Cost-Effectiveness of Radiofrequency Catheter Ablation Compared With Antiarrhythmic Drug Therapy for Paroxysmal Atrial Fibrillation

Matthew R. Reynolds, MD, MSc; Peter Zimetbaum, MD; Mark E. Josephson, MD; Ethan Ellis, MD; Tatyana Danilov, MD; David J. Cohen, MD, MSc

Background—Radiofrequency catheter ablation (RFA) has emerged as an important treatment strategy for atrial fibrillation (AF). The potential cost-effectiveness of RFA for AF, relative to antiarrhythmic drug (AAD) therapy, has not been fully explored from a US perspective.

Methods and Results—We constructed a Markov disease simulation model for a hypothetical cohort of patients with drug-refractory paroxysmal AF, treated either with RFA with/without AAD or AAD alone. Costs and quality-adjusted life-years were projected over 5 years. Model inputs were drawn from published clinical trial and registry data, from new registry and trial data analysis, and from data prospectively collected from patients with AF treated with RFA at our institution. We assumed no benefit from ablation on stroke, heart failure or death, but did estimate changes in quality-adjusted life expectancy using data from several AF cohorts. In the base case scenario, cumulative costs with the RFA and AAD strategies were $26 584 and $19 898, respectively. Over 5 years, quality-adjusted life expectancy was 3.51 quality-adjusted life-years with RFA versus 3.38 for the AAD group. The incremental cost-effectiveness ratio for RFA versus AAD was thus $51 431 per quality-adjusted life-year. Model results were most sensitive to time horizon, the relative utility weights of successful ablation versus unsuccessful drug therapy, and to the cost of an ablation procedure.

Conclusions—RFA with/without AAD for symptomatic, drug-refractory paroxysmal AF appears to be reasonably cost-effective compared with AAD therapy alone from the perspective of the US health care system, based on improved quality of life and avoidance of future health care costs.

Key Words: atrial fibrillation • ablation • antiarrhythmia agents • cost-benefit analysis

Since its earliest reports a little more than a decade ago1,2 radiofrequency catheter ablation (RFA) for atrial fibrillation (AF) has undergone rapid evolution in its techniques and emerged as an important option in the treatment of patients with AF.3 Several small, randomized studies have suggested that the up-front costs of catheter ablation may be partly—if not fully—offset by the avoidance of later AF-related resource use11–14 or adverse events such as stroke,15 none of these studies has directly integrated data on changes in quality of life related to maintenance of sinus rhythm.

To gain a better understanding of the benefits and costs of AF ablation relative to medical therapy, we developed a disease-simulation Markov model for a hypothetical cohort of patients with paroxysmal AF who had failed previous treatment with 1 or more AADs. Drawing from a variety of sources, we estimated costs, quality-adjusted life expectancy, and cost-effectiveness of RFA with/without AAD relative to continued AAD therapy alone over a 5-year time horizon.

Methods

Modeling Strategy and Basic Assumptions

We developed a Markov disease-simulation model comparing RFA with/without AAD with AAD therapy alone for patients with AF. The online-only Data Supplement is available at http://circep.ahajournals.org/cgi/content/full/CIRCEP.108.837294/DC1.

Received November 23, 2008; accepted March 19, 2009.
From the Beth Israel Deaconess Medical Center (M.R.R., P.Z., M.E.J., E.E., T.D.), Boston, Mass; and St Luke’s Mid-America Heart Institute (D.J.C.), Kansas City, Mo.
Charles I. Berul, MD, handled this article.

Circ Arrhythmia Electrophysiol is available at http://circep.ahajournals.org DOI: 10.1161/CIRCEP.108.837294

362
paroxysmal AF refractory to 1 or more AADs. This population was chosen because consensus guidelines have endorsed ablation in these patients1,16; because ablation appears to potentially yield better results in patients with paroxysmal AF compared with patients with persistent AF17–19; and because there is a larger body of randomized evidence available for patients with paroxysmal AF (as opposed to those with persistent AF or mixed populations) from which to derive model parameters. The published literature suggests that the majority of patients currently referred for ablation are male, under age 60, and do not have advanced heart failure.4 We therefore modeled outcomes of patients with paroxysmal AF (as opposed to persistent AF17–19; and because there is a larger body of randomized results in patients with paroxymal AF compared with patients with disease.

