Comparative Effectiveness Review

Number 15

Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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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.

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).

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	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

[1]Quality 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."

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

[3] It 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.

Introduction

The Agency for Healthcare Research and Quality (AHRQ) commissioned this report to review the evidence for the clinical effects and safety of radiofrequency catheter ablation (RFA) for the management of atrial fibrillation (AF). Over the past decade, RFA has rapidly evolved as a tool for managing AF in select patients.[1] This rapid evolution has been driven by an enhanced understanding of the triggers and etiology of AF and the development of advanced catheter and imaging technologies.

Background

AF remains the most common sustained arrhythmia in clinical practice.[2] Its prevalence increases with age, from 0.1% in people younger than 55 years to more than 9% by 80 years of age.[3] It is estimated that the prevalence of AF will increase with the aging of the population – the projected number of people with AF will exceed 10 million by 2050 according to one estimate.[4]

The burden of AF is manifested in associated symptoms such as dyspnea, fatigue, decreased exercise tolerance, congestive heart failure related to reduction in left ventricular function, a reduced quality of life, an approximately 2-fold increased risk of death, and a 5-fold increased risk of stroke.[3] In addition to the risk of morbidity and mortality for the patient, AF constitutes a heavy burden on healthcare expenditure due to the high costs associated with AF-related hospitalization, evaluation, management, and loss of productivity.[1] The heavy burden of AF creates a pressing need for novel approaches to management. This is especially the case given the suboptimal clinical effect of current therapeutic strategies, which typically fall into two broad categories: rate control of the ventricular response; and rhythm control to maintain normal sinus rhythm. 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 such as beta blockers, calcium channel blockers, and digoxin. Occasionally, adequate rate control is not achievable with medications, and requires AV nodal ablation with implantation of a permanent pacemaker. In other patients, controlling the ventricular response rate is not an adequate treatment. In such cases, the lack of an atrial "kick" (an atrial contraction that contributes up to 20% of the left ventricular volume at the end of diastole), as well as the irregularity of the ventricular response, result in symptoms and deleterious hemodynamic consequences. The appropriate treatment is, therefore, the restoration of normal sinus rhythm which is performed electrically and/or chemically.[3] Class IC and class III antiarrhythmic drugs (AADs) are most commonly used. However, each AAD has a particular side effect profile. These management strategies must also be combined with appropriate anticoagulation strategy (i.e., aspirin or coumadin) based on the patient's risk factors (age, hypertension, underlying structural heart disease, congestive heart failure, diabetes mellitus, and history of stroke or a transient ischemic attack).[3]

Several randomized controlled trials (RCTs) have compared the two strategies of rhythm control versus rate control in patients with AF.[5-9] Individually, these RCTs have failed to show that one strategy is superior to the other.[5-9] However, a metaanalysis of 5,239 patients with AF enrolled in RCTs comparing rhythm and rate control found that a strategy of rhythm control with AADs was associated with worse outcomes, including an increased rate of all-cause death and thromboembolic stroke.[10]

It is well-recognized though, that a rhythm control strategy with AADs is not equivalent to maintenance of sinus rhythm.[11] In other words, the worse outcomes associated with a rhythm

control strategy in the clinical trials is not equivalent to worse outcomes with maintenance of sinus rhythm, per se, and should not be a cause to abandon novel strategies aimed at maintaining sinus rhythm. This is especially crucial in patients who have highly symptomatic AF, in which case restoring sinus rhythm is required to improve symptoms. Importantly, restoring sinus rhythm may provide benefits beyond symptomatic relief.[11] In the Atrial Fibrillation Followup Investigation of Rhythm Management (AFFIRM) Study, the largest trial comparing rhythm and rate control, 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 treatments 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. This suggests that the beneficial effects of maintaining sinus rhythm with AADs may be offset by their serious side effects, leading the AFFIRM investigators to conclude that "if an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might be beneficial."[11] RFA for AF could be promising in that regard.

Catheter ablation for AF is based on the understanding that in many patients electrical activity emanating from the pulmonary veins (PVs) serves as a trigger for AF.[12] Sleeves of atrial muscle fibers extend from the left atrium into the PVs for 1 to 3 cm.[13-16] In a proof-of-concept study in 1998, Haissaguerre and colleagues studied 45 patients with paroxysmal AF (PAF) refractory to drug therapy. In the study, 94% of the points of AF origin were mapped to foci inside the PVs. They observed that elimination of local electrograms at these foci with radiofrequency energy rendered 62% of the patients free of AF recurrence over 8 months of followup.[12] This observation formed the basis for future development of RFA for AF.

