

# Systematic Review: Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation

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**Background:** Atrial fibrillation is the most common sustained arrhythmia. Medical treatment often fails to control symptoms.

**Purpose:** To compare the benefits and harms of radiofrequency catheter ablation and medical therapy in adults with atrial fibrillation.

**Data Sources:** MEDLINE and the Cochrane Central Register of Controlled Trials (2000 to December 2008) were searched for English-language reports of studies in adults.

**Study Selection:** 6 independent reviewers screened abstracts to identify longitudinal studies of adults with atrial fibrillation who underwent radiofrequency catheter ablation. Studies reported arrhythmia or other cardiovascular outcomes at least 6 months after ablation or any adverse events.

**Data Extraction:** Data were extracted by 1 of 4 reviewers and were verified by a cardiac electrophysiologist. Study quality and overall strength of evidence for each question were rated by 2 independent reviewers; disagreements were resolved by consensus.

**Data Synthesis:** 108 studies met eligibility criteria. Moderate strength of evidence (3 trials;  $n = 30$  to 198) showed that radiofrequency ablation after a failed drug course was more likely than

continuation of drug therapy alone to lead to maintained sinus rhythm. Low strength of evidence (4 trials [ $n = 30$  to 137] and 1 retrospective study [ $n = 1171$ ]) suggested that radiofrequency ablation improved quality of life, promoted avoidance of anticoagulation, and decreased readmission rates compared with medical treatment. Major adverse events occurred in fewer than 5% of patients in most of 84 studies.

**Limitations:** Study follow-up was generally 12 months or less. Large heterogeneity of applied techniques and reporting of outcomes precluded many definitive conclusions. Reporting of adverse events was poor. Publication and selective reporting biases could not be ruled out. Studies with small samples and studies reported in a language other than English were excluded.

**Conclusion:** Radiofrequency catheter ablation is effective for up to 12 months of rhythm control when used as a second-line therapy for atrial fibrillation in relatively young patients with near-intact cardiac function. Longer studies that use primary end points of stroke and mortality are needed.

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Atrial fibrillation is the most common sustained arrhythmia in clinical practice (1). Its prevalence increases with age, from 0.1% in people younger than 55 years to more than 9% by 80 years of age (2). The heavy burden of atrial fibrillation on morbidity, mortality, and health care resources creates a pressing need for novel approaches to management. In some patients, adequate pharmacologic slowing of the ventricular response rate (a rate-control strategy) is sufficient to control symptoms. However, many patients remain symptomatic from the lack of organized atrial contraction and the persistent irregularity of the ventricular response in atrial fibrillation. In such patients, the appropriate treatment is restoration of normal sinus rhythm, achieved electrically or chemically (a rhythm-control strategy) (2).

Overall, a rhythm-control strategy with antiarrhythmic drugs offered no survival advantage over a rate-control strategy in 1 large trial (3). An “on-treatment” analysis, however, suggested that sinus rhythm was associated with a considerable reduction in the risk for death, although antiarrhythmic drugs resulted in increased mortality (4). The benefits of maintaining sinus rhythm with antiarrhythmic drugs appeared to be offset by the serious adverse effects of the drugs.

Radiofrequency catheter ablation is a promising approach that offers the benefits of maintaining sinus rhythm

without the adverse effects of antiarrhythmic drugs. Catheter ablation for atrial fibrillation is based on the understanding that electrical activity emanating from the pulmonary veins frequently serves as a trigger for atrial fibrillation. In the late 1990s, Haïssaguerre and colleagues (5) observed that elimination of local electrograms at these foci with radiofrequency energy reduced the risk for recurrence of atrial fibrillation. Currently, the foundation of most atrial fibrillation ablation procedures is to target and electrically isolate the pulmonary veins (6). This may be achieved by delivering lesions immediately outside the ostia of the pulmonary veins or along a wider area in the left atrium encircling the veins. Additional lesion sets have been used to ablate nonpulmonary vein triggers of atrial fibrillation and to target atrial areas thought to be responsible for maintaining atrial fibrillation (6). These linear

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## Web-Only

Appendix Table

Conversion of graphics into slides

**Context**

Is radiofrequency catheter ablation a better alternative than medical therapy for patients with atrial fibrillation?

**Contribution**

This systematic review found that radiofrequency ablation after a failed drug course maintained sinus rhythm more often than continuation of drug therapy alone. Some studies found that ablation improved quality of life but did not necessarily reduce stroke rates compared with medical therapy. Fewer than 5% of patients undergoing ablation reportedly experienced major adverse events, such as pulmonary-vein stenosis or cardiac tamponade.

**Caution**

Most available evidence was obtained in middle-age adults with preserved left ventricular function and involved follow-up periods of 1 year or less.

—The Editors

lesions may be created in 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 or left atrial appendage.