The model has a 5-year time horizon, which we believe is long enough to capture most of the major changes in resource consumption and quality of life after an initial decision on AF management and because this corresponds roughly with the longest follow-up of outcomes with either ablation or AAD therapy published in the literature.20,21 The impact of time horizon was tested in sensitivity analysis. The cycle length was 1 month, and all analyses were based on the societal perspective.22

For the sake of estimating cost-effectiveness over a medium-term time horizon, we assumed that patients assigned to drug therapy cannot “cross over” to ablation within the model. This construction more accurately estimates the true incremental value of ablation compared with drug therapy, as opposed to one that ultimately compared an up-front ablation strategy with “delayed” ablation after additional drug failure, assuming that the rate of drug failure would be significant.5,6,13

**Model Structure**

Figures 1 through 3 summarize the basic structure, health states, and possible transitions between health states used in the model. Two basic Markov processes were constructed: one for patients completing an uncomplicated ablation or having a reversible procedural complication, and another for the AAD therapy cohort (Figure 1). With the exception of a procedure-related stroke, ablation patients having a nonfatal procedural complication incurred an immediate cost and short-term disutility, but after that followed the same path as patients without a procedural complication. On the other hand, we assumed that a procedure-related stroke would affect both quality-adjusted life expectancy and costs in the long term, and these effects were estimated from previous literature (states not shown in Figure 2).15

The ablation Markov process (Figure 2) assumes that patients will progress stepwise from one therapy to the next, based on whether or not they have symptomatic AF recurrences on their current treatment. Thus, patients recurring after a first ablation restart guideline-recommended first-line AAD therapy with either sotalol or flecainide (moving from the “well Abl 1” to the “AAD 1” health state).16 Based on numerous reports that some patients respond to previously ineffective AADs after ablation. Patients with recurrent AF despite 1 ablation and the addition of first-line AAD therapy (or those experiencing drug toxicity) proceed to repeat ablation (moving from AAD 1 to Abl 2). Those who recur despite a second ablation commence treatment with second-line AAD treatment (moving from Abl 2 to AAD 2), and patients failing second-line drug treatment cease further efforts at rhythm control and are treated with pharmacological rate control. We made the conservative assumption that ablation patients would not be treated with amiodarone.

The AAD Markov process follows generally similar logic (Figure 3). Patients initially receive a first-line drug (sotalol or flecainide) and enter the “well 1st drug” state. In the event of toxicity or therapeutic failure, they proceed to treat with amiodarone (“well amio” state), and in the event of amiodarone failure are treated with rate control (“RC/AC”). Amiodarone was chosen as the second-line treatment. For the sake of estimating cost-effectiveness over a medium-term time horizon, we assumed that patients assigned to drug therapy cannot “cross over” to ablation within the model. This construction more accurately estimates the true incremental value of ablation compared with drug therapy, as opposed to one that ultimately compared an up-front ablation strategy with “delayed” ablation after additional drug failure, assuming that the rate of drug failure would be significant.5,6,13

Figure 1. Simplified structure of the decision analytic model. After the initial decision (square box) to pursue ablation, patients face a finite probability (chance node represented by open circle) of procedural death, nonfatal complication, or no complication. All patients surviving ablation then enter the ablation Markov process (see subsequent figures).

Figure 2. Ablation Markov process. This simplified diagram demonstrates the major health states (boxes) and possible transitions between health states (arrows) in the ablation limb of the decision tree. In each state, patients face a finite risk of age-associated mortality (not shown). Otherwise, patients with symptomatic recurrence of AF (or drug toxicity) progress to the next treatment, and patients remaining in sinus rhythm continue in the same state.

Figure 3. AAD Markov process. The 3 main treatment options in the AAD group are shown from top to bottom on the left. Within each well state, patients may have recurrent symptomatic AF or drug toxicity, in which case they would progress to the next treatment (next Rx), or they could remain well. All failures of first-line drug treatment would next try amiodarone, and all amiodarone failures would move on to rate control and anticoagulation (RC/AC).
agent for all patients in the drug arm, based on its superiority over other drugs at maintaining sinus rhythm.23–25

All patients face a background rate of mortality based on their age and sex and can therefore transition from any health state directly to death in either arm of the model (not shown in figure).26 Aside from small risks of procedural death or fatal drug toxicity (see Appendix), the model assumes that the risk of death is the same for all health states and interventions except after major stroke after an ablation. Further, because the potential for either drug therapy or ablation to reduce the long-term risk of stroke has not been proven, we assumed that the incidence of stroke would be the same for both therapies and therefore did not explicitly consider stroke as an outcome in the model, except as a potential complication of ablation. In keeping with current recommendations,3 we also assumed that long-term anticoagulation practices and related costs and complications would be equivalent between groups.

Risks of both fatal and nonfatal antiarrhythmic drug toxicity were taken from the literature (see online-only Data Supplement) and applied equally to ablation and nonablation patients. In the ablation arm of the model, it was assumed that patients having drug toxicity after a single ablation would have recurrent AF and undergo repeat ablation, whereas patients having drug toxicity after 2 ablations would then be treated with rate control.

Model Inputs

Inputs for the model were drawn from a variety of sources, including completed clinical trials, a large registry of patients with new-onset AF, prospectively collected data from patients treated at our institution, and analysis of Medicare claims data. Risks of events were allowed to vary over time by incorporating probability tables and tunnel states into the model. The base case estimate, range of values used in sensitivity analysis, data sources, and additional details are provided in the Appendix. Some general discussion regarding data sources and key inputs is provided here.