Since the publication of Haissaguerre's study, the technique for RFA has rapidly evolved. The initial RFA strategy involved delivery of radiofrequency 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 potential complication of such an approach, the lesion set was moved to a more proximal, or antral, position within the atrium.[17] Some centers adopted this method of PV isolation (also known as segmental or focal PV 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, or left atrial circumferential ablation) in which radiofrequency energy is delivered in a circumferential fashion around the ipsilateral veins (with or without a lesion set at the carina which divides the ipsilateral veins).[18] In this anatomic-based procedure in which two encircling lesions are created, the endpoint of the procedure is an abatement of the voltage of the signal at the ablation site, which may be confirmed by a 3-dimensional voltage map of the PVs and left atrium at the end of the procedure.

The above strategies have been used in patients with AF, but these strategies have been most effective in patients with PAF, which is defined as two episodes or more of AF that spontaneously converts into normal sinus rhythm within 7 days.[3] RFA of persistent AF (an arrhythmia duration of greater than 7 days, with or without cardioversion) or longstanding persistent AF[a] (continuous AF of greater than 1 year duration) has required the development of additional lesions sets in order to improve clinical outcomes.[1]

[a] According to the consensus statement on RFA for the treatment of AF published by the Heart Rhythm Society in 2007, the term chronic or permanent has been replaced by longstanding persistent to define continuous AF of greater than 1 year duration.[1]

Additional lesion sets have been variably used in RFA of PAF and, in particular, in RFA of persistent or chronic AF in an attempt to ablate non-PV triggers of AF and also to target the substrate, or atrial areas thought to be responsible for maintenance of AF.[1] 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 veins/left atrial appendage. In another effort to identify and ablate substrate sites, areas of complex fractionated atrial electrograms (CFAEs) have also been targeted.[19] When atrial flutter has been documented as a clinical rhythm, the cavotricuspid isthmus, which is the substrate for the maintenance of atrial flutter has been a target of ablation. On occasion, RFA of the cavotricuspid isthmus has been performed empirically, as atrial flutter could degenerate into AF.[1]

The above techniques have been used in isolation or in combination at the discretion of the operator such that there is great variability in the techniques used in published studies of RFA as well as in clinical practice. At present, there is no standardization of technique. However, 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.[1]

After discussion with the technical expert panel (TEP) convened for this comparative effectiveness review, and in accordance with the HRS Consensus Statement, we reviewed only studies that included targeting of the PVs or PV antrum, with or without the addition of other strategies.

Variability has been observed not only in technique but also in the technologies used to perform this procedure. Initially, conventional radiofrequency catheters with a 4 mm tip were used. Over the decade during which RFA for AF evolved, there has been a transition to use an 8 mm tip catheter and then to an ablation catheter with a saline-irrigated tip.[1] The irrigated catheters have either an internal or external cooling system. Following a discussion with the TEP, the decision was made to exclude studies that exclusively used a conventional 4 mm tip ablation catheter since, at present, it is infrequently used in the United States.

Numerous observational studies have been published describing different techniques and their associated outcomes, and several RCTs have examined the clinical effect of this approach in maintaining sinus rhythm. Based on these trials and other lines of evidence, current guidelines for the management of AF consider RFA a reasonable alternative in patients with symptomatic AF who have failed AAD therapy.[3]

The present review examines the evidence for the short- and long-term clinical effect and safety of RFA for AF. After extensive discussion with AHRQ and the TEP, the key questions to be addressed in this report are:

Key Questions

1. What is the effect of RFA on short- (6 to 12 months) and long- (>12 months) term 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?

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

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

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

Methods

Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program drafted the initial key questions and, after approval from AHRQ, posted them to a public web site. The public was invited to comment on these questions. After reviewing the public commentary, the Scientific Resource Center drafted final key questions and submitted them to AHRQ for approval.

This comparative effectiveness review of radiofrequency ablation (RFA) for the treatment of AF is based on a systematic review of the literature. The Tufts Medical Center Evidence-based Practice Center held teleconferences with a technical expert panel (TEP) formed for this project. The TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence. The TEP included cardiologists who are familiar with RFA and methodologists who are familiar with the evidence review process.

