



Effective Health Care

Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation *Executive Summary*

Background

The Agency for Healthcare Research and Quality commissioned this report to review the evidence for the clinical effect and safety of radiofrequency (RF) catheter ablation for the management of atrial fibrillation (AF). AF is the most common sustained arrhythmia seen in clinical practice. Its prevalence increases with age, from 0.1 percent in people under 55 years to more than 9 percent by 80 years of age.

The heavy burden of AF creates a pressing need for novel approaches to management. In some patients, symptoms as well as the hemodynamic effects of the arrhythmia can be controlled if the ventricular response is adequately slowed by atrioventricular (AV) nodal blocking agents. In other patients, the lack of an atrial “kick,” or atrial contraction (which contributes up to 20 percent of the left ventricular volume at the end of diastole), as well as the irregularity of the ventricular response, results in symptoms and deleterious hemodynamic consequences. The appropriate treatment is, therefore, the restoration of normal sinus rhythm, which is performed electrically and/or chemically.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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Several randomized controlled trials (RCTs) have compared the two strategies of rhythm control vs. rate control. Individually, these RCTs have failed to show that one strategy is superior to the other. When a meta-analysis of 5,239 patients with AF enrolled in RCTs of rhythm vs. rate control was performed, a strategy of rhythm control with anti-arrhythmic drugs (AADs) was associated with a worse outcome, including an increased risk of all-cause death and thromboembolic stroke.

However, it is well recognized that a rhythm-control strategy with AADs is not equivalent to maintenance of sinus rhythm. In other words, the worse prognosis associated with a rhythm-control strategy in the clinical trials is not the equivalent of a worse prognosis with sinus rhythm per se, and it should not be a cause to abandon novel strategies aimed at maintaining sinus rhythm. Moreover, restoring sinus rhythm may provide benefits beyond symptomatic relief. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study, a rhythm-control strategy with AADs offered no survival advantage over a rate-control strategy. However, in an “on-treatment” analysis of the relationship of survival to cardiac rhythm and treatment as they changed over time, the presence of sinus rhythm was associated with a considerable reduction in the risk of death and AAD use was associated with increased mortality. The beneficial effects of maintaining sinus rhythm with AADs may be offset by their serious side effects, leading the AFFIRM investigators to conclude that maintaining sinus rhythm might be beneficial if it could be achieved effectively with fewer adverse effects. Catheter ablation for AF could be promising in that regard.

Catheter ablation for AF is based on the understanding that electrical activity emanating from the pulmonary veins (PVs) serves as a trigger for AF in many patients. Sleeves of atrial muscle fibers have been shown to extend from the left atrium into the PVs for 1 to 3 cm. In a proof-of-concept study in 1998, Haissaguerre and colleagues studied 45 patients with paroxysmal AF (PAF) refractory to drug therapy, in whom 94 percent of the points of AF origin were mapped to foci inside the PVs. They observed that elimination of local electrograms at these foci with RF energy rendered 62

percent of the patients free of AF recurrence over 8 months of followup. This observation formed the basis for future development of RF catheter ablation (RFA) for AF.

The initial strategy of RFA involved delivery of RF energy at the sites of earliest activation in a segmental fashion at the ostium of the PVs. After the recognition of PV stenosis as a complication, the lesion set was moved to a more antral position within the atrium. Some centers adopted this method of PV isolation (also known as segmental or focal pulmonary vein isolation), which is guided by a circular multipolar catheter placed in the PV. The endpoint of the procedure is electrical isolation of the PVs or dissociation of PV potentials from atrial potentials.

Pappone reported a variation of Haissaguerre’s initial technique known as wide area circumferential ablation (WACA), in which RF energy is delivered in a circumferential fashion around the ipsilateral veins. In this anatomic-based procedure, two encircling lesions are created. The endpoint of the procedure is an abatement of the voltage of the signal at the ablation site.

Additional lesion sets have been used in an attempt to ablate non-PV triggers of AF and also to target atrial areas thought to be responsible for maintenance of AF. These linear lesions are placed in different regions in the left atrium and may include the posterior left atrium, the roof of the left atrium, the interatrial septum, and the isthmus formed between the mitral annulus and the pulmonary vein/left atrial appendage. In another effort to identify and ablate substrate sites, areas of complex fractionated electrograms have also been targeted. The cavotricuspid isthmus, which is the substrate for the maintenance of atrial flutter, has been a target of ablation when atrial flutter has been documented as a clinical rhythm. On occasion, RFA of the cavotricuspid isthmus has been performed empirically, as atrial flutter could degenerate into AF.

At present, the Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, put forth by the Heart Rhythm Society (HRS) and endorsed by several professional organizations, states that the foundation of most AF ablation procedures is to target the PVs and/or PV antrum. After discussion with a technical expert

panel convened for this Comparative Effectiveness Review and in accordance with the HRS Consensus Statement, we reviewed only studies that included the targeting of the PVs or PV antrum, with or without the addition of other strategies.

The present review examines the evidence for the short- and long-term effect and safety of RF catheter ablation for AF.

Conclusions

Summary Table A gives an overview of the studies reviewed for this report. Findings are described below in terms of Key Questions.

Key Question 1. What is the effect of RFA on short-term (6 to 12 months) and long-term (>12 months) rhythm control, rates of congestive heart failure, left atrial and ventricular size changes, rates of stroke, quality of life, avoiding anticoagulation, and readmissions for persistent, paroxysmal, and long-standing persistent (chronic) atrial fibrillation?

Our literature search identified six RCTs and two retrospective cohort studies of patients with AF that compared RFA with medical treatment. Studies included mainly patients with PAF whose treatment with AADs had not been effective. The patients underwent various ablation approaches and medical treatments across studies, and clinical outcomes were assessed in nonuniform ways. The methodological quality of five RCTs was rated fair and one RCT was rated poor. The studies reported heterogeneous followup durations which make classification of certain reported outcomes into a binary scheme somewhat problematic. We chose to report the actual mean followup duration associated with each outcome of interest in those instances.

Rhythm control

There is a moderate level of evidence to show that patients who received RFA as a second-line therapy (i.e., patients who did not respond to medical therapy) had a higher chance of maintaining sinus rhythm than those treated with medical therapy alone (relative risk (RR) 3.46, 95-percent confidence interval (CI) 1.97-

6.09) at 12 months postprocedure. The summary estimate was derived from meta-analysis of three RCTs that assessed the rhythm control of patients exclusively after a single procedure.

There is insufficient evidence to compare freedom from AF recurrence in patients who had RFA as first-line therapy vs. medically treated patients. One fair quality RCT of 67 patients (96 percent PAF) reported an increased freedom from AF recurrence at 12 months for RFA as first-line therapy compared with medical treatment (88 percent vs. 37 percent, $P < 0.001$).

Rates of congestive heart failure

There is insufficient evidence to compare the rates of congestive heart failure between RFA and medical treatment. There was only one observational study with data. This study reported that patients who underwent RFA had a lower risk of developing congestive heart failure than those treated with medical therapy (5 percent vs. 10 percent, P value not reported) at a mean followup of 30 months.

Left atrial and ventricular size changes

There is a low level of evidence showing no statistically significant difference in the improvement of left atrial diameter (LAD), left ventricular end diastolic diameter (LVED), or ejection fraction (EF) at 12 months in patients who underwent RFA compared to those treated with medical therapy.

Rates of stroke

There is a low level of evidence showing no statistically significant difference in the risk of cerebrovascular events at 12 months in patients who underwent RFA compared to those treated with medical therapy (risk difference 0.6 percent, 95-percent CI -1.1 to 2.3 percent favoring AAD). The summary estimate was derived from meta-analysis of six RCTs.

Quality of life

There is a low level of evidence to suggest that RFA improves quality of life more than medical treatment. Three RCTs and one observational study reported more improvement in the general or physical functioning score of the SF-36 health survey in patients who underwent RFA than in patients who had medical treatment alone (net difference between the two

treatments, +1 to +25 favoring RFA). However, these studies assessed the results at nonuniform time points and therefore the findings may be difficult to interpret.

Avoiding anticoagulation

There is a low level of evidence suggesting that patients treated with RFA have a better chance of avoiding anticoagulation than those treated with AADs. There was only one RCT. It found a higher proportion of patients treated with RFA than patients treated with medical therapy reporting freedom from anticoagulation at 12 months (60 percent vs. 34 percent, $P=0.02$).

Readmissions

There is a low level of evidence on differences in readmission rates between patients treated with RFA and those treated with AADs. Two RCTs compared the rates or number of readmissions between RFA and medical treatment. One RCT reported a lower readmission rate in patients treated with RFA than medical treatment (9 percent vs. 54 percent, $P<0.001$), while the other RCT reported no statistically significant difference in the median number of readmissions between RFA and medical treatment (1 readmission vs. 2 readmissions, $P=0.34$). The findings on the rates of readmissions are inconsistent. This may be because readmission rates depend on many other factors besides the recurrence of disease (e.g., the particular health care system, bed availability, severity of illness).

Key Question 2. What are the patient-level and intervention-level characteristics associated with RFA effect on short- and long-term rhythm control?

There is a low level of evidence to show that AF type, namely nonparoxysmal AF, is predictive of a higher rate of AF recurrence. Univariable analyses within 31 studies that reported recurrence rates for PAF vs. other types of AF were clinically and statistically heterogeneous, but meta-analysis found statistically significant higher rates of recurrence in patients with nonparoxysmal AF, with relative risks of about 1.6. However, only a minority of multivariable analyses bear this out. Overall, 25 studies reported multivariable analyses of the association between patient-level characteristics and AF recurrence. Among these, 17

evaluated AF type but only 6 of them found statistically significant independent associations between AF type and recurrence rates. In the 8 studies that reported hazard ratios, these ranged from 1.1 to 22, suggesting lower recurrence rates in patients with PAF. Among 11 comparisons that reported both univariable and multivariable analyses, 6 found statistically significant crude and adjusted higher recurrence rates in patients with nonparoxysmal AF, 3 found significant crude but nonsignificant adjusted associations, and 2 found nonsignificant crude and adjusted associations. In both univariable and multivariable analyses reported, no study or population factors were found to explain the heterogeneity among the studies.

There is a moderate level of evidence to show that among patients with approximately normal EF or LAD, these parameters are not independent predictors of AF recurrence. In multivariable analyses, 5 of 17 studies found an association between lower EF and AF recurrence, and 4 of 20 found an association between larger LAD and AF recurrence. However, the reported data suggest that only a small proportion of patients included in the analyses had EFs below about 40 percent or LADs above about 60 mm. The evidence is insufficient to estimate the predictive value of abnormal EF or LAD on recurrence rates.

There is a high level of evidence to show that sex, the presence of structural heart disease, and duration of AF are not associated with AF recurrence. None of the 23 studies found an independent association between sex and AF recurrence. Only 1 of 21 studies found a consistent association between structural heart disease and AF recurrence. Only 3 of 16 studies found a statistically significant association between duration and recurrence of AF, with hazard ratios of 1.03 and 1.08 for longer duration.

There is a high level of evidence to show that age, within the approximate range of 40 to 70 years, is not independently associated with AF recurrence. Only 1 of 24 studies found an association (that higher age was associated with lower rates of AF recurrence). However, the reported data suggest that only a small proportion of patients included in the analyses were younger than about 40 years or older than about 70 years. The evidence is insufficient to estimate the predictive value of young or very old age.

There is insufficient evidence for other potential predictors of AF recurrence, as other predictors were only rarely evaluated.

There is insufficient evidence to show that intervention-level characteristics, such as operator experience or setting, are predictors of AF recurrence, as no study addressed this question.

Key Question 3. How does the effect of RFA on short- and long-term rhythm control differ among the various techniques or approaches used?

Different approaches

Sixteen RCTs, 2 nonrandomized comparative trials, 2 prospective cohort studies, and 17 retrospective cohort studies met eligibility criteria and reported outcomes of AF after RFA using different approaches. Approaches used in these studies included pulmonary vein isolation (PVI) with RFA within and around the PV ostia and a wide-area circumferential ablation (WACA), with or without additional ablation lines. The majority of the studies included a mixture of patients with either PAF or persistent/longstanding persistent AF.

PVI vs. WACA. There is a moderate level of evidence to show that WACA may result in lower rates of AF recurrence than ostial PVI in patients with either PAF or persistent AF, with followup ranging from 6 to 15 months. Five RCTs of ostial PVI vs. WACA with or without additional ablation lines compared their efficacy to maintain sinus rhythm. Only two studies reported results after a single procedure and off AADs. Both studies found that patients who had WACA had a higher rate of success (freedom from AF recurrence) than patients who had ostial PVI (67 percent vs. 49 percent, $P \leq 0.05$; 88 percent vs. 67 percent, $P = 0.02$). Of the three studies that included patients who had reablation during followup, two reported similar findings.

RFA with or without additional left-sided ablation lines. There is insufficient evidence to make definitive conclusions concerning the effects of the addition of left-sided ablation lines to RFA. The substantive heterogeneity of the different types of additional left-

sided ablation lines that were used by the studies preclude meaningful comparisons. Six RCTs compared the efficacy of one RFA technique with vs. without the addition of left-sided ablation lines (e.g., mitral-isthmus line (MIL), roof or posterior left atrial lines). The majority of the studies reported AF recurrence rates that included patients who had reablation or were continued on AADs. Three of five studies on patients with PAF or nonparoxysmal AF found that patients who had additional left-sided ablation lines had less AF or atrial arrhythmia recurrence at followup than patients who did not (MIL 71 percent vs. 53 percent, $P = 0.01$; roof line 87 percent vs. 69 percent, $P = 0.04$; MIL 74 percent vs. 83 percent, no P value reported). Two studies did not find a significant difference in AF recurrence with the addition of left-sided ablation lines.

PVI vs. PVI with right-sided lines. There is insufficient evidence concerning the effects of adding right-sided lines on AF recurrence after RFA. One RCT examined the incremental benefit of adding a cavotricuspid isthmus ablation line in patients undergoing RFA for AF. This study, which included patients with AF and at least one episode of atrial flutter, found no significant difference in AF recurrence at 12 months followup between the group that had ostial-antral PVI and the group that had ostial-antral PVI with cavotricuspid isthmus ablation. Another RCT compared WACA with vs. without additional ablation of the superior vena cava. This study of patients with PAF found no significant difference at 12 months followup in the recurrence of atrial tachyarrhythmia between the patients who had WACA with superior vena cava ablation and the patients who had only WACA.

Different approaches in retrospective studies

There is insufficient evidence to draw conclusions from this group of retrospective studies. These observational studies compared many different approaches to RFA. They have limitations in the comparability among groups. Historical controls were used in the majority of the studies. In some instances, the proportions of patients with different types of AF differed between groups, and the length of followup also differed. None of the studies adjusted for potential confounders.

Technical issues

There is a moderate level of evidence suggesting no differences in long-term rhythm control in patients with AF by using an 8 mm tip catheter vs. an irrigated tip catheter for RFA. Data from four RCTs did not show significant differences in long-term rhythm control comparing 8 mm tip catheters to irrigated (closed or open) tip catheters in patients undergoing PVI for drug-refractory AF.

There is a low level of evidence suggesting no differences in rhythm control in patients with drug-refractory AF when comparing different imaging modalities used during RFA. Data from three fair quality RCTs with fewer than 100 patients in each trial did not show significant differences in the outcomes of PVI in patients with drug-refractory AF up to 1 year followup.

There is insufficient evidence to draw conclusions from the rest of the studies, as they were all poor quality individual studies that addressed separate technical issues. These studies analyzed the outcomes of PVI for AF comparing different energy outputs, different postprocedure durations of observation in the electrophysiology laboratory, various mapping techniques (e.g., circular mapping alone vs. circular mapping enhanced with intracardiac echocardiogram with or without monitoring of microbubbles), or different ablation times.

Key Question 4. What are the short- and long-term complications and harms associated with RFA?

There is a low level of evidence that adverse events associated with RFA are relatively uncommon. The level of evidence was rated low because the studies reviewed employed nonuniform definitions and assessments of adverse events. There were 84 studies that reported at least one adverse event associated with RFA. Most of the studies did not report the time of occurrence of the adverse events. Based on the study description, we surmised that most of the adverse events either took place in a peri-procedural timeframe or shortly after being discharged home postprocedure. The only exception was the diagnosis of PV stenosis, which was routinely screened for at around 3 months. Major adverse events included PV stenosis, cardiac

tamponade, stroke and/or transient ischemic attack, and peripheral vascular complications such as bleeding/hematoma, pseudoaneurysm, femoral vein thrombosis, or arteriovenous fistula. Seventy-eight studies assessed the rates of asymptomatic or symptomatic PV stenosis. The majority of these studies reported asymptomatic PV stenosis rates of between 0 percent and 19 percent (median 0.3 percent); 36 studies did not identify a single case of PV stenosis. Symptomatic PV stenosis requiring interventions occurred in less than 1 percent of patients in six studies. Cardiac tamponade was reported to occur in 0 percent to 5 percent (median 1 percent) of patients in the 70 studies that reported this adverse event. Cerebrovascular events were reported in 0 percent to 7 percent (median 0.9 percent) of patients in 72 studies; 19 studies reported no cerebrovascular events. Atrioesophageal fistula was reported in 26 studies: 5 studies reported 1 case each, with event rates ranging from 0.1 percent to 0.9 percent; the remainder did not identify any cases. Among 16 studies, five deaths were reported within 30 days postprocedure: one patient died from a pulmonary infection, one died from anaphylaxis after the procedure, and three died from atrioesophageal fistulas. (Three publications from the same group of investigators each reported one death from atrioesophageal fistula.)

Major adverse events associated with RFA are relatively uncommon. Overall, they occurred in less than 5 percent of patients in most studies. However, it is difficult to compare the rates of adverse events across studies, as the descriptions of the various adverse events were not always comparable.

Remaining Issues and Future Research

Over 1 year of followup, RFA was superior to medical treatments at maintaining sinus rhythm in patients with PAF for whom first-line medical treatment was not effective. It should be noted that the primary endpoint in all published RCTs to date has been the recurrence of AF, and no randomized trial has examined the effect of catheter ablation on the risk of stroke or death. To fully comprehend outcomes like stroke, death, or quality of life, much longer followup will be needed.

Studies reported different approaches to followup evaluations and treatments for recurrent AF. Some used Holter monitoring to assess for asymptomatic AF recurrence; some relied only on symptomatic AF recurrence; some outcome assessments reported aggregate data including reablation (but did not report separate data on those without reablation); some outcome assessments reported aggregate data from both patients who were on AADs and those who were off AADs (but did not segregate the data). These differences in followup monitoring and management across studies limit the comparability across studies and hamper our ability to assess the true effect of RFA. Future studies should strive to adopt standardized post-RFA monitoring and use modalities that are more sensitive to asymptomatic recurrences of AF (e.g., event monitors, implantable loop recorders, or existing pacemakers). In addition, followup durations longer than the typical 6 to 12 months observed in the current literature are needed before more reliable inferences can be made concerning the longer term efficacy of this procedure. Moreover, to further understand why some patients benefit from RFA and some do not, a uniform system of defining the various types of AF and conditions under which outcomes were evaluated (e.g., on or off AADs, after one or more than one ablation, symptomatic or asymptomatic AF outcomes, with or without Holter recordings) should be implemented in future studies.