Event Probabilities

The risks of procedural complications after AF ablation were taken from published randomized and nonrandomized series and a large international survey on AF ablation outcomes.27 The likelihood of successful sinus rhythm maintenance for each of the strategies in both the ablation and drug arms of the model were taken as much as possible from recent randomized studies5,28–29 but were cross referenced with more general sources.27

We assumed a single-procedure efficacy rate of 60% for ablation and calibrated the model to achieve a 25% rate of repeat ablation (with some patients achieving successful rhythm control on AAD therapy after 1 ablation) and a 10% overall failure rate with the ablation strategy. We assumed that 75% of patients treated with first-line drugs (and no ablation) would recur within 1 year and that 65% of patients treated with amiodarone as second-line therapy would recur within 1 year. These recurrence rates with AAD therapy are slightly higher than in a recent AAD comparative efficacy trial24 but are consistent with recurrence rates in recent randomized studies comparing ablation with drug therapy in patients with paroxysmal AF with previous drug failure.5,28–29

Costs

The costs of drug therapy for AF were primarily derived from the FRACTAL registry30 and the health economic substudy of the AFFIRM trial.31 The cost of catheter ablation was estimated from our local cost-accounting system, and recently published estimates from the United States and Canada12,15 were used in sensitivity analysis.

Quality-of-Life Adjustment

Although quality of life has been assessed in studies of many AF interventions,28,29 there is very little published information available regarding utilities in patients with AF,33 particularly in AF ablation populations. To address this lack of data, we derived utilities for 3 separate populations of patients with AF to estimate the likely

changes that might be observed after successful ablative or drug therapy.

For drug-treated patients, we used SF-12 questionnaire34 data from the FRACTAL registry35 and calculated utilities for these patients using the method proposed by Brazier.26 For ablation patients, we used a similar transformation of responses to the SF-36 questionnaire37,38 to estimate the change in utility experienced by a prospective cohort of patients undergoing catheter ablation at Beth Israel Deaconess Medical Center. Finally, we also calculated utilities using SF-36 data for patients enrolled in the Atrial Fibrillation versus Antiarrhythmic Drugs (A4) trial5,39 to estimate the comparative changes in utility for patients treated with drugs versus ablation. Based on these analyses, the change in utility from baseline to successful sinus rhythm maintenance was set at 0.065 (see Appendix for additional details). In the model, utilities corresponding with each health state were summed over the amount of time spent in that health state to calculate QALYs.

Secondary Analyses

One-way sensitivity analyses40 for all model inputs were performed and plotted in a “tornado” diagram. Two-way sensitivity analysis was performed on the utility of successful sinus rhythm maintenance after ablation and the utility of the rate control health state to better display the joint impact of these important variables on the model’s cost-effectiveness estimates.

Results

Base-Case Results

Figure 4A and 4B display the state probabilities for the ablation and AAD cohorts, respectively, plotted against time. Based on the model inputs, 60% of ablation patients remain well after a single procedure, ~10% eventually fail all therapies and progress to a rate control and anticoagulation strategy, and the remainder of ablation patients either achieve control of their AF with a second ablation and/or adjunctive AAD therapy or die during follow-up. For the AAD cohort, the majority of patients fail first-line treatment over 1 year and transition to amiodarone. However, over time, roughly two thirds of patients fail AAD treatment altogether and progress to a rate-control and anticoagulation strategy. Based on the low estimates of fatality from procedural complications or drug toxicity, projected all-cause mortality was equivalent between groups (7.7% ablation versus 7.8% AAD).

In the base-case scenario, cumulative costs with the RFA and AAD strategies were $26 584 and $19 898, respectively. The initial difference in costs between strategies is roughly $10 000 but narrows over time as a larger proportion of AAD patients have symptomatic recurrences, leading to increased resource consumption and changes in therapy. Over 5 years, the RFA cohort lived 3.51 QALYs, versus 3.38 for the AAD group. The incremental cost-effectiveness ratio (iCER) for RFA versus AAD was thus $51 431/QALY. Removing the age- and sex-related background mortality from the model increased costs in both groups to a similar extent and modestly increased the incremental quality-adjusted life expectancy in favor of ablation (3.64 versus 3.50 QALYs), slightly reducing the iCER to $47 333 per QALY.

Sensitivity Analysis

Figure 5 displays the impact of varying key input variables on the iCER. Within the plausible ranges for these variables (see also Appendix), the model was insensitive to changes to the
discount rate, the probability or cost of procedural complications or drug toxicity, or assumptions about the efficacy or cost of first-line antiarrhythmic drug therapy. In no case did changes in these parameters increase the iCER above $60 000 per QALY.