The methods for this comparative effectiveness review follows the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by AHRQ (available at http://effectiveheealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf).

Please note that because of the large number of abbreviations for technical terms, their explanations have been repeated within each chapter. Also see the **Abbreviations** table listed after the references.

Search Strategy

Our search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. The searches were limited to the English language. The primary MEDLINE® and Cochrane Clinical Trials Registry search strategy is presented in **Appendix A**.

We searched the MEDLINE® and Cochrane Central Trials Registry databases from 2000 to December, 2008 for studies involving adults with atrial fibrillation (AF) who underwent RFA. We combined search terms or MeSH terms for atrial fibrillation, pulmonary vein, radiofrequency ablation, and catheter ablation, and we limited the search to English language articles of studies in adult humans. We included peer reviewed, primary studies of RFA treatment for AF. We excluded case reports and did not search systematically for unpublished data. We invited TEP members to provide additional citations.

Study Selection

Key questions concerning the comparative effectiveness of RFA with other available treatments (e.g., medical treatment, surgery) were proposed and refined with input from the TEP over a series of teleconferences. Specifically, the questions that should be addressed, the

populations of interest, the interventions and appropriate comparators, the outcomes, and the study designs were discussed and refined (see below).

The TEP advised us that the 8 mm and irrigated tip catheters are now the catheters of choice for RFA in the United States, and the conventional 4 mm tip catheter is no longer being used (or is rapidly being phased out). Thus, information on the conventional 4 mm tip catheter was thought to be no longer relevant to current practice. Because the 8 mm and the irrigated tip catheters were introduced in 2003, we decided to restrict our literature search from 2000 onward to ensure that preapproval studies were included.

We assessed titles and abstracts of citations identified from our literature search for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Results published only as abstracts were not included in our reviews because adequate information is not available to assess the validity of the data and these reports have generally not been peer-reviewed.

Population and Condition of Interest

We included studies of adults (≥18 years old) with paroxysmal, persistent, or permanent/chronic AF. We accepted the definitions of the various types of AF used by the study authors. For the purpose of this report, the terms "permanent" and "chronic" AF were used as reported in the individual studies, even though the definitions varied. It should be noted that the consensus statement on RFA for the treatment of AF published by the Heart Rhythm Society in 2007 no longer used the term chronic or permanent, the term adopted is longstanding persistent to define a continuous AF of greater than 1 year duration.[1] For a study to be included, at least 80 percent of the patients had to be treated with a first time RFA for AF. Study eligibility was not based on type or duration of AF or comorbid conditions. We excluded studies that were limited to patients with congenital heart disease, hypertrophic cardiomyopathy, or Wolff-Parkinson-White syndrome. We excluded studies that included only participants with successful ablations or other postprocedure eligibility criteria.

Interventions of Interest

The intervention of interest was catheter-directed RFA of the left atrium (LA) with the goal of preventing AF recurrence. The RFA could be used as first or second line treatment of AF, with or without concurrent antiarrhythmic drugs (AADs).

We included studies of RFA strategies in which the explicit or intended goal was targeting of the pulmonary veins (PVs) or PV antra, with or without additional ablation. Studies in which PV electrical isolation was not the goal of ablation were excluded (e.g., standalone RFA of complex fractionated atrial electrograms (CFAE) and linear ablations). We also excluded studies of RFA of the atrioventricular (AV) junction, supraventricular tachycardia, standalone atrial flutter and RFA in conjunction with cardiac surgery.

We did not evaluate cryoablation or microwave ablation. We excluded studies that examined only surgical or medical approaches (without comparing to RFA). Studies of only periprocedural variables such as electrical mapping, atrial imaging techniques, or complications due to RFA that did not report patients' outcomes were excluded. As stated above and per recommendations from the TEP, we included only studies that used 8 mm tip or irrigated tip catheters. We excluded studies that included only 4 mm tip catheters. However, if the

comparative arm in the 8 mm or irrigated tip catheter study were a 4 mm tip catheter, that study was included.

Comparators of Interest

Given the known paucity of comparative studies, we included both uncontrolled and controlled studies, with any medical or surgical comparator.