Only one small RCT suggested that first-line RFA (prior to a trial of AADs) may be of benefit for patients with less than 3 months of AF. Further studies are needed to confirm this finding.

Whether AF type is predictive of a higher rate of AF recurrence after RFA is still unsettled. Data from a large registry of patients with uniformly defined AF types and AF recurrence outcomes may help improve future analyses examining this important question.

Even though major adverse events were not commonly reported in the studies reviewed, serious and life-threatening events (e.g., atrioesophageal fistula) do happen. Studies on identifying the patients who are most likely to benefit from RFA and studies on different RFA approaches and techniques to improve efficacy and minimize complications should be undertaken. Furthermore, adverse events should be uniformly defined so that informative comparative analyses can be performed. All studies should actively collect adverse event data from study participants.

Further investigations are also needed on the effect of RFA for AF on quality of life, including patient populations underrepresented in the current literature but often encountered in clinical practice (e.g., the elderly, women, those with very low EF or enlarged LAD, and patients with multiple comorbidities).

Full Report

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Table A. Summary of reviewed studies: radiofrequency catheter ablation for atrial fibrillation

Comparisons	Study type	Number of studies	Number of studies by quality ¹			Number of patients
			Good	Fair	Poor	
Radiofrequency ablation vs. open surgical procedures						
	Any	0				
Radiofrequency ablation vs. antiarrhythmic drugs						
First-line therapy	RCT	1	1		70	
Second-line therapy	RCT	5	4	1	623	
	Non-RCS	2		2	1,341	
Comparison of various radiofrequency ablation techniques						
PVI vs. WACA	RCT	5	4	1	500	
RFA with or without additional left-sided ablation lines	RCT	6	4	2	1,069	
PVI vs. PVI with right-sided lines	RCT	2		1	214	
8 mm vs. closed irrigated tip catheter	RCT	2	2		91	
8 mm vs. open irrigated tip catheter	RCT	2	2		233	
	Non-RCS	1		1	221	
Different imaging modalities	RCT	5	3	2	340	
	Non-RCS	3		3	330	
Miscellaneous comparisons	RCT, non-RCS, cohort	33	4	29	4,854	
Predictors of recurrence of atrial fibrillation						
Multivariable analyses	Any	25	3	9	13	6,747
Atrial fibrillation type (univariable analyses)	Any	31	2	6	23	7,412
Adverse events	² Cohort	100	Quality not rated		³ ≤20,000	

¹Quality ratings:

- Good** Studies that have the least bias and results that are considered valid. Studies that mostly adhere to the commonly held concepts of high quality including the following: a formal randomized controlled design; clear description of the sample, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; < 20% dropout rate; clear reporting of dropouts; and no obvious bias. Studies rated “good” must have reported the atrial fibrillation recurrence rate off anti-arrhythmic drugs after the initial radiofrequency catheter ablation. Only randomized controlled trials could receive a “good” grade.
- Fair** Studies are susceptible to some bias that is not sufficient to invalidate the results. They do not meet all the criteria in the “good” category because they have some deficiencies, but none likely to cause major bias. The studies may be missing information, making it difficult to assess limitations and potential problems.
- Poor** Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. All retrospective studies were graded “poor.”

²The radiofrequency catheter ablation groups in 6 randomized controlled trials and 2 nonrandomized comparative studies comparing catheter ablation with medical treatment were analyzed as cohorts.

³It is likely that some patients were included in multiple studies from the same centers.

Abbreviations: non-RCS=nonrandomized comparative study; PVI=pulmonary vein isolation; RCT=randomized controlled trial; RFA=radiofrequency catheter ablation; WACA=wide area circumferential ablation.