The model was moderately sensitive to the cost of amiodarone therapy, the cost of drug loading, the cost of AF care under a rate control strategy, and the assumed rate of single procedure efficacy with ablation. Changes in these parameters did not increase the iCER to more than $80 000 per QALY.

The model results were most sensitive to the time horizon of the analysis, the cost of ablation, and to the relative utility weights of successful ablation versus unsuccessful drug therapy. Predictably, higher assumed values for the cost of ablation increased the iCER, which was $100 000 per QALY at a single procedure ablation cost of $20 000. Holding all other parameters constant, a time horizon of 3 years resulted in incremental costs of $9900 and an unfavorable iCER of $157 000 per QALY, whereas a time horizon of 10 years resulted in near cost neutrality and larger...
incremental QALY gains favoring ablation, resulting in an iCER of <$1000 per QALY.

As shown in Figure 5, relatively small changes in the utility weights assigned to either the well states after ablation or the rate control state had a significant impact on the estimated iCER. The interplay between these variables is further highlighted in Figure 6. In general, the iCER for ablation versus AAD therapy was <$100,000 as long as the difference between these utility scores was 0.04 or greater. Larger differences in utility resulted in quite favorable iCERs, whereas smaller differences yielded iCERs in the economically unattractive range.

Discussion

Multiple studies have demonstrated clinical benefits of catheter ablation for AF, including improved maintenance of sinus rhythm and improved quality of life, compared with AAD therapy. In the current study, we used a disease simulation model to project costs and quality-adjusted life expectancy for a population of 60-year-old men with drug-refractory atrial fibrillation who were treated with either RF ablation (with/without adjunctive AADs) or continued medical therapy. Using assumptions based largely on the current medical literature, we found that ablation was reasonably cost-effective compared with AAD therapy alone from the perspective of the US health care system, even within a relatively short time horizon and even without assuming that ablation reduces the risk of stroke, heart failure, or death. The modeled results were most sensitive to assumptions about the cost of ablation and the difference in quality of life (utility) between successful and unsuccessful sinus rhythm maintenance.

Few previous studies have examined the potential cost-effectiveness of catheter ablation for AF. Chan et al,15 also using a Markov model, projected the potential cost-effectiveness of left atrial catheter ablation, compared with amiodarone or rate control, based on hypothetical reductions in the risk of stroke after ablation. Potential improvements in quality-adjusted life expectancy resulting from successful maintenance of sinus rhythm alone were not considered. Although a large nonrandomized series from 1 center has suggested that AF ablation reduces morbidity and mortality relative to drug therapy,20 adequately powered randomized studies to test this hypothesis have not been completed. We constructed our model assuming no benefit for ablation on the risk of stroke; if such a benefit is eventually proven, it would only improve the cost-effectiveness of ablation.

Khaykin et al12 performed a cost comparison of catheter ablation for AF and antiarrhythmic drug therapy based on health care utilization patterns from Canada and France using Canadian price weights and concluded that costs would equalize over 3 to 8 years of follow-up (4.5 to 11 years with 3% discounting applied) due to higher long-term health care costs with AAD treatment. Although we used a US rather than Canadian perspective, our results regarding the relative costs of ablation and drug therapy are qualitatively similar to this previous study. Longer-term extrapolations of our model indicate cost neutrality after ~10 years, an estimate within the range of the previous authors' sensitivity analyses. The longer time for this equalization of costs in our model may be due both to the higher up-front cost of ablation in the United States and to the fact that our model shunts the drug cohort toward less expensive rate-controlling drugs over time. In contrast, the Khaykin et al study12 assumed that the use of antiarrhythmic drugs would remain constant over long periods of time, an assumption we find unlikely.41

Most recently, an economic model of a randomized pilot study of AF ablation as first-line therapy for paroxysmal AF was performed,13 again using Canadian price weights. In this study, costs were nearly equal after 2 years, in large part because of a 49% rate of crossover to ablation in patients initially assigned to AAD therapy. We did not explicitly evaluate a delayed ablation strategy in our model because we believe the pertinent health policy and reimbursement question is not the timing of ablation but its incremental value over available rhythm control therapies.

The major difference between our study and prior economic assessments of AF ablation is the explicit incorpora-
tion of quality-of-life adjustment as it pertains to sinus rhythm maintenance, which permits the expression of results in dollars per QALY, the recommended metric of cost-effectiveness analysis. The utility weights used in our analysis were derived from analysis of empirical SF-12 and SF-36 data from 3 separate AF populations (2 treated with ablation), with highly concordant results (see Appendix). In these populations, mean utilities varied from ≈0.72 to 0.80, which agree well with cross-sectional EQ-5D scores published by the Euro Heart Survey for AF.