Outcomes of Interest

After discussion with the TEP, it was agreed that only relatively long-term clinical outcomes and serious adverse events were of interest, given the chronic nature of AF. For clinical outcomes, we required studies to have a minimum of 6 month followup and where possible, we excluded arrhythmia outcomes that occurred during the blanking period (a period postprocedure during which an episode of AF was not considered a recurrence; this typically ranged from 1 to 3 months after the procedure, as defined by the studies). For safety outcomes, we included all studies regardless of the length of followup.

Outcomes of interest included:

- Rhythm control
    - Rhythm control is defined as the absence of atrial fibrillation or atrial arrhythmia during followup. Surveillance for this outcome varied among studies and included reliance on symptomatic recurrence of the arrhythmia, documentation of the arrhythmia via periodic 12-lead electrocardiograms, continuous cardiac monitoring, or a combination of these approaches.
    - Rhythm control after RFA can be achieved with or without the use of AADs, and if separately reported, both outcomes (with and without AADs) were extracted for this review.
    - We did not exclude studies or findings based on whether a “blanking” period was defined.
- Congestive heart failure
- Left atrial and ventricular size changes
- Stroke
- Quality of life measures
- Avoiding anticoagulation
- Readmissions for AF
- Adverse events due to RFA
    - Symptomatic or severe pulmonary vein stenosis
    - Cardiac tamponade or pericardial effusion requiring intervention
    - Peri-procedural stroke or transient ischemic attack
    - Atrioesophageal fistula
    - Peripheral vascular complication, including deep vein thrombosis, pseudoaneurysm, catheter insertion site hematoma requiring transfusion or invasive intervention, or other vascular injury requiring transfusion or invasive intervention
    - 30-day mortality
    - Other major adverse events reported by the investigators and thought to be related to RFA (e.g. , phrenic nerve paralysis)

Study Designs of Interest

We included studies of any design: randomized controlled trials and nonrandomized trials; prospective and retrospective cohorts. Where the study design of an observational study was unclear (prospective versus retrospective), we assumed it was retrospective.

We also made the following *a priori* decisions. We included randomized controlled trials (RCTs) of any sample size. For non-randomized comparative studies (RFA versus other intervention or RFA versus RFA), we included only studies with at least 10 subjects per intervention arm, whether prospective or retrospective. For prospective cohort studies (no comparison), we included only those with at least 50 subjects receiving RFA. For retrospective cohort studies reviewed for adverse events, we included only those with at least 100 patients.

Data Extraction

Data from each study were extracted by one of the reviewers and confirmed by another. The data on RFA techniques in all studies were also confirmed by a clinical cardiac electrophysiologist in the Tufts Medical Center evidence review team. The extracted data included information on patient samples, RFA characteristics (e.g., type of catheter tip, verification of electrical isolation), outcomes, adverse events, study design, and quality. For most outcomes, 6 months, 12 months, and/or only data from the last reported time point were included. Mortality data regardless of postprocedure duration were extracted.

Quality Assessment

We used predefined criteria to grade study quality as good, fair, or poor. This system defines a generic grading system that is applicable to varying study designs including RCTs, nonrandomized comparative trials, and observational studies. For RCTs, we mainly considered the methods used for randomization, blinding, as well as the use of intention-to-treat analysis, the report of dropout rate and the extent to which valid primary outcomes were described and how well they were reported. Only RCTs could receive a "good" grade. For nonrandomized comparative studies and observational studies, the following elements were considered in assessing quality: clear reporting of eligibility criteria, similarity of comparative groups in terms of baseline characteristics and prognostic factors, use of intention-to-treat analysis, reporting on crossovers, differential loss to followup between the comparative groups or overall high loss to followup, and validity and adequacy of the description of outcomes and results. All retrospective studies were graded poor.

Good (low risk of bias)

Studies rated "good" have the least bias and results are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias. Studies rated "good" must have reported the

AF recurrence rate off AADs after the initial RFA procedure. Only RCTs could receive a "good" grade.

Fair

Studies rated "fair" are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "good", they have some deficiencies but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

Poor (high risk of bias)

Studies rated "poor" have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information, or discrepancies in reporting. All retrospective studies received a "poor" grade.

Rating the Body of Evidence

We assigned an overall grade describing the strength of evidence for each key question that was based on the number and quality of individual studies, duration of followup and the consistency across studies. The overall grade for each key question was rated by the authors who are responsible for the respective question. Differences were resolved by consensus. The grades corresponded to the following definitions:

High – High confidence that the evidence reflects the true effect.