The Agency for Healthcare Research and Quality commissioned this report to review the evidence for the clinical effects and safety of radiofrequency catheter ablation for the management of atrial fibrillation. At present, the “Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation,” put forth by the Heart Rhythm Society and endorsed by several professional organizations, states that the foundation of most atrial fibrillation ablation procedures is to target the pulmonary veins, pulmonary vein antra, or both (6). After discussion with a technical expert panel convened for this comparative effectiveness review and in accordance with the Heart Rhythm Society’s consensus statement, we reviewed only studies that included the targeting of the pulmonary veins or pulmonary vein antra, with or without the addition of other strategies.

**METHODS**

We developed and followed a standard protocol for all steps of the review. A technical report that describes our methods in detail, including the literature search strategies, results, and conclusions, is published elsewhere (7).

**Key Questions**

Key questions on the effectiveness of radiofrequency catheter ablation compared with other available treatments (for example, medical treatment or surgery) were refined with input from the technical expert panel. The panel advised us that 8-mm-tip and irrigated-tip catheters are now the catheters of choice for radiofrequency ablation of atrial fibrillation in the United States. The conventional 4-mm-

tip catheter is rapidly being phased out of use for this indication. Thus, we limited our review to studies that used 8-mm-tip or irrigated-tip catheters as a comparator.

The following 3 key questions were formulated:

1. What is the effect of radiofrequency catheter ablation on short-term (6 to 12 months) and long-term (>12 months) rhythm control; rates of congestive heart failure; changes in the size of the left atrium and ventricle; rates of stroke; quality of life; avoiding anticoagulation; and readmissions for paroxysmal, persistent, and long-standing persistent (chronic) atrial fibrillation?
2. How does the effect of radiofrequency ablation on rhythm control differ among the various techniques used?
3. What are the short- and long-term complications and harms associated with radiofrequency ablation?

**Data Sources and Selection**

We searched MEDLINE and the Cochrane Central Register of Controlled Trials from 2000 to December 2008 for studies of adults with atrial fibrillation who underwent radiofrequency catheter ablation. We combined keywords and Medical Subject Heading terms for atrial fibrillation, pulmonary vein, radiofrequency ablation, and catheter ablation. We limited the search to English-language reports of primary studies in adults that were published in peer-reviewed journals. We did not include unpublished data. Six reviewers screened titles and abstracts to identify potentially relevant articles. They also examined the full-text articles of the potentially relevant abstracts for inclusion eligibility.

We accepted longitudinal studies and excluded case series. We included randomized trials of any sample size. For pragmatic reasons, we restricted the sample sizes in nonrandomized studies. For nonrandomized comparative studies and case-control studies, we included only those with at least 10 patients per intervention group. Noncomparative prospective cohort studies had to have at least 50 patients receiving radiofrequency catheter ablation, and retrospective cohort studies must have had at least 100 patients. We included studies of adults ( $\geq 18$  years of age) with paroxysmal, persistent, or permanent or chronic atrial fibrillation. We accepted the definitions of the various types of atrial fibrillation used by the study authors, using the terms “permanent” and “chronic” atrial fibrillation as reported in the individual studies, even though the definitions varied. Notably, the consensus statement on radiofrequency catheter ablation for the treatment of atrial fibrillation published by the Heart Rhythm Society in 2007 no longer used the term “chronic,” instead adopting the term “long-standing persistent” for continuous atrial fibrillation lasting more than 1 year (6). For a study to be included, at least 80% of the patients had to be treated with first-time radiofrequency ablation for atrial fibrillation. We excluded studies that were limited to patients with congenital heart disease, hypertrophic cardiomyopathy, or the Wolff-Parkinson-White syndrome.

The intervention of interest was catheter-directed radiofrequency ablation of the left atrium to prevent atrial fibrillation by using an 8-mm-tip or irrigated-tip catheter. We included studies that compared 4-mm-tip catheters to other catheters, but not studies that evaluated only 4-mm-tip catheters. Radiofrequency ablation could be used as first- or second-line treatment (that is, before or after a course of antiarrhythmic drugs) and with or without concurrent antiarrhythmic drugs. We included studies of radiofrequency ablation strategies in which the explicit or intended goal was targeting of the pulmonary veins or pulmonary vein antra, with or without additional ablation. We did not evaluate cryoablation or microwave ablation.

We included only studies that reported outcomes of interest at 6 months or more after the initial intervention or that reported adverse events at any time. Outcomes of interest included rhythm control, congestive heart failure, changes in the size of the left atrium or ventricle, stroke, quality-of-life measures, avoidance of anticoagulation, readmissions, and reinterventions for atrial fibrillation. We excluded arrhythmia outcomes that occurred during the blanking period, which is defined as a postprocedure period (typically between 1 and 3 months) during which an episode of atrial fibrillation was not considered a recurrence.