Our sensitivity analyses indicate that until and unless morbidity and mortality benefits are proven, the cost-effectiveness of AF ablation relative to AAD therapy will remain highly contingent on the incremental gains in quality of life the procedure can provide, at least over a short- to medium-term time horizon. This implies that AF ablation is unlikely to be cost-effective for patients who enjoy preserved baseline quality of life despite their AF or for patients whose quality of life is not likely to substantially improve despite elimination of AF (eg, patients with poor quality of life mainly due to other health problems). We believe these observations offer insights into patient selection for AF ablation that are congruent with clinical judgment and current consensus recommendations.

Our model may suggest additional insights into what factors may increase or decrease the likelihood of ablation being cost-effective. Increased single-procedure efficacy, reduced procedural cost, and/or increased symptomatic benefit would all improve the cost-effectiveness of ablation relative to AADs. On the other hand, a short time horizon, reduced costs for drug loading and follow-up care, better baseline quality of life, a smaller change in quality of life after ablation, and a greater probability of symptom reduction on AAD therapy would all tend to make ablation less attractive from a cost-effectiveness perspective.

We believe the assumptions used in our base case were conservative and, if anything, slightly biased against ablation. For example, longer time horizons would improve the cost-effectiveness of ablation, but we do not think that the current evidence base permits extrapolation of results beyond 5 years. Additional conservative assumptions in our model included not using amiodarone (known to have greater efficacy than alternative drugs) in the ablation arm of the model and estimating single-procedure efficacy with ablation at 60%, with a 25% rate of repeat ablation. Although centers of excellence have reported better results than these, we think that these estimates are probably representative of current general practice. Although nonrandomized studies have suggested that AF ablation in patients with reduced left ventricular systolic function can improve left ventricular function, functional status, and quality of life, we did not incorporate improvements in heart failure into our model.

Our study has important limitations. First, the results of this model cannot be directly applied to other subsets of the AF population (eg, newly detected, persistent, or long-standing persistent) because the baseline characteristics of those patients, the ablation methods required to achieve long-term success, and the outcomes with ablation and drug therapy are probably all different than those we estimated.

We did not model all possible treatment strategies for patients with paroxysmal AF. In selected patients, pharmacological rate control alone or pacemaker implantation in conjunction with ablation of the AV junction may be reasonable alternatives. At present, however, there are limited data directly comparing these strategies with ablation from which to draw model inputs, and our model assumed that patients were seeking rhythm control strategies because of dissatisfaction with rate control alone.

As always with cost-effectiveness modeling studies, ours required simplifying assumptions and use of some uncertain parameters. One area of particular difficulty in this model was estimating when symptomatic AF recurrences would prompt a change in therapeutic strategy, as trials of AF interventions typically report all detected recurrences (or time to first recurrence) regardless of whether or not such recurrences would actually be considered a true therapeutic failure. For this reason, we attempted to define model parameters that mimic published results, for example, in terms of repeat ablation, drug discontinuation, and concomitant use of AADs after ablation.

Finally, we recognize that not all technical approaches to catheter ablation for AF are the same and that ablation techniques are rapidly evolving. This was another reason that we chose to focus on ablation for paroxysmal AF, in which the procedural focus remains more or less focused on electrical isolation of the pulmonary veins.

Sources of Funding
Dr Reynolds was supported by grant K23 HL077171 from the National Institutes of Health.

Disclosures
Dr Reynolds reports consulting fees from Biosense Webster and Sanofi-Aventis. Dr Josepshon reports consulting fees from Biosense Webster.

References


**CLINICAL PERSPECTIVE**

Studies of selected patients with atrial fibrillation have shown that a clinical strategy involving radiofrequency catheter ablation results in a higher likelihood of remaining in sinus (normal) rhythm than a strategy of using only antiarrhythmic drugs, along with greater improvements in quality of life. Catheter ablation, however, is an expensive procedure; therefore the added costs of catheter ablation must be weighed against the proven benefits before this strategy can be endorsed on a widespread basis. In the current study, we created a disease simulation model (Markov model) to assess the cost-effectiveness of radiofrequency catheter ablation, compared with continued antiarrhythmic drug therapy without ablation, for patients with paroxysmal atrial fibrillation. The model projected likely outcomes for each treatment over a period of 5 years, based on previously published studies, as well as analysis of some newly collected quality-of-life data. We found that the initial extra costs of ablation are partly offset over time by a reduced need for repeat episodes of care for atrial fibrillation and that the radiofrequency catheter ablation strategy was associated with slightly better quality-adjusted life expectancy over this time frame. Combining these findings resulted in a cost-effectiveness ratio of \( \approx $51,000 \) per quality-adjusted life-year gained, a value generally considered acceptable within the US health care system.
Cost-Effectiveness of Radiofrequency Catheter Ablation Compared With Antiarrhythmic Drug Therapy for Paroxysmal Atrial Fibrillation
Matthew R. Reynolds, Peter Zimetbaum, Mark E. Josephson, Ethan Ellis, Tatyana Danilov and David J. Cohen

_Circ Arrhythm Electrophysiol._ 2009;2:362-369; originally published online April 17, 2009; doi: 10.1161/CIRCEP.108.837294

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/2/4/362

Data Supplement (unedited) at:
http://circep.ahajournals.org/content/suppl/2009/04/30/CIRCEP.108.837294.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Arrhythmia and Electrophysiology_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Arrhythmia and Electrophysiology_ is online at:
http://circep.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

This supplemental appendix is intended to provide additional detail beyond that in the primary manuscript regarding model structure and assumptions, and the sources or derivation of model inputs. The input values used in the model, with the range of plausible estimates used in sensitivity analysis, and references of all sources, are shown in Table 1.