Further research is very unlikely to change our confidence in the estimate of effect. There is a high level of assurance with validity of the results for the key question based on at least two high quality studies with long-term followup of a relevant population. There is no important scientific disagreement across studies in the results for the key question.

Moderate – Moderate confidence that the evidence reflects the true effect.

Further research may change our confidence in the estimates of effect and may change the estimate. There is a moderate level of assurance with validity of the results for the key question based on fewer than two high quality studies or in high quality studies that lack long-term outcomes of relevant populations. There is little disagreement across studies in the results for the key question.

Low – 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. There is a low level of assurance with validity of results for the key question based on poor quality studies. There could be disagreement across studies in the results for the key question.

Insufficient – Evidence either is unavailable or does not permit estimation of an effect.

The grades provide a shorthand notation of the strength of evidence supporting the answers to the key questions. However, they may oversimplify the many complex issues involved in appraising a body of evidence. The individual studies involved in formulating the composite grade differed in their design, reporting, and quality. As a result, the strengths and weaknesses of the individual reports addressing each key question should also be considered, as described in detail in the text and tables.

Data Synthesis

For key question 1 (RFA versus other interventions and RFA with versus without AAD) and key question 3 (ostial PVI versus other RFA techniques), relevant eligible studies were compiled into sets of summary tables that succinctly present the study features including design, patient-level and intervention-level characteristics, results, and study quality. For key question 2 (predictors of outcomes), the summary tables included only basic information about the type of RFA, the timing of the outcome measurement, the sample size, and the results. All studies included in these summary tables are also included in the summary tables for key questions 1 and 3, and study details can be found there. For key question 4 (adverse events), summary tables included the followup time and the event rates for the specific adverse events of interest.

We found that a large number of studies performed multivariable analyses of the association between preprocedure variables and AF recurrence (key question 2). Given the heterogeneous nature of patients analyzed within individual studies and the clinical heterogeneity across studies, multivariable analyses are best suited to address the association between predictor variables and outcomes. This is particularly the case in analyses of RFA for AF since many of the predictors of interest are correlated or confounded with each other. Thus, for most predictors, we evaluated only studies that reported multivariable analyses. We focused on the following predictors: type of AF, duration of AF, left ventricular ejection fraction, left atrial diameter, sex, age, structural heart disease, and hypertension. We also included other predictors that could be assessed prior to RFA. In this section, we did not analyze whether specific RFA techniques or procedures were associated with outcomes, as this was covered under key questions 1 and 3.

Because of particular interest by the TEP and study researchers in the question of whether AF type is associated with rate of AF recurrence, we also evaluated univariable (uncontrolled) analyses of AF type. Based on the studies that were performed we included the following comparisons: paroxysmal versus persistent AF, paroxysmal versus long-standing persistent (permanent/chronic) AF, and paroxysmal versus nonparoxysmal AF (combined persistent and long-standing persistent (permanent/chronic)). In studies in which detailed data for AF recurrences by each AF type were available, the corresponding relative risk (RR) was calculated. For these comparisons, we performed metaanalysis, as described below.

For adverse event data collection (KQ4), we consulted the TEP concerning the major adverse events that would be of relevance to RFA. We collected the rates reported for the following major adverse events: PV stenosis, cardiac tamponade or pericardial effusion requiring intervention, stroke and/or transient ischemic attack, bleeding requiring transfusion, atrioesophageal fistula, 30-day mortality, any deaths, and other major adverse events as reported in the studies. We organized the section according to whether the RFA was ostial or extra-ostial PVI and further subcategorize them by the types of catheter tips used in the RFA. We did not assess the quality of the study with respect to the adverse event reporting.

Metaanalysis

Where the data were amenable to metaanalysis – based on the degree of clinical heterogeneity of studies, patients, and outcomes and the statistical heterogeneity of results – we performed meta-analyses using the random effects model.[20] For clinical outcomes (except for stroke), we employed the RR as the metric of choice to quantify relative benefit comparing RFA

to medical treatment. For stroke, our primary analysis was a summary of the risk difference (RD) by the Mantel-Haenszel fixed-effects model because events (strokes) were rare and some studies reported no strokes.[21] For sensitivity analysis, we used the Peto method to combine odds ratios (ORs), which effectively excludes studies with zero events in both arms from the analysis.[22] We also performed random effects model meta-analyses of RR for AF type as a predictor of AF recurrence in univariable analyses.