#### Data Extraction and Quality Assessment

Data from each study were extracted by 1 of 4 reviewers and were confirmed by a clinical cardiac electrophysiologist author. The extracted data included information on patient characteristics, ablation characteristics (for example, type of catheter tip, verification of electrical isolation, and ablation techniques), other interventions, outcomes, study design, and quality. For most outcomes, 6-month, 12-month, and last-reported-time-point data were included. All mortality and adverse event data were extracted. We used predefined criteria to grade study quality as good, fair, or poor. We also rated the strength of the overall body of evidence for each key question as high, moderate, low, or insufficient (**Appendix Table**, available at [www.annals.org](http://www.annals.org)). The quality assessment and strength of the overall body of evidence were rated by 1 of the reviewers and confirmed by at least 1 other. Disagreements were resolved by consensus.

#### Data Synthesis

For adverse event data collection, we consulted the technical expert panel about the major adverse events that would be relevant. These included pulmonary-vein stenosis, cardiac tamponade or pericardial effusion requiring intervention, stroke or transient ischemic attack, bleeding requiring transfusion, atrioesophageal fistula, 30-day mortality, any deaths, and other major adverse events as reported in the studies. For primary clinical outcomes with sufficient events, including freedom from recurrence of atrial fibrillation (maintaining sinus rhythm), we performed random-effects meta-analysis of randomized, controlled trials whenever it was suitable to do so, based on at least 3 trials without a large degree of clinical heterogeneity

(8). For secondary outcomes with no events in several trials, such as stroke, we performed fixed-effects meta-analysis of risk difference (8).

## RESULTS

We screened 2169 abstracts and evaluated 390 full-text articles. A total of 108 unique studies (reported in 130 articles) met our eligibility criteria: 32 randomized, controlled trials (9–40); 9 nonrandomized comparative studies (41–49); and 67 cohort studies (50–116) (**Figure 1**). The **Table** summarizes the major comparisons, the studies and their quality, and the total number of patients analyzed.

### Effects of Radiofrequency Catheter Ablation on Short- and Long-Term Outcomes

#### Characteristics of Reviewed Studies

No study compared radiofrequency catheter ablation with an open surgical procedure. We identified 6 randomized, controlled trials (15, 19, 27, 29, 33, 39) and 2 nonrandomized comparative studies (47, 49) of patients with atrial fibrillation that compared radiofrequency ablation with medical treatment. Studies primarily included patients with paroxysmal atrial fibrillation in whom antiarrhythmic drugs had failed. Various ablation techniques and medical treatments were used across studies, and clinical outcomes were assessed in nonuniform ways. Follow-up lasted 12 to 30 months.

#### Rhythm Control

Our meta-analysis of 1 poor-quality (19) and 2 fair-quality (29, 33) randomized, controlled trials that assessed rhythm control exclusively after a single procedure showed that patients who received radiofrequency ablation as a second-line therapy had a higher chance of maintaining sinus rhythm than those treated with medical therapy alone (relative risk, 3.46 [95% CI, 1.97 to 6.09]) at 12 months after the procedure (**Figure 2**). One fair-quality randomized, controlled trial that compared radiofrequency ablation as first-line therapy with medical treatment in 67 patients reported a higher rate of freedom from recurrence of atrial fibrillation at 12 months with ablation (88% vs. 37%;  $P < 0.001$ ) (15).

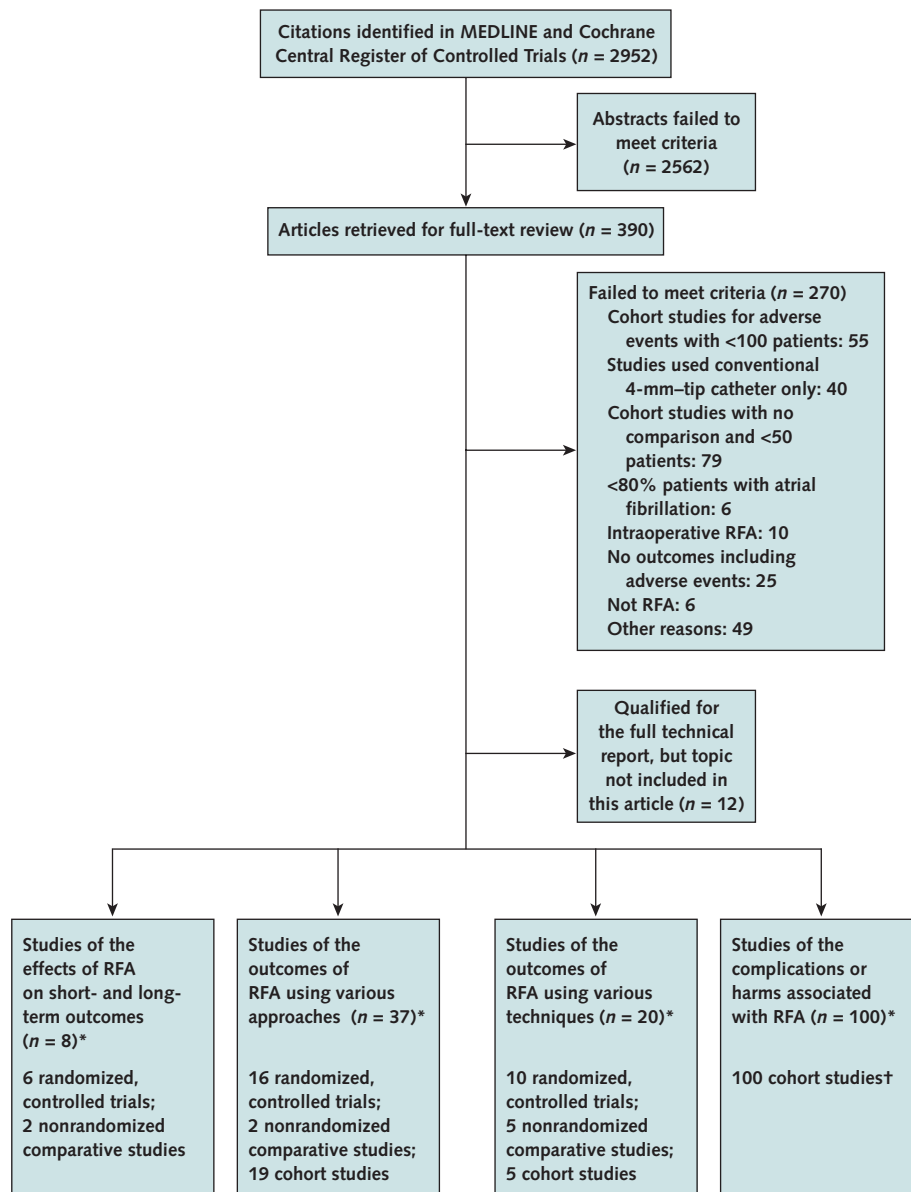
#### Rate of Congestive Heart Failure

No randomized, controlled trial examined the incidence of congestive heart failure in radiofrequency ablation versus medical treatment of atrial fibrillation. One poor-quality observational study reported that patients who underwent radiofrequency ablation had a lower risk for congestive heart failure than those receiving medical therapy (5% vs. 10%;  $P$  value not reported) at a mean follow-up of 30 months (47).

#### Changes to Size of Left Atrium and Ventricle

One fair-quality randomized, controlled trial of radiofrequency ablation versus medical treatment reported no

Figure 1. Study flow diagram.



RFA = radiofrequency catheter ablation.

\* The RFA groups in 6 randomized, controlled trials and 2 nonrandomized studies that compared catheter ablation with medical treatment were used as cohorts.

† 56 studies met criteria for  $\geq 2$  questions.

statistically significant differences in changes in left atrial diameter and left ventricular ejection fraction at 1-year follow-up (15).

**Rate of Stroke**

Our meta-analysis of 1 poor-quality (19) and 5 fair-quality (15, 27, 29, 33, 39) randomized, controlled trials found no statistically significant difference in the risk for cerebrovascular events at 12 months in patients who underwent radiofrequency ablation compared with those who

received medical therapy (risk difference, 0.6% [95% CI, -1.1% to 2.3%]; medical treatment favored).

**Quality of Life**

One poor-quality (19) and 2 fair-quality (15, 39) randomized, controlled trials and 1 poor-quality observational study (47) measured quality of life by using the 36-item Short Form General Health Survey, which has scores ranging from 0 (worst) to 100 (best). The 3 trials reported larger improvement in general or physical functioning

score in patients who underwent radiofrequency ablation than in patients who had medical treatment alone (net difference in score between the 2 treatments, 1 to 17;  $P < 0.05$ ; ablation favored). The observational study reported similar findings, but no statistical comparisons were provided. It is difficult to compare these results across studies because they were assessed at nonuniform time points.

### Avoiding Anticoagulation

One fair-quality randomized, controlled trial found that radiofrequency ablation was associated with a higher rate of freedom from anticoagulation compared with medical therapy (60% vs. 34%;  $P = 0.02$ ) (15).

### Readmissions

Two fair-quality randomized, controlled trials compared the rates or number of readmissions between the radiofrequency catheter ablation and medical treatment groups. One trial reported a lower readmission rate in patients treated with radiofrequency ablation than in those receiving medical treatment (9% vs. 54%;  $P < 0.001$ ) (39), whereas the other reported no statistically significant difference in the median number of readmissions between radiofrequency ablation and medical treatment (1 vs. 2 readmissions;  $P = 0.34$ ) (33). Neither study provided the specific reasons for readmissions.

### Summary of Evidence

A moderate level of evidence shows that patients who received radiofrequency catheter ablation as a second-line therapy and had not responded to antiarrhythmic drugs had a greater chance of maintaining sinus rhythm than those receiving medical therapy alone. Evidence is insufficient to compare freedom from recurrence of atrial fibrillation in patients who had radiofrequency ablation as first-line therapy with that in patients who received antiarrhythmic drugs. Similarly, evidence is insufficient for comparing the rate of congestive heart failure between the radiofrequency ablation and medical treatment groups. We found low strength of evidence for finding no statistically significant difference between radiofrequency ablation and medical therapy in the improvement of left atrial diameter or left ventricular ejection fraction, or in the risk for cerebrovascular events at 12 months. The strength of evidence is also low for suggesting that radiofrequency ablation improves quality of life, promotes avoidance of anticoagulation, or decreases readmission rates compared with medical treatment.

### Effects of Different Ablation Techniques

#### Characteristics of Reviewed Studies

As discussed in the introduction, different approaches to radiofrequency catheter ablation for atrial fibrillation are used. Sixteen randomized, controlled trials (9, 12–14, 17,

**Table. Summary of Reviewed Studies**

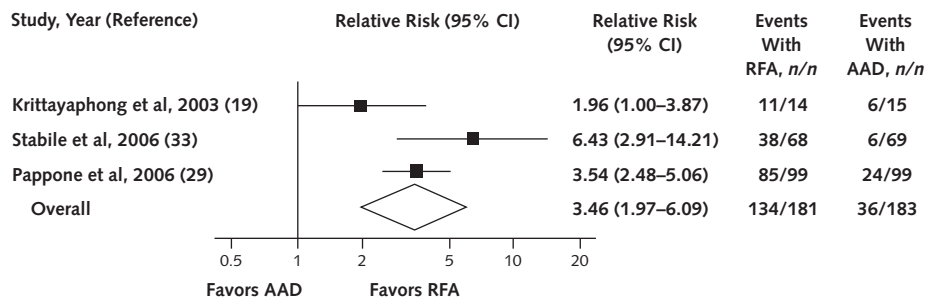
Comparison	Study Type	Studies (Reference), <i>n</i>	Study Quality, <i>n</i>			Patients, <i>n</i>
			Good	Fair	Poor	
<b>RFA vs. open surgical procedures</b>	Any	0	–	–	–	–
<b>RFA vs. antiarrhythmic drugs</b>						
First-line therapy	RCT	1 (39)	–	1	–	70
Second-line therapy	RCT	5 (15, 19, 27, 29, 33)	–	4	1	623
	Nonrandomized comparison	2 (47, 49)	–	–	2	1341
<b>Comparison of RFA techniques</b>						
PVI vs. WACA	RCT	5 (9, 17, 21, 23, 24)	–	4	1	500
RFA with or without additional left-sided ablation lines	RCT	6 (12–14, 28, 31, 40)	–	4	2	1069
PVI vs. PVI with right-sided lines	RCT	2 (37, 38)	–	1	1	214
8-mm-tip vs. closed irrigated-tip catheter	RCT	2 (10, 11)	2	–	–	91
8-mm-tip vs. open irrigated-tip catheter	RCT	2 (16, 22)	–	2	–	233
	Nonrandomized comparison	1 (44)	–	–	1	221
Different imaging methods	RCT	5 (18, 30, 32, 34, 35)	–	3	2	340
	Nonrandomized comparison study	3 (41, 43, 48)	–	–	3	330
Miscellaneous comparisons	RCT, nonrandomized comparison, cohort study	33 (16, 20, 25, 26, 36, 42, 44–46, 50, 59, 64, 69, 72–74, 82, 87–90, 93, 95, 97, 99, 100, 102, 108, 109, 112–114)	–	4	29	4854
<b>Adverse events</b>	Cohort study*	100 (9–12, 14–24, 26–31, 33–49, 51–63, 65–81, 83–92, 94, 96–116)	Quality not rated			≤20 000†

PVI = pulmonary-vein isolation; RCT = randomized, controlled trial; RFA = radiofrequency catheter ablation; WACA = wide-area circumferential ablation.

\* The RFA groups in 6 RCTs (15, 19, 27, 29, 33, 39) and 2 nonrandomized comparative studies (47, 49) that compared catheter ablation with medical treatment were analyzed as cohorts.

† Some patients were probably included in multiple studies from the same centers.

**Figure 2. Random-effects model meta-analysis of relative risk for maintaining sinus rhythm in patients with atrial fibrillation treated with RFA or AADs.**



The diamond shows the summary relative risk centered on a combined estimate and extending to 95% CIs. Squares and horizontal lines indicate relative risks and 95% CIs, respectively, for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. Studies are ordered by sample size. AAD = antiarrhythmic drug; RFA = radiofrequency catheter ablation.

20, 21, 23–26, 28, 31, 37, 38, 40); 2 nonrandomized comparative studies (42, 46); 2 prospective cohort studies (50, 100); and 17 retrospective cohort studies (59, 64, 69, 72–74, 82, 87, 89, 90, 93, 95, 99, 102, 108, 109, 114) reported outcomes of radiofrequency catheter ablation for atrial fibrillation by using different approaches. Ten randomized, controlled trials (10, 11, 16, 18, 22, 30, 32, 34–36); 5 nonrandomized comparative studies (41, 43–45, 48); and 5 retrospective cohort studies (73, 88, 97, 112, 113) reported outcomes of pulmonary-vein isolation for atrial fibrillation by comparing catheter tips, energy outputs, imaging guidance, or postprocedure duration of observation in the electrophysiology laboratory. The randomized, controlled trials included a mixture of patients with paroxysmal or persistent/long-standing persistent atrial fibrillation. The comparisons in retrospective studies were similarly diverse. Our full report provides complete details of the various comparisons (7).

**Pulmonary-Vein Isolation Versus Wide-Area Circumferential Ablation**

Five randomized, controlled trials examined the efficacy of ostial pulmonary-vein isolation versus wide-area circumferential ablation, with or without additional ablation lines for maintaining sinus rhythm (9, 17, 21, 23, 24). Only 2 studies reported results after a single procedure and while patients were not receiving antiarrhythmic drugs. Both studies found that patients who underwent wide-area circumferential ablation had a higher rate of success (freedom from recurrence of atrial fibrillation) than patients who had ostial pulmonary-vein isolation (67% vs. 49%,  $P \leq 0.05$  [9]; 88% vs. 67%,  $P = 0.02$  [24]). Two (21, 23) of 3 (17, 21, 23) studies that included patients who had reablation during follow-up also reported similar findings. Three (9, 23, 24) of 4 (9, 21, 23, 24) studies in which wide-area circumferential ablation was coupled with mapping and ablation of residual potentials reported higher rates of success compared with segmental ostial

pulmonary-vein isolation. The study that did not couple wide-area circumferential ablation with mapping and ablation of residual potentials found that segmental ostial pulmonary-vein isolation was more effective than empirical anatomical wide-area ablation alone in controlling recurrence of atrial fibrillation (17).

**Radiofrequency Catheter Ablation With or Without Additional Ablation Lines**

Six randomized, controlled trials compared the efficacy of one radiofrequency catheter ablation technique with or without the addition of left-sided ablation lines (for example, mitral isthmus, roof, or posterior left atrial lines) (12–14, 28, 31, 40). Three of 5 studies in patients with paroxysmal or nonparoxysmal atrial fibrillation found that patients who had additional left-sided ablation lines had less recurrence of atrial fibrillation or atrial arrhythmia than patients who did not (mitral isthmus line, 71% vs. 53%,  $P = 0.01$  [12]; roof line, 87% vs. 69%,  $P = 0.04$  [14]; mitral isthmus line, 74% vs. 83%,  $P$  value not reported [13]). Two studies did not find a significant difference in recurrence of atrial fibrillation with the addition of left-sided ablation lines (28, 31). One randomized, controlled trial examined the incremental benefit of adding a cavo-tricuspid isthmus ablation line in patients with atrial fibrillation and at least 1 episode of atrial flutter who were undergoing radiofrequency ablation for atrial fibrillation (38); the investigators found no significant difference in recurrence of atrial fibrillation with the addition of cavo-tricuspid isthmus ablation at 12-month follow-up. Another randomized, controlled trial compared wide-area circumferential ablation with versus without additional isolation of the superior vena cava (37) in patients with paroxysmal atrial fibrillation; at 12-month follow-up, there was no significant difference in the recurrence of atrial tachyarrhythmia between the 2 groups.

### Different Catheter Tips

Data from 4 randomized, controlled trials did not show significant differences in long-term rhythm control between 8-mm-tip and irrigated-tip (closed or open) catheters in patients undergoing pulmonary-vein isolation for drug-refractory atrial fibrillation (10, 11, 16, 22).

### Summary of Evidence

A moderate level of evidence showed that wide-area circumferential ablation coupled with ablation of residual potentials resulted in lower rates of atrial fibrillation recurrence than segmental ostial pulmonary-vein isolation in patients with paroxysmal or persistent atrial fibrillation. Evidence is insufficient to make definitive conclusions about the effects of adding left- or right-sided ablation lines to radiofrequency catheter ablation. The substantial heterogeneity of the additional ablation lines used in the studies precludes meaningful comparisons. Evidence is also insufficient to draw conclusions from retrospective studies. These observational studies compared many different approaches to radiofrequency ablation, and most studies used historical controls. In some instances, the proportions of patients with different types of atrial fibrillation differed between groups, and follow-up results from different time points were compared between groups. None of the studies adjusted for potential confounders.

A moderate level of evidence suggests no differences in long-term rhythm control in patients with atrial fibrillation achieved with an 8-mm-tip versus an irrigated-tip catheter for radiofrequency ablation. A low level of evidence suggests no differences in rhythm control in patients with drug-refractory atrial fibrillation among different imaging methods used during radiofrequency ablation. Evidence is insufficient to draw conclusions in the studies that analyzed atrial fibrillation outcomes among different energy outputs, postprocedure durations of observation, various mapping techniques, or different ablation times because they all had deficiencies in study methods.

### Complications and Harms

#### Rates of Events

Eighty-four studies reported at least 1 adverse event associated with radiofrequency catheter ablation (9–12, 14–21, 23, 28, 29, 31, 33, 34, 36–48, 51–54, 56–60, 62, 63, 65–79, 81, 84, 85, 87–92, 94, 96, 97, 99, 100–107, 109–111, 114–116). Sixteen additional studies reported no adverse events (22, 24, 26, 27, 30, 35, 49, 55, 61, 80, 83, 86, 98, 108, 112, 113). We could not confirm whether several of the studies were independent of each other or included overlapping patients. Therefore, all counts should be considered to be the maximum number of individual patients across studies. Most of the studies did not explicitly report the time of occurrence of the adverse events. On the basis of the study description, we surmised that most of the adverse events took place in a periprocedural time frame or shortly after the patient was discharged

home. The only exception was the diagnosis of pulmonary-vein stenosis, which was routinely screened for approximately 3 months after ablation in many studies. Major adverse events included pulmonary-vein stenosis, cardiac tamponade, stroke or transient ischemic attack, and peripheral vascular complications (such as bleeding or hematoma requiring intervention, pseudoaneurysm, femoral-vein thrombosis, and arteriovenous fistula).

Seventy-eight studies with approximately 16 400 patients assessed the rates of asymptomatic or symptomatic pulmonary-vein stenosis (9–11, 14–24, 26–28, 30, 31, 33–39, 41, 43–49, 51, 52, 54–56, 58–61, 63, 65–68, 72–76, 78, 80, 81, 83–90, 97–105, 108, 109, 112–115). Most of these studies reported rates of asymptomatic pulmonary-vein stenosis ranging from 0% to 19% (median, 0.3%); 36 studies did not identify a single case of pulmonary-vein stenosis (10, 11, 16, 19, 22, 24, 26–28, 30, 31, 33–35, 37, 41, 44, 45, 47, 48, 52, 55, 61, 65, 72–74, 80, 83, 85–87, 104, 108, 112, 113). Symptomatic pulmonary-vein stenosis requiring interventions occurred in fewer than 1% of patients in 6 studies that had a total of 4413 patients (15, 54, 63, 67, 68, 115).

Cardiac tamponade was reported in 0% to 5% (median, 1%) of patients in 70 studies (approximately 15 500 patients) that reported this adverse event (9–12, 14–20, 26–28, 30, 31, 33–36, 40–42, 44, 46–48, 53, 54, 56, 58–63, 65–73, 75, 78–80, 83–85, 87, 89, 92, 94, 96, 98, 100, 101, 103–108, 110–112, 115). Cerebrovascular events were reported in 0% to 7% (median, 0.9%) of patients in 72 studies (approximately 16 900 patients) (10–12, 15–17, 19, 20, 23, 26–31, 33–41, 43–47, 49, 52–54, 56, 58–63, 65–68, 70, 75–81, 84–88, 91, 92, 94, 98, 101, 103–106, 108, 110–112, 115, 116); 19 studies reported no cerebrovascular events (15, 26–28, 30, 34–36, 38, 39, 47, 61, 80, 85, 86, 94, 106, 108, 112).

Twenty-six studies (approximately 5100 patients) commented on atriopharyngeal fistula (10, 11, 15, 16, 19, 22, 26, 27, 30, 31, 34, 35, 41, 48, 61, 62, 65, 68, 73, 80, 83, 85, 98, 101, 104, 115), 4 of which reported 1 case each, with event rates ranging from 0.1% to 0.9% (10, 11, 68, 115); the remainder did not identify any cases. Among 16 studies (approximately 4500 patients) (10, 11, 15, 16, 27, 33, 34, 49, 54, 65, 68, 85, 94, 101, 104, 116), 5 deaths were reported within 30 days after the procedure; 1 patient died of a pulmonary infection (116), 1 died of anaphylaxis after the procedure (68), and 3 died of atriopharyngeal fistulas (3 reports [10, 11, 68] from the same group of investigators, each of which reported 1 death related to atriopharyngeal fistula).

### Summary of Evidence

A low level of evidence showed that adverse events associated with radiofrequency catheter ablation are relatively uncommon. The level of evidence was rated low because of nonuniform definitions and assessments of ad-

verse events across studies. Given that many studies had overlapping investigators, institutions, and years of enrollment, it was frequently difficult to ascertain whether patients had been included in multiple studies. Therefore, accurate estimates of summary adverse event rates across studies are not possible. Nevertheless, adverse events generally occurred in fewer than 5% of patients in most studies.

## DISCUSSION

Radiofrequency catheter ablation was superior to medical treatment at maintaining sinus rhythm at 1-year follow-up in patients with paroxysmal atrial fibrillation in whom medical therapy had failed. The finding from our meta-analysis is in general agreement with previous meta-analyses (117–120). However, previous meta-analyses allowed for broad inclusion criteria, and it is unclear whether their summary estimates separated the effect of a single ablation procedure from the effect of multiple ablation procedures in the same patients. Our meta-analysis focused exclusively on freedom from recurrence of atrial fibrillation after a single ablation procedure as second-line treatment. The summary estimate is thus applicable only to this clinical context.

Most patients described in the reviewed studies were relatively young (mean age, approximately 55 years) and had generally preserved left ventricular ejection fraction (approximately 0.60) and minimally increased left atrial diameter (approximately 5 cm). Thus, our findings may not be generalizable to older patients with left ventricular dysfunction or severely dilated left atria. In addition, the primary end point in all published randomized, controlled trials to date has been the recurrence of atrial fibrillation, and no randomized trial has examined the effect of ablation on the risk for stroke or death. To fully assess such outcomes as stroke, death, or quality of life, much longer follow-up is needed. Only 1 small randomized, controlled trial suggested that first-line radiofrequency catheter ablation may be of benefit for patients with atrial fibrillation of less than 3 months' duration; further studies are needed to confirm this finding.

The reviewed studies were heterogeneous with regard to monitoring for recurrence of atrial fibrillation (symptomatic vs. monitoring for asymptomatic episodes), reporting outcomes with or without repeated ablations, and separating rhythm control with from that without antiarrhythmic drugs after ablation. These differences in follow-up monitoring and management limit comparability across studies and reliable assessment of the effect of radiofrequency catheter ablation. Future studies should strive to adopt standardized postablation monitoring, such as those recommended in the Heart Rhythm Society consensus statement (6). Postprocedure follow-up could also take advantage of methods that are more sensitive to asymptomatic recurrences of atrial fibrillation (for example,

event monitors or existing pacemakers). In addition, follow-up durations longer than the typical 6 to 12 months observed in the literature are needed before more reliable inferences can be made about longer-term efficacy of this procedure. To further understand why some patients benefit from radiofrequency ablation and some do not, future studies should implement a uniform system of defining the various types of atrial fibrillation and conditions under which outcomes were evaluated.

For adverse event reporting, it was not always clear whether the lack of information on a particular adverse event meant that no events occurred or simply that the event was not assessed. In addition, the sample sizes in most studies were generally small, precluding reliable risk estimates of the adverse events. Many of the studies had a mean follow-up of no more than 12 months; any long-term events (such as late recurrence or death) or delayed adverse effects from procedural radiation exposure could not be assessed. Furthermore, the lack of clarity regarding possible overlap in patients between studies severely hampered efforts to estimate event rates across all studies.

Our searches were limited to the English-language literature, and studies with certain prespecified small sample sizes were not reviewed. Judging by findings from previous systematic reviews on the same topic that did not have language-restricted searches (117–120), it is unlikely that including non-English-language reports would have substantially altered our conclusions. Nonetheless, pertinent data may be missing because of these search restrictions. Finally, we could not rule out selective reporting and publication biases (121, 122).

In summary, radiofrequency catheter ablation is effective at restoring and maintaining sinus rhythm in patients with paroxysmal atrial fibrillation in whom medical therapy had failed. Notably, the data were mostly obtained from relatively young patients with near-intact cardiac function. To further understand how this intervention will fare in the wider population, more studies in elderly persons and in patients with abnormal cardiac function are needed. In addition, future studies will need longer follow-up to evaluate long-term survival, maintenance of sinus rhythm, quality of life, and stroke events and will need to systematically monitor and assess for anticipated and unanticipated adverse events.

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*Appendix Table. Study Quality and Strength of Evidence Ratings\**

Rating Category	Explanation
<b>Quality</b>	
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 while the patients were not receiving antiarrhythmic 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."
<b>Strength of body of evidence</b>	
High	There is high confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.
Moderate	There is moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	There is low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence is unavailable or does not permit estimation of an effect.

\* Modified after the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, version 1.0 (8).