SUPPLEMENTAL METHODS

Event Probabilities

The frequencies of specific procedural complications were estimated from published literature.\textsuperscript{1-4} Because relatively minor complications may be under-reported in single center series, and the bulk of published data on AF ablation comes from selected centers of excellence, we placed particular emphasis on multi-center and survey data\textsuperscript{3} in deriving these estimates.

Recurrence of AF following ablation was estimated from published literature. Published studies are inconsistent on reporting of results\textsuperscript{2} with respect to whether recurrence rates are obtained after 1 or multiple procedures or included supplemental antiarrhythmic drug therapy. The published rate of repeat ablation procedures varies widely, and rates as low as 9-12\% have been reported in small randomized studies involving paroxysmal AF patients.\textsuperscript{5, 6} However, a worldwide survey of AF ablation reported a 25\% repeat procedure rate,\textsuperscript{3} and individual studies have reported even higher
repeat procedure rates. We therefore conservatively calibrated the model to a 25% rate of repeat procedures. The rate of recurrence requiring a change in therapy was presumed to be higher than this (and was set at 40%), given that many centers have reported that some patients achieve control of their AF on previously ineffective AAD therapy after one procedure. We assumed that no patients would undergo more than 2 ablation procedures. The ultimate “failure” rate of the ablation strategy was targeted at 10% based on randomized studies reporting symptomatic recurrences at one year. As most reported AF recurrences after ablation take place early, we assumed a uniform rate of AF recurrence over 6 months following the initial or repeat ablation.

Base case estimates of recurrent, symptomatic AF on antiarrhythmic drugs were derived to the greatest extent possible from randomized studies involving AF ablation patients. While not all AF recurrences on drug therapy necessarily prompt a change in treatment, we used the rates of crossover to ablation in these studies as a lower bound of the estimate for treatment failure. We also compared these rates to reported success in comparative antiarrhythmic drug studies. For first line drugs, we assumed a base case rate of drug failure of 75% over one year, and for second-line treatment with amiodarone, the base case rate of drug failure was set at 65% over one year. These estimates were taken from randomized studies of AF ablation compared with AADs in patients with paroxysmal (or a mixture of paroxysmal and persistent) AF refractory to one or more AADs.

Rates of serious drug toxicity and drug discontinuation due to adverse events were taken from older literature as well as more recent sources.
Costs

The cost of an AF ablation procedure was set at $15,000. The mean encounter-level cost of hospital care (procedure + median 1 night observation) in 82 patients who underwent AF ablation and provided informed consent to participate in an economic and quality of life study at our institution was $11,898. This does not include physician fees for the operator or anesthesiologist, when present, and does not include pre-procedure evaluation (such as an office visit and standard pre-procedure imaging). The higher cost of an ablation procedure therefore included these additional expenses.

The costs for procedural complications were estimated from an analysis of Medicare Provider Analysis and Review (MedPAR) files. We identified Medicare admissions to US hospitals between 2001-2006 (N=8288) with AF as the principal diagnosis during which an RFA was performed (based on diagnosis and procedure codes), and excluded patients who underwent implantation of a pacemaker or ICD, or had a surgical ablation during the same hospitalization, or who had a discharge diagnosis of atrial flutter, Wolff-Parkinson-White syndrome, AV nodal tachycardia, or prior pacemaker or ICD. The incremental cost of each of the defined procedural complications was determined by regression modeling on the outcome of hospital costs, adjusting for demographics, comorbid diagnoses, and the year of treatment.

Following successful ablation without AF recurrence we assumed follow-up costs of $1300 in the first year (to include short term anticoagulation in all patients, and follow-up office visits and routine diagnostic testing)\textsuperscript{4}, and $200 per year thereafter.

Follow-up costs for patients in the AAD cohort were taken from the FRACTAL registry\textsuperscript{16} (specifically, the group with no documented symptomatic recurrences during
the first year of follow-up, N=650) and a sub-study of the AFFIRM trial. It was
assumed that antiarrhythmic drug toxicity or a change in antiarrhythmic drug therapy
would incur the costs of a typical telemetry unit hospital admission.

Utilities.

We are aware of no previously published data on health state utilities measured in
an AF ablation population. To address this, we estimated utilities using raw item
responses to the SF-36 and SF-12 general health surveys from three populations of AF
patients – one treated almost exclusively with drug therapy, and two involving AF
ablation. Results of these analyses are plotted together in Figure 1.

We first transformed SF-12 responses to utilities using the method proposed by
Brazier and colleagues for patients enrolled in the FRACTAL registry, a population of
~1000 subjects enrolled at the time for first AF diagnosis. In order to estimate the
change in utility achieved with successful pharmacologic rhythm control of AF, we
compared baseline utilities with follow-up values from 3, 6, and 12 months in patients
with no documented recurrences of AF during the first year of registry follow-up (N=507,
see Figure 1). Baseline mean utility was 0.76 ± 0.13. In paired comparisons at 6 and 12
months, the mean increase in utilities in this group were 0.042 and 0.046, respectively
(p<.0001 by the signed rank test for both comparisons).

We next performed a similar transformation of SF-36 data to utilities for patients
enrolled in the A4 study, a randomized trial comparing antiarrhythmic drugs with
catheter ablation for patients with paroxysmal AF despite ≥1 attempts at drug therapy
(N=112). Baseline mean utility scores were 0.72 in the ablation group and 0.71 the
AAD group (p=0.22, see Figure 1). At 6 and 12 months, mean utility scores in the ablation group had increased significantly, by 0.053 and 0.064, respectively, in paired comparisons (p<0.001 by signed rank for both comparisons). Assessment of changes in utility in the AAD group were hampered by the 67% rate of crossover to ablation in the study; prior to crossover, utility scores did not appear to improve at all in AAD patients. In Figure 1, utility results are plotted for the AAD group using a “last carried forward” assumption for crossover patients.

Lastly, we obtained SF-36 data on 78 consecutive patients undergoing catheter ablation for paroxysmal or persistent AF at Beth Israel Deaconess Medical Center who provided informed consent to collection of quality of life data. Mean baseline utilities in this population were 0.74 ± 0.13. As with the A4 ablation patients, utility scores significantly increased in this population after ablation. While follow-up of this cohort is ongoing, interim analysis has shown mean changes of 0.064 and 0.059 in paired comparisons at 6 and 12 months, respectively (p<0.01 by signed rank test for both comparisons).

Based on the above data, we used a baseline utility value 0.725 for our model, which is closest to that seen in A4 study, but similar to that obtained from our local population. We set the increase in utility with successful AF treatment at 0.065, which was approximately equal to the 12-month change in the A4 study population, and the 6-month change in our local population (based on preliminary data). While the increase in utility with successful pharmacologic management in FRACTAL was slightly smaller (~0.045), the FRACTAL population appeared to be less severely impaired at baseline, and was a new-onset population, rather than a paroxysmal population seeking alternative
treatment after failing one more drugs. Further, we did not feel the improvement in
utility with successful AAD treatment in the model should differ from that with
successful ablative therapy. We therefore set the utility for each of the model’s ‘well’
states following ablation or AAD therapy to 0.79.

We believe the utility change of 0.065 with successful sinus rhythm maintenance
in this population may be a conservative estimate, because the above data comparing pre-
and post-ablation scores were based on all respondents, not just those who remained in
sinus rhythm during follow-up.
# SUPPLEMENTAL TABLES

Table 1: Event probabilities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case (Range)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event probabilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural death</td>
<td>0.05% (0–0.12%)</td>
<td>1, 3, 22</td>
</tr>
<tr>
<td>Vascular access</td>
<td>1.2% (0.9–5%)</td>
<td>1, 3, 22</td>
</tr>
<tr>
<td>Perforation/tamponade</td>
<td>0.8% (0.6–1.5%)</td>
<td>1-4</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.3% (0.1–0.5%)</td>
<td>1-4</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0.4% (0.1–0.6%)</td>
<td>1-3</td>
</tr>
<tr>
<td>PV stenosis</td>
<td>0.4% (0.1–1.6%)</td>
<td>1-4</td>
</tr>
<tr>
<td>Pnuemothorax/hemothorax</td>
<td>0.18% (0–0.4%)</td>
<td>1-3</td>
</tr>
<tr>
<td>Phrenic nerve palsy</td>
<td>0.1% (0–0.2%)</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>Follow-up Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recur after 1st ablation (6 months)</td>
<td>40% (25–50%)</td>
<td>3, 9, 22</td>
</tr>
<tr>
<td>AAD success post 1st ablation</td>
<td>30% (20-40%)</td>
<td>Extrapolation from 3 and 5</td>
</tr>
<tr>
<td>Redo ablation</td>
<td>25% (9 – 30%)</td>
<td>3, 5, 6, 22</td>
</tr>
<tr>
<td>Recur after 2nd ablation</td>
<td>50% (40-60%)</td>
<td>Extrapolation from 3</td>
</tr>
<tr>
<td>Success on drugs after 2nd ablation (6 months)</td>
<td>35% (20-50%)</td>
<td>Assumption</td>
</tr>
<tr>
<td>Recur on IC/sotalol (no ablation) (over 12 months)</td>
<td>75% (60-90%)</td>
<td>5, 8-10</td>
</tr>
<tr>
<td>Toxicity on IC/sotalol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0.5% year one, (0-3%), then 0.32% per year</td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>9.5% year one (5-25%), then 1.28% per year</td>
<td></td>
</tr>
<tr>
<td>Recur on amiodarone (no ablation) (over 12 months)</td>
<td>65% (50-80%)</td>
<td>5, 8, 10</td>
</tr>
<tr>
<td>Toxicity on amiodarone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0.1% per year (0-1%)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>9.9% year one (5%-20%), then 0.9% (0.5 – 3%) per year</td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation procedure</td>
<td>$15,000</td>
<td>Cost-accounting, 4,</td>
</tr>
<tr>
<td></td>
<td>($10,000 - $20,000)</td>
<td>24</td>
</tr>
<tr>
<td>Condition</td>
<td>Cost (Range)</td>
<td>Ref.</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------------</td>
<td>------</td>
</tr>
<tr>
<td>Vascular access</td>
<td>$8,000 ($6,000 - $10,000)</td>
<td>15</td>
</tr>
<tr>
<td>Perforation/tamponade</td>
<td>$7,500 ($5,000 - $10,000)</td>
<td>15</td>
</tr>
<tr>
<td>Stroke</td>
<td>$8,200 ($3,000 - $12,000)</td>
<td>15</td>
</tr>
<tr>
<td>TIA</td>
<td>$8,200 ($3,000 - $13,000)</td>
<td>15</td>
</tr>
<tr>
<td>PV stenosis</td>
<td>$7,800 ($3,000 - $10,000)</td>
<td>4, 15</td>
</tr>
<tr>
<td>Pmuemothorax/hemothorax</td>
<td>$13,000 ($5,000 - $20,000)</td>
<td>15</td>
</tr>
<tr>
<td>Telemetry admission</td>
<td>$5,000 (0 - $7,000)</td>
<td>25</td>
</tr>
<tr>
<td>Well post ablation</td>
<td>$1,300 year one, ($500-$3,000) then $200/year ($0-1,000)</td>
<td>Assumption, 4</td>
</tr>
<tr>
<td>Rate control/anticoagulation</td>
<td>$2,800/yr ($900 - $5,000)</td>
<td>16, 17</td>
</tr>
<tr>
<td>Cost well on 1st line drug</td>
<td>$4,000 ($2,500 - $6,000)</td>
<td>4, 16, 17</td>
</tr>
<tr>
<td>Drug toxicity 1st line drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>$10,000 ($0-$20,000)</td>
<td>24, assumption</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>$5,100 ($3,000 - $6,000)</td>
<td></td>
</tr>
<tr>
<td>Cost well on amiodarone</td>
<td>$3,500 ($1,200 - $5,000)</td>
<td>16, 17</td>
</tr>
<tr>
<td>Amiodarone toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>$10,000 ($0 - $20,000)</td>
<td>24, 26</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>$5,000 ($3,000 - $6,000)</td>
<td></td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic States</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well after ablation</td>
<td>.79 (.76 -.82)</td>
<td>20, 21, unpublished data</td>
</tr>
<tr>
<td>Well on drug therapy</td>
<td>.79 (.76 -.82)</td>
<td>Assumption, 20</td>
</tr>
<tr>
<td>Rate control/anticoagulation</td>
<td>.725 (.69 -.76)</td>
<td>20, 21, unpublished data</td>
</tr>
<tr>
<td>Following major stroke</td>
<td>0.39 (0-1)</td>
<td>24</td>
</tr>
<tr>
<td>Following minor stroke</td>
<td>0.76 (0.14 – 1.0)</td>
<td>24</td>
</tr>
<tr>
<td>Disutility for short term events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal drug toxicity</td>
<td>7 days (1 -30)</td>
<td></td>
</tr>
<tr>
<td>Telemetry admission</td>
<td>3 days (1-7)</td>
<td>24,25</td>
</tr>
<tr>
<td>Ablation complication</td>
<td>4 days (0-10)</td>
<td>Opinion</td>
</tr>
</tbody>
</table>
SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

Figure 1. Changes in utility scores following treatment with either antiarrhythmic drugs or catheter ablation in 3 study populations: the FRACTAL registry (green line), the randomized A4 study (ablation group = red line; drug therapy group = blue line) and a consecutive series of patients treated with catheter ablation at Beth Israel Deaconess Medical Center. For all groups, baseline utility scores ranged from 0.71 – 0.76, and for the 3 groups that maintained sinus rhythm, increased to 0.79 – 0.81. Utility scores did not improve in A4 control group patients. See text for details.
Figure 1.
REFERENCES