Peer Review and Public Commentary

A draft version of this report was reviewed by a panel of expert reviewers **(see Appendix D)**, including representatives from professional society and industry. These experts were either directly invited by the Tufts Medical Center Evidence-based Practice Center or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by staff from the Scientific Resource Center at Oregon Health and Science University. However, the findings and conclusions are those of the authors, who are responsible for the content of the report.

Results

The MEDLINE® and Cochrane Central database search yielded 2,169 citations. We identified 390 of these as potentially relevant and retrieved the full-text articles for further evaluation. Of these, 270 did not meet eligibility criteria. A total of 120 studies were included in our analyses. **(Figure 2)**

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 longstanding persistent (chronic) atrial fibrillation?

RFA Versus Open Surgical Procedures

No study compared RFA with an open surgical procedure.

RFA Versus Medical Therapy (Table 1)

Randomized controlled trials (RCTs). Six RCTs enrolling a total of 693 patients with atrial fibrillation (AF) compared radiofrequency ablation (RFA) with medical therapy.[23-28] Sample sizes ranged from 30 to 198. One trial compared RFA as first line therapy to antiarrhythmic drugs (AADs),[24] while the other four trials included patients who had failed at least one AAD. One study[27] included only patients with symptomatic paroxysmal AF (PAF) and one study[26] focused only on patients with chronic AF.[b] The other three RCTs included patients with PAF and those with persistent AF (patients with PAF ranged from 67% to 96%).

Although techniques employed for RFA varied across studies, all studies targeted the pulmonary veins (PVs). Post-RFA AAD use varied both within and between studies. One RCT[24] compared patients who had RFA with patients who had taken AADs continuously as a first-line therapy. Three second-line therapy trials[23,27,28] compared patients treated with RFA followed by up to 3 months postprocedure AADs to patients who had taken AADs continuously. In another second-line therapy RCT,[25] comparison was made between patients who underwent RFA and then received AADs continuously throughout the study period with patients who had taken AADs continuously. One study permitted reablations within 3 months postprocedure in the RFA arm and modifications of AADs in the medical therapy arm.[28] One second-line trial[26] compared patients treated with amiodarone for 3 months after RFA to those treated with 3 months of amiodarone alone. This study also permitted reablation beyond the 3-month period in the RFA arm and crossover salvage ablation in the medical therapy arm.

The methodological quality of five studies was rated fair and one study was rated poor. Common reasons for downgrading the quality ratings in these studies were suboptimal reporting (e.g., unclear descriptions on the conduct of a trial or discrepancies in reporting of results) or

[b] Chronic AF was defined as AF that had been present for more than six months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion.

failure to report the rates of AF recurrence after a single ablation while off AADs (i.e., only rates of AF recurrence after multiple ablations and/or remaining on AADs were reported).

Retrospective studies. Two retrospective cohorts[29,30] reported comparisons between RFA and medical treatments in a total of 1,341 patients with AF refractory to at least one AAD. Patients who underwent RFA also received AAD for the first 3 months after the procedure. Methodological quality of these two studies were rated poor.[29,30]

Rhythm Control (Study Duration 6 Months or Greater) (Table 2)

Rhythm control, typically reported as freedom from recurrence of AF or atrial arrhythmias, was described as a primary outcome in all the RCTs and observational studies.

Six RCTs consistently reported statistically significant improved rhythm control at 12 months post-RFA compared to medical therapy. We performed metaanalysis on four RCTs (one first-line and three second-line therapy) involving a total of 431 patients (**Figure 3**).[23-25,27] One RCT[26] was excluded because it reported the participants' rhythm status only at 12 months postprocedure irrespective of recurrence during the entire followup period. Another RCT[28] was also excluded because up to two additional ablations were allowed if patients had AF recurrence during the 3 months postprocedure blanking period. Overall, patients who underwent RFA (either as a first- or second-line therapy) had about a 3-fold higher chance of maintaining sinus rhythm at 12 months compared to those treated with medical therapy (relative risk (RR) 3.09, 95% confidence interval (CI) 2.02-4.73). In a subgroup analysis including three studies that used RFA as a second-line therapy, it was similarly superior to medical treatment (RR 3.46, 95% CI 1.97-6.09). There was no evidence of statistical heