delaying AF progression. To our knowledge, this analysis is the first to assess the estimated lifetime health and economic impact of delaying progression from early AF to advanced AF for patients receiving RFCA or AAD treatment from a US payer perspective.

METHODS

Authors declare that all publicly available data excluding data of sensitive nature are available within the article (and its Supplemental Material).

A time-heterogeneous, individual-level state-transition health economic model was developed to estimate the impact of delayed AF progression in a simulated cohort of patients with PAF, managed with either RFCA or AAD treatment. Differential rates of AF recurrence and progression for each treatment arm resulted in differential cost and utility estimates, given differences in medical resource utilization and health-related quality of life as a function of disease severity. The time-heterogenous nature of the model allowed for state-transition probabilities to vary over time to more closely approximate real-world changes in health status. The base-case model structure, that is, a model structure with the most standard, realistic, or likely set of parameters or inputs, included RFCA crossover for patients in the AAD treatment group, and a 5-year effect on AF progression for RFCA.

To isolate the effect of progression, the model characterized AF disease using 2 severity levels: Early AF, wherein patients were in normal sinus rhythm with or without PAF recurrences, and advanced AF, wherein patients could experience persistent/long-standing persistent AF. Advanced AF was intended to characterize generally sicker patients due to having experienced PsAF with potentially higher steady-state health care resource utilization rates but was not intended to represent a patient's exact rhythm status over the simulation period. The model incorporated the risk of progression from early AF to advanced AF and generated lifetime discounted costs and quality-adjusted life year (QALYs) based on AF severity-dependent rates of resource consumption, health outcomes, and complications.

The model commenced with the entry of patients with PAF refractory to at least one AAD or rate control drug, average age of 67 years and a HATCH score (Hypertension, Age, Stroke or transient ischemic attack, Chronic obstructive pulmonary diease, and Heart failure) of 1 to 4, to simulate patients similar to those included in ATTEST. Figure 1 summarizes each
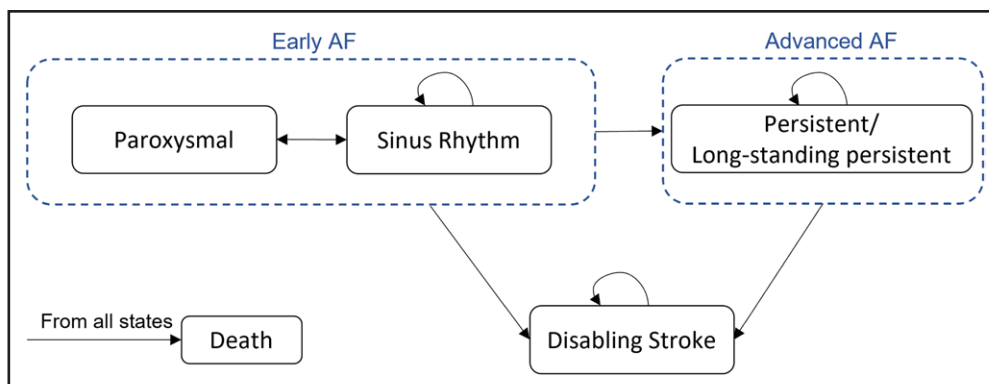
Figure 1. Atrial fibrillation (AF) state-transition model.
At any given time, a patient's health state was represented by one of the states shown by rectangles. Solid arrows between states represented possible transitions based on model cycle (3 months) probabilities. Patients received either radiofrequency catheter ablation (RFCA) or antiarrhythmic drugs (AADs) in the first cycle and transitioned from paroxysmal AF (PAF) to a sinus rhythm state for the next cycle. In subsequent cycles, patients could experience PAF recurrence, progression to advanced AF (with persistent AF [PsAF] occurrence), experience disabling stroke, or maintain sinus rhythm. Advanced AF did not represent a patient's exact rhythm status over the simulation period but was intended to characterize patients with more severe AF disease. Transition to death was included from all states.

possible health-state transition (excluding death) from one cycle to another. Patients received either RFCA or AADs in the first cycle (3 months) and transitioned from PAF to a sinus rhythm state for the next cycle. In subsequent cycles, patients could experience PAF recurrence, progression to advanced AF (with first occurrence of PsAF) or remain in normal sinus rhythm. After a PAF recurrence, patients returned to a normal sinus rhythm state. After first occurrence of PsAF, patients remained in the advanced AF until they experienced a disabling stroke or died. Patients could experience stroke while in early or advanced AF, though only disabling stroke was included as a separate absorbing state due to its long-term impact on quality of life.

Transition probabilities for PAF recurrence and AF progression (triggered by PsAF occurrence) were estimated based on ATTEST patient-level data.[12] ATTEST was the first randomized controlled trial to specifically investigate the impact of AF progression between RFCA and AADs. It minimized heterogeneity in the patient population and ensured a similar, structured management protocol for all patients. Parametric survival curves were fit to the empirical survival data from ATTEST to extrapolate beyond the trial follow-up time (Analytic Methods in the Supplemental Material). Patient's treatment (RFCA versus AADs) and time since treatment were predictors within the parametric survival models and affected transition probabilities. In the base-case analysis, the incremental effect of RFCA versus AADs on AF progression was conservatively assumed to persist for 5 years from procedure time, after which RFCA was assumed to have no incremental effect on disease progression relative to AADs. We used deidentified patient-level data for our modeling, and therefore, the study did not constitute human subjects research and was exempt from IRB approval.

Treatment Scenarios

Treatment scenarios were designed to isolate the economic impact of delayed AF progression due to RFCA. In addition to primary treatment assignment (RFCA versus AADs [with or without crossover]), treatment scenarios differed as a result of the speed at which patients experienced PAF recurrence or advanced AF.

Patients within the same model health state—regardless of initial treatment assignment—were assumed to have the same medical resource utilization, utilities, and risk of stroke.

In the AAD scenario, all patients entering the model received an AAD. In case of PAF recurrence, patients could switch to another AAD, or cross over to receive RFCA at an annual rate of 12%, as seen in ATTEST,[12] for 5 years from model initiation, the same duration considered for RFCA effect on reduced AF progression. The 12% annual rate reflects a cumulative 47% crossover rate for patients in the AAD by the end of year 5. Reduced RFCA-specific AF recurrence and progression rates were applied for a limited duration of 5 years, to patients who crossed over. A proportion of patients started/remained on AADs after RFCA procedure while in normal sinus rhythm (Table 1).

In the RFCA scenario, all patients entering the model received RFCA and continued in sinus rhythm unless they transitioned to another health state. However, a proportion of patients started/remained on AADs after RFCA while in normal sinus rhythm (Table 1). In the event of PAF recurrence, patients started/switched AAD and returned to sinus rhythm.

Patients could transition to advanced AF based on the estimated parametric survival curves for PsAF occurrence (Analytic Methods in the Supplemental Material). Regardless of the treatment scenario in early AF, all patients were treated the same in advanced AF. Patients who transitioned to advance AF underwent an RFCA procedure and a proportion of patients remained on AADs (Table 1). The details of resource utilization rates for each health state are presented below.

Model Inputs

Clinical parameters included patient demographics, cardiovascular-related inpatient admissions, office visits, emergency department visits, outpatient cardioversions, AAD nonfatal toxicity, ischemic stroke (with or without disability), oral anticoagulant medication use (Health Care Resource Utilization Rates in the Supplemental Material), and mortality (Table 1). Rates of health care resource utilization were calculated based on a posthoc analysis of data used in a study by Friedman et al[17]

Table 1. Clinical Parameters

Parameter	Value	Reference
Population characteristics		
Age, mean (SD)	67 (4.7)	Kuck et al[12]
Maximum age	100	
Male, %	43	
Treatment effect (delayed AF recurrence and progression)	ATTEST data	Kuck et al[12]
Treatment effect duration	5 y	Expert opinion
Crossover rate in early AF (annually for 5 y)	12%	Kuck et al[12] and expert opinion
Ischemic stroke (quarterly probability)		
Early AF	0.00432	Steinberg et al[15]
Advanced AF	0.00546	Steinberg et al[15]
Proportion of disabling ischemic stroke	37.8%	Han et al[16]
Health care resource utilization AF state/severity* (quarterly probability)		
Early AF: sinus rhythm	Once/quarter	Expert opinion
AF-related office visits for patients on AADs	Once/quarter	Expert opinion
Early AF: paroxysmal AF†		
CV-related inpatient admissions	0.132	Friedman et al[17]
CV-related office visits	0.930	
CV-related emergency department visits	0.206	
Outpatient cardioversions	0.094	
Advanced AF: persistent/long-standing persistent AF†		
CV-related inpatient admissions	0.051	Friedman et al[17]
CV-related office visits	0.814	
CV-related emergency department visits	0.065	
Outpatient cardioversions	0.070	
Other resource utilization		
Patients remaining on AADs after RFCA		
Early AF	54%	Friedman et al[17]
Advanced AF	62%	Friedman et al[17]
AAD nonfatal toxicity	9.5%	Reynolds et al[13]
OAC medication use in early AF, %		
RFCA		
First 3 mo‡	100	Arbelo et al[18]
4–12 mo	67.8	
13+ mo	59.3	
AAD	83.7	Arbelo et al[18]
OAC medication use in advanced AF, %	100	Expert opinion
Mortality		
Background mortality	US life tables	Arias and Xu[19]

(Continued)

Table 1. Continued

Parameter	Value	Reference
Mortality among CV-related hospitalizations and emergency department visits, %	1.42	[20]

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CV, cardiovascular; OAC, oral anticoagulant; and RFCA, radiofrequency catheter ablation.

*The CV-related health care resource utilization rates were inclusive of complications such as pericardial effusion, tamponade, pericarditis, intracardiac thrombus, congestive heart failure, cerebrovascular accidents/stroke, and tachycardia. We assumed that emergency department visits and inpatient admissions for disabling stroke state were captured through CV-related health care resource utilization rates in paroxysmal and persistent states.

†Resource utilization probabilities for paroxysmal AF (in early AF) were higher than those for advanced AF since probabilities for paroxysmal AF represented utilization while patients experienced arrhythmia, whereas probabilities for Advanced AF represented utilization for patients with more severe AF disease averaged across time spent in arrhythmia and normal sinus rhythm (steady-state long-term utilization).

‡It was assumed that all patients who received RFCA were on oral anticoagulants for the 3-mo postablation period, as this is the current best practice.

(Supplemental Methods II). These rates were applied according to AF severity and were not dependent on treatment scenario, except for resource utilization specific to the use of oral anticoagulants (Table 1). Thus, treatment assignment affected patients' probabilities of PAF recurrence and transition to advanced AF while in normal sinus rhythm but were not assumed to have differential impact on cardiovascular-related resource within the same health states.

Unit costs (Table 2) for health resource utilization included those incurred by third-party payers according to insurance claims data within the Optum De-Identified Clinformatics Data Mart Database.[21] Additional cost information, such as that for anticoagulation care was sourced from published literature.[22–24] Where applicable, 2020 Medicare fee schedules were used to supplement cost information.[25] Costs directly related to the ablation procedure were derived from the Premier Healthcare Database.[26]

The QALY was the primary measure of health-related quality of life and effectiveness within the model. Utility/disutility values, which quantify the QoL consequences of clinical conditions or events (eg, adverse events), were obtained from previously published analyses (Table 3). Durations for time spent in a health state (eg, PAF recurrence), with a specific health outcome (eg, hospitalization), or adverse event (eg, stroke) were obtained from the literature. All patients who achieved sinus rhythm with either RFCA or AAD treatment were assigned baseline, age-adjusted utilities. Disutilities associated with adverse events were applied over the expected duration of impairment within the cycle in which they occurred, after which patients returned to their baseline QoL. The disutility of major disabling ischemic stroke, however, endured over a patient's lifetime. The disutility due to AF was applied over the duration that patients remained symptomatic. Major adverse events associated with RFCA were captured in the cardiovascular-related hospitalization and emergency room visit rates, which have been applied in previous models and health technology appraisals.[30–32] Although treatment-associated adverse events affected QoL, no QoL decrements were applied for the RFCA procedure itself or solely due to the use of AADs.

Table 2. Cost Parameters

Costs parameter	Cost, $	Reference
Ablation-specific costs		
Preoperative lab costs	119.46	US Department of Health & Human Services for Medicare & Medicaid Services[25]
Preoperative workup	409.00	US Department of Health & Human Services for Medicare & Medicaid Services[25]
Long-term follow-up cost (annual)	114.34	US Department of Health & Human Services for Medicare & Medicaid Services[25]
Cost of ablation	20 446.25	[26]
AAD-specific costs (quarterly)		
Pretreatment workup*	163.24	US Department of Health & Human Services for Medicare & Medicaid Services[25]
Drug cost	233.91	[27]
Follow-up monitoring†	268.55	US Department of Health & Human Services for Medicare & Medicaid Services[25]
Nonfatal drug toxicity, per incident	6594.00	Reynolds et al[13]
Resource utilization cost (per incident)		
CV-related inpatient admission	21 707.42	Friedman et al[17]
CV-related emergency department visit	1784.99	
Outpatient cardioversion	2660.00	
CV-related office visit†	152.90	
Disabling ischemic stroke (annual)‡	20 424.00	Godwin et al[22]
Annual weighted average cost of oral anticoagulants, $§	2185.73	Deitelzweig et al[28] and Canestaro et al[29]

AAD indicates antiarrhythmic drug; and CV, cardiovascular.

*Applied once, only when patient initiated AADs.

†Follow-up monitoring cost for AADs only applied to patients one year after treatment initiation and then replaced by the cost of office visits to avoid double counting.

‡Applied for 1 y only.

§Weighted average cost of oral anticoagulants, given their prices and respective market shares available in Health Care Resource Utilization Rates in the Supplemental Material.

Model Outcomes

All outcomes were reported as incremental results for RFCA relative to AADs (with or without crossover). Measures included per-patient total discounted costs, total discounted QALYs, discounted monetized QALYs (QALY valued at $100 000), net monetary benefit (total discounted monetized QALY gains net total discounted costs), and changes in the average number of cardiovascular-related health care visits (hospitalizations, emergency department visits, office visits, and outpatient cardioversions). All analyses were from a US payer perspective. All outcomes were discounted at 3.0% annually and presented in 2020 USD. Average time to AF progression across all patients under each treatment scenario was also calculated. Detailed analytic methods are available in the Supplemental Material.

Table 3. Annual Utility and Disutility Values Associated With Health States and Complications

	Utility/disutility	Reference
Normal sinus rhythm, y		
65–74 y	0.738	Sharma et al[33]
≥75 y	0.688	Sharma et al[33]
AF disutility	−0.05	Blackhouse et al[34]
Major AAD-related toxicity disutility	−0.5	Chan et al[35]
Major hospitalization disutility*	−0.205	Lacey et al[36]
Outpatient cardioversion disutility	−0.016	Chan et al[35]
Disabling ischemic stroke disutility multiplier†	0.482	Simpson et al[37]

Utility weights estimated by EQ-5D instrument were prioritized. When unavailable, utility values measured by other instruments were converted to utility weights ranging from 0 to 1, per data availability.[38] AAD indicates antiarrhythmic drug; AF, atrial fibrillation; and mRS, modified Rankin Scale.

*The disutility associated with a major hospitalization was an average of the disutility for transient ischemic stroke and acute embolism, acute ischemic stroke, acute myocardial infarction, acute intracranial hemorrhage, and other clinically relevant bleeds.[36,39,40]

†Utility multipliers for patients with mRS score 3–5 for ischemic stroke.

Uncertainty and Scenario Analyses

Probabilistic sensitivity analysis was incorporated by conducting 5000 stochastic model iterations to generate base-case results reflective of parameter uncertainty. A scenario analysis was designed to investigate the impact of variable RFCA effect duration on the reduction of disease progression relative to AADs (3, 7, and 10 years instead of 5 years in the base case). A second scenario analysis was designed to investigate the impact of alternate crossover rates in the AAD treatment scenario on model results. Compared with the base case, which assumed 47% cumulative crossover to RFCA over 5 years, this scenario analysis evaluated results with a lower bound of 28% crossover as seen in the CABANA clinical trial (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation),[6] and an upper bound of 77% crossover as seen in a cost-effectiveness model developed by the National Institute for Health and Care Excellence as part of the AF guideline review.[41] A counterfactual scenario with no crossover in the AAD-only scenario was also analyzed to isolate the impact of RFCA from AADs.

RESULTS

Under the base-case analysis with a limited 5-year treatment effect of RFCA for the reduction of AF progression and a 12% annual RFCA crossover rate for 5 years in the AAD scenario, RFCA reduced costs to payers by a mean (95% CI) of $73 (−$2700 to $2200) and increased mean QALYs by 0.084 (0.00–0.17) per patient over lifetime (Table 4). With each QALY valued at $100 000, the mean net monetary benefit per patient was estimated to be $8516 ($148–$16 681). Over a patient's lifetime, mean (percent reduction) per-patient utilization for cardiovascular-related hospitalization, emergency department visits, office visits, and outpatient cardioversions decreased by 0.25 (−29%), 0.36 (−30%), 2.63 (−7%), and 0.27 (−28%), respectively, under the RFCA scenario compared

Table 4. Model Results: Incremental Outcome Values Under the RFCA Scenario, Relative to the AAD Scenario

Outcome (per patient)	Base case mean (95% CI)	Scenario analyses of treatment effect duration mean (95% CI)		
	5-y treatment effect	3-y treatment effect	7-y treatment effect	10-year treatment effect
Total discounted costs, $	−73 (−2700 to 2200)	1900 (−1400 to 4300)	−1500 (−3900 to −600)	−3100 (−5800 to −900)
Total discounted QALYs	0.084 (0.0 to 0.17)	0.063 (−0.02 to 0.14)	0.099 (−0.02 to 0.19)	0.111 (0.02 to 0.19)
Total discounted monetized QALYs,* $	8443 (153 to 16640)	6100 (−2100 to 14100)	9600 (1500 to 18000)	10700 (2100 to 18800)
Net monetary benefit (discounted total gains net discounted total costs), $	8516 (148 to 16681)	4100 (−3300 to 12100)	11100 (2700 to 19300)	13800 (5800 to 22000)
ICER ($/QALY)	Dominant (−5298)	43200	Dominant (−21200)	Dominant (−34900)
Change in mean number of CV-related health care resource utilization encounters				
Hospitalizations	−0.25 (−0.34 to −0.18)	−0.20 (−0.27 to −0.13)	−0.28 (−0.37 to −0.21)	−0.32 (−0.43 to −0.23)
Emergency department visits	−0.36 (−0.48 to −0.26)	−0.28 (−0.38 to −0.20)	−0.39 (−0.52 to −0.28)	−0.44 (−0.58 to −0.32)
Office visits	−2.63 (−3.42 to −1.80)	−2.11 (−2.88 to −1.22)	−2.76 (−3.51 to −2.03)	−2.94 (−3.71 to −2.16)
Outpatient cardioversions	−0.27 (−0.36 to −0.19)	−0.19 (−0.26 to −0.13)	−0.31 (−0.42 to −0.22)	−0.38 (−0.52 to −0.26)

AAD indicates antiarrhythmic drug; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; and RFCA, radiofrequency catheter ablation.

*Each QALY was valued at $100000.

with the AAD scenario. Patients assigned to RFCA treatment also had total mean reduction in cardiovascular-related health care encounters of 24% (21%–26%).

Figure 2A illustrates the proportion of patients in each health state over time under each treatment scenario, demonstrating the impact of RFCA on delayed progression to advanced AF over the 5-year period of its effect. The mean time to AF progression under the AAD scenario was estimated to be 6.5 years, ≈2.5 years earlier than that for the RFCA scenario (9 years).

From the payer perspective, the RFCA scenario was the dominant strategy versus AADs, generating cost-savings and improved QoL for the cohort of patients with PAF. The incremental cost-effectiveness ratio (ICER) was estimated at −$5298/QALY. The incremental cost-effectiveness scatterplot (Figure 3) illustrates the incremental cost versus incremental effectiveness (difference in QALY gains) of the RFCA scenario compared with the AAD scenario for all 5000 simulation iterations. RFCA was cost saving and increased QALYs in 50% and 98% of the iterations, respectively, compared with AADs. The proportion of model iterations where RFCA was cost-effective varied by willingness-to-pay thresholds as shown in the cost-effectiveness acceptability curve (Figure 4). Willingness-to-pay threshold is an estimate of the economic value of one QALY for a health care consumer and is often based on a country's per capita gross domestic product. At a willingness-to-pay threshold of $100000 per QALY, RFCA was cost effective in 98.5% of model iterations. This percentage was modestly reduced to 97.4% and 93.1%, at willingness-to-pay thresholds of $50000 and $25000 per QALY, respectively.

Scenario Analysis

Extending the duration for the incremental effect of RFCA versus AADs on AF progression to 7 and 10 years, compared with 5 years in the base case, respectively, reduced incremental discounted costs by $1500 ($600–$3900) and $3100 ($900–$5800) and increased incremental QALY gains to 0.099 (−0.02 to 0.19) and 0.111 (0.02–0.19) per-patient lifetime (Table 4). Per-patient net monetary benefit was estimated to be $11100 ($2700–$19300) for 7-year treatment effect duration and $13800 ($5800–$22000) for 10-year treatment effect duration, ≈$2600 and $5300 more than in the base-case analysis. RFCA remained the dominant strategy.

Reducing the duration of incremental RFCA effect versus AADs on reducing AF progression to 3 years, that is, without extrapolation of treatment effect based on ATTEST data, increased per-patient discounted cost by $1900 (−$1400 to $4300) compared with base case (Table 4). Patients in the RFCA scenario maintained increased QALYs compared with the AAD scenario, by 0.063 (−0.02 to 0.14). Per-patient net monetary benefit was estimated at $4100 (−$3300 to $12100). ICER was estimated at $43200/QALY, indicating that RFCA was a cost-effective strategy compared with AADs at willingness-to-pay threshold of $100000/QALY.

With a lower crossover rate than assumed for the base-case analysis (27% versus 47% cumulative at 5 years), mean per-patient costs for the RFCA were $2000 (95% CI, −$700 to $4600) higher than for AADs. The mean incremental per-patient QALY gain was 0.10 (0.02–0.18), net monetary benefit was estimated to be $7700 ($100–$15900), and the ICER was $23800/QALY. A higher crossover rate than in the base-case analysis (77% versus 47% cumulative at 5 years), increased mean cost savings to $2600 ($700–$4800). However, incremental QALY gains decreased to 0.06 (−0.03 to 0.14), yielding a net monetary benefit of $8400 ($500–$16000) per patient. RFCA remained the dominant strategy. No crossover in the AAD-only scenario compared with the
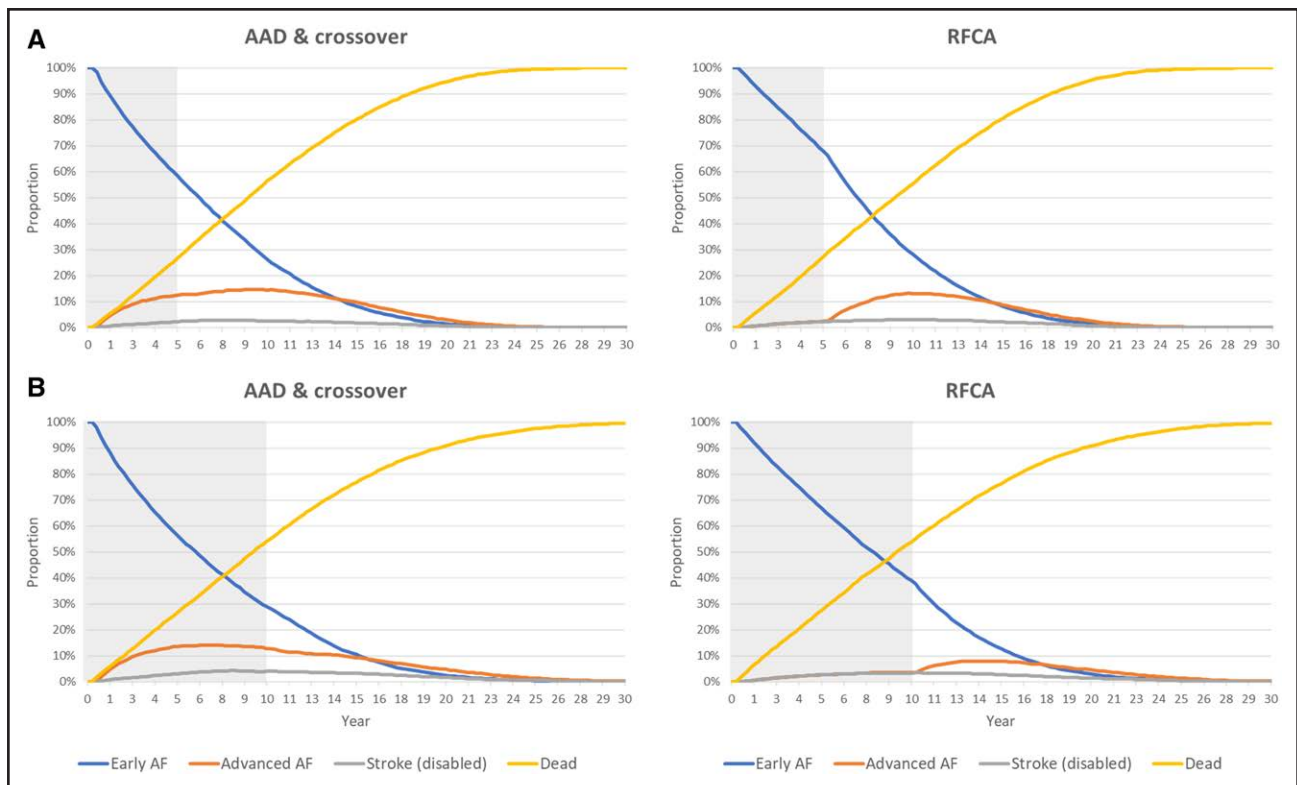
Figure 2. Proportion of patients in each health state over time for radiofrequency catheter ablation (RFCA) and antiarrhythmic drug (AAD) treatment scenarios.
A, Base case analysis: 5-year incremental treatment effect of RFCA compared with AADs. **B**, Scenario analysis: 10-year incremental treatment effect of RFCA compared with AADs. Gray zones indicate treatment effect duration/period in each scenario.

base-case analysis increased mean per-patient cost ($4500 [−1200 to 7500]; Supplemental Table S2). Net monetary benefit per patient and ICER were estimated at $6600 and $38 500/QALY, indicating RFCA was a cost-effective strategy.

DISCUSSION

Our model demonstrated that RFCA was the dominant treatment (less costly and more effective) for patients with AF compared with AADs, especially for patients with early AF for whom RFCA could considerably delay AF progression. Model results indicated that RFCA reduced total per-patient costs from a payer perspective, and increased QALYs over a lifetime horizon. As a result of delaying disease progression relative to AAD treatment, RFCA reduced hospitalizations, emergency department visits, and cardioversions.

To our knowledge, this economic model is the first to explicitly incorporate the impact of delayed progression from early to advanced AF for RFCA versus AAD treatment and to assess differential health care utilization among patients based on the AF severity. Previous studies have demonstrated that patients with advanced AF exhibit increased comorbidity burden, higher rates of adverse events, and greater health care resource utilization than patients with early stage AF.[42,43] These factors underscore the importance of incorporating the impact of AF progression and AF subtype in economic analyses examining AF treatment.

In this study, the per-patient lifetime net monetary benefit for RFCA relative to AADs was $8516 under the base case. The comparison of treatment costs for RFCA versus AADs is challenging, as RFCA incurs a large one-time procedural cost, whereas the costs of AADs are lower but accrue continuously. This comparison is made more complex when considering the possibility of repeat ablations, medication switching during episodes of arrythmia recurrence and differences in quality of life. Despite these uncertainties and the upfront costs of ablation, our model shows RFCA to be the cost-saving AF treatment strategy versus AADs for payers, resulting from long-term maintenance of sinus rhythm, significant reductions in patient lifetime health care utilization and modest gains in patient quality-adjusted life years.

Currently, there is limited data on the durability of RFCA's treatment effect on reducing arrhythmia recurrence and progression over a patient's lifetime. To date, the CABANA study provides the longest trial-based follow-up data, showing that ablation sustained superiority in reducing arrhythmia recurrence compared with AAD therapy at a follow-up of 5 years. However, observational
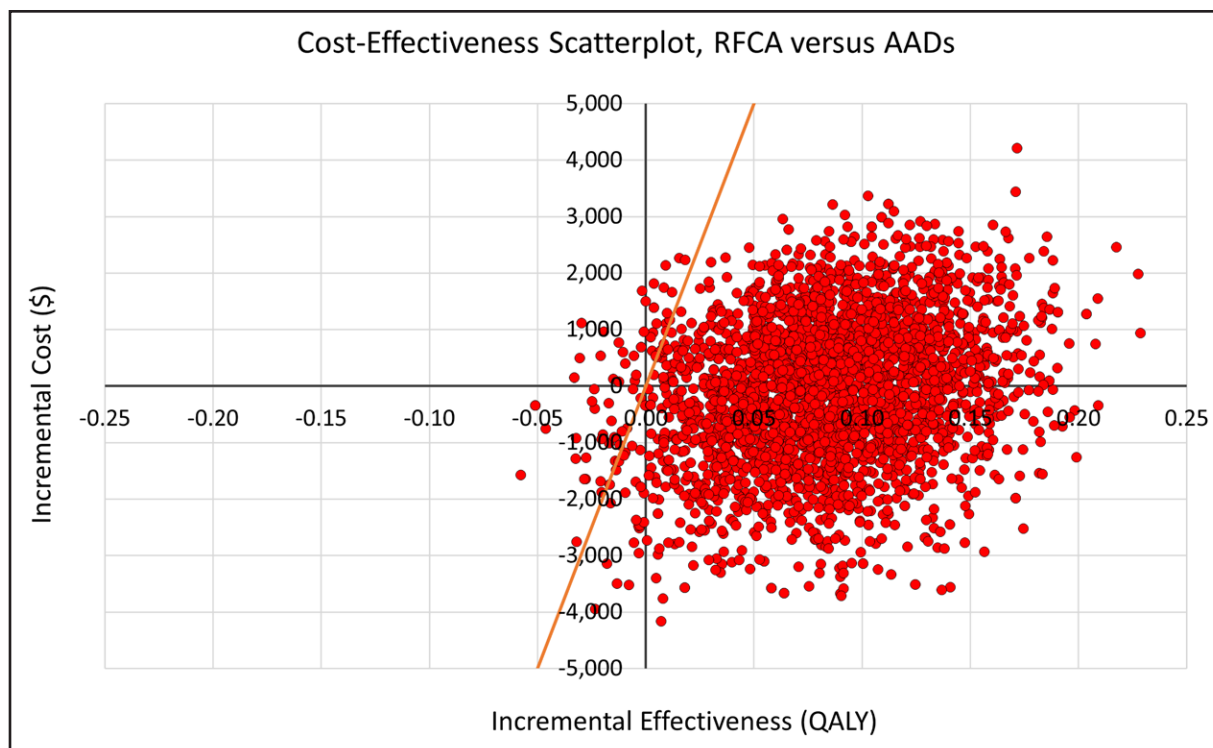
Figure 3. Incremental cost-effectiveness scatterplot.
The incremental cost-effectiveness scatterplot illustrates the incremental cost versus incremental effectiveness of the radiofrequency catheter ablation (RFCA) scenario compared with antiarrhythmic drug (AAD) scenario for all simulation iterations. Orange line indicates willingness-to-pay threshold of $100 000 per quality-adjusted life year. QALY indicates quality-adjusted life year.

data from Takigawa et al[44] suggests that ablation's protective effect against AF progression may persist up to ten years postprocedure. For the sake of conservatism, in our base-case model we assumed that RFCA's treatment effect versus AADs tapered off completely after 5 years. In a scenario analysis, we also assumed a treatment effect of 3 years as shown in ATTEST, under which RFCA was cost-effective. However, we contemplate that the assumption of RFCA treatment effect tapering off after 5 years may underestimate the duration of ablation's effect, in which case the true net monetary benefit of ablation may be closer to more favorable results demonstrated in the 7- and 10-year scenario analysis (net monetary benefit of $11 100 and $13 800, respectively).

Few studies have compared the cost-effectiveness of RFCA to medical therapy in the United States. Previous health economic analyses on RFCA versus AAD therapy have consolidated all patients with AF into a general AF cohort.[34,35,45] A cost-effectiveness analysis by Reynolds et al[13] examined drug-refractory patients with PAF who received either RFCA or drug therapy and found RFCA to be more cost-effective from the US payer perspective. Their study found the ICER for catheter ablation versus AAD treatment to be ≈$51 000/QALY over a 5-year time horizon. However, Reynolds et al only examined patients with early AF (PAF), who typically consume fewer health care resources than patients with more advanced AF. Recently, Chew et al[46] used prospectively collected billing data for

US patients from the multicenter CABANA randomized controlled trial to examine cost-effectiveness of catheter ablation compared with antiarrhythmic drug therapy. Chew et al determined a favorable of ICER of $57 893/QALY for ablation over a patient lifetime perspective but did not consider the effect of AF disease progression.

Our study is unique as it both included patients with both early and progressive forms of AF and assessed the economic impact of the treatment strategies over a lifetime. Previous studies did not simulate AF progression using empirical data, and as a result may overlook the consequences of disease progression and its attendant morbidity. The current model, therefore, elucidates differences in health care resource utilization based on disease severity, enabling a more accurate representation of clinical and economic outcomes for AF treatment.

To better mirror current clinical practice, our model was designed to allow for RFCA crossover, and leveraged real-world data for treatment costs and clinical parameters. Real-world data from insurance claims[21] allowed this model to take into account and simulate real-world costs throughout the course of AF treatment, which may be of practical interest for health care payers and economic decision makers. When drug-to-ablation crossover rates were varied in the scenario analyses, a lower crossover rate was associated with lower net monetary benefit and a less favorable cost-effectiveness ratio, whereas a higher crossover rate corresponded with greater net monetary
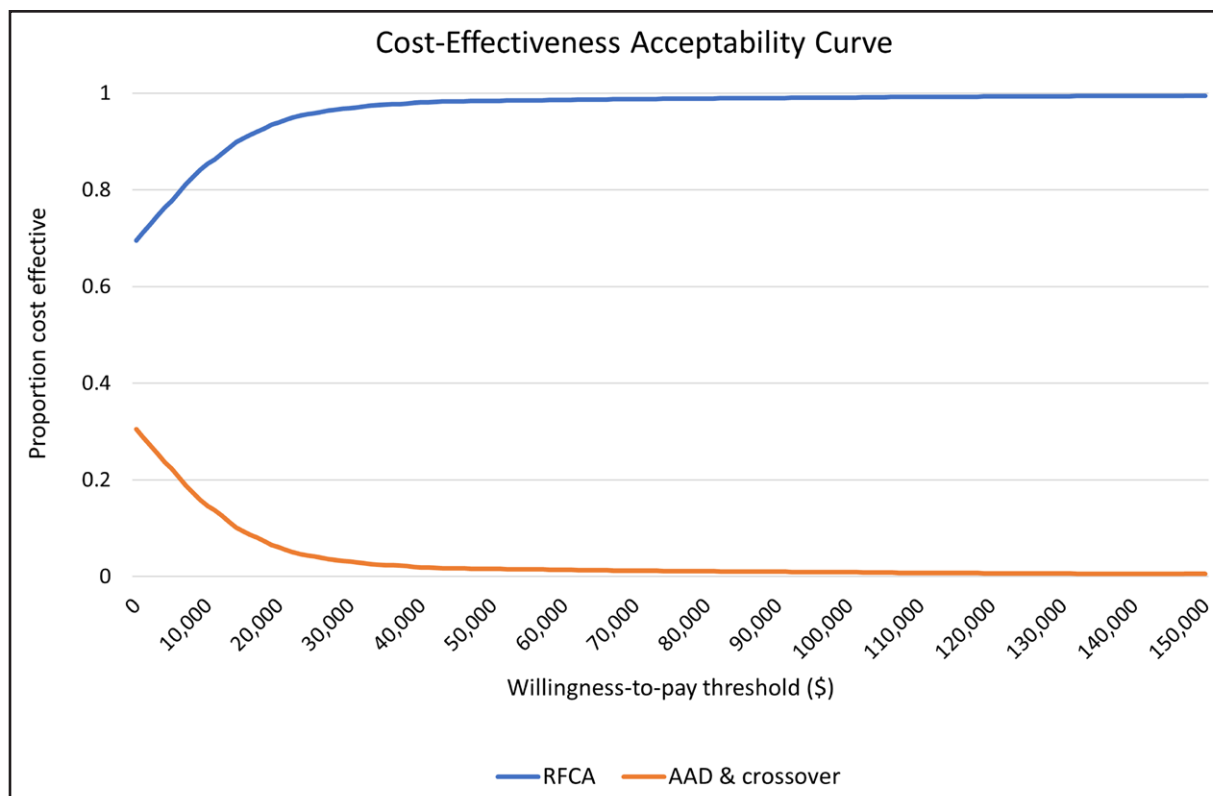
Figure 4. Cost-effectiveness acceptability curve.
AAD indicates antiarrhythmic drug; and RFCA, radiofrequency catheter ablation.

benefit. A counterfactual no-crossover scenario analyses also showed positive net monetary benefit with an ICER well below the accepted $100K/QALY in the Unites States. From a patient and payer perspective, these findings support earlier referral for RFCA, owing to long-term reduction in total cost of care for the chronic disease. Payers with patients enrolled for the long-term, such as Medicare, may experience significant economic benefit by capturing the advantages of slowing AF progression in early disease stages through increased use of early RFCA intervention. Commercial payers, particularly those in closed health care or capitation systems, may also see economic benefit through reductions in avoidable health care encounters.

Due to conservative assumptions, our analysis may underestimate the economic benefits of RFCA. Our model assumed identical rates of health resource utilization among patients with AF in sinus rhythm regardless of treatment assignment (RFCA or AADs). However, data from the MANTRA-PAF trial showed that ablation patients in normal sinus rhythm experience less AF burden than patients with AAD in normal sinus rhythm, suggesting that ablation patients may require fewer health care resources in sinus rhythm than their AAD patient counterparts.[47] Additionally, the payer perspective of our model does not consider broader societal benefits that may accrue due to RFCA, including those related to productivity, reduced health care system burden, and reduced downstream out-of-pocket costs for patients

(eg, cost-sharing, caregiver time, and nursing home residence). Finally, we acknowledge that our simulations models suggest that earlier implementation of RFCA in the disease course of AF my provide not only clinical, but economic benefits. Future studies designed to verify our model's findings appear warranted.

Limitations

This study is limited by a lack of generalizability to all age groups, as simulated rates of progression were specific to younger patients with PAF, though published evidence showing a meaning relationship between age and AF progression rate is also lacking. Rates of disease progression were also obtained from clinical trial data, which may not be completely generalizable to a real-world populations and practice. However, the clinical profiles of patients enrolled in the ATTEST trial and the trial treatment protocols were both generally similar to those of real-world patients with AF. Second, limited published data were available to inform AF subtype-specific input parameters. Until widespread adoption of the *International Classification of Diseases*, *Tenth Revision*, Clinical Modification, which was implemented in October 2015, researchers could not distinguish between PAF and PsAF in large administrative data sets. However, the recent real-world analysis of health claims data that was used to inform this model used a previously validated set of *International Classification of*

Diseases, *Tenth Revision* based claims, thus capturing the majority of relevant health care encounters for each AF subtype. Additionally, data availability on AF progression was limited to only the ATTEST trial.Although multiple data sources to inform this parameter would be ideal, because the ATTEST trial is a randomized clinical trial, the progression data is of robust caliber. Third, not all input parameters obtained from the literature, particularly for health outcome rates, were estimated from samples matched to subjects within the ATTEST trial. Finally, there were limited data on long-term rates of health outcomes and resource utilization associated with RFCA and AAD treatment. Although the last 2 limitations could introduce bias in study results, model structure was aimed to minimize bias by incorporating health outcome and resource utilization rates for each health state independent from the treatment received. The impact of RFCA compared with AADs was estimated according to the speed at which patients experienced AF recurrence and progression and not a direct of RFCA and AADs on resource utilization rates.

Conclusions

This health economic analysis demonstrates that in patients with early AF who have previously failed drug therapy, RFCA is associated with greater clinical and economic value than AAD treatment. Earlier intervention with RFCA may provide considerable benefits for both patients and payers due to the long-term reduction in total cost of AF care and other chronic diseases associated with it.

Supplemental Material

Supplemental Methods I and II
Tables S1 and S2
Figures S1 and S2
References [48–50]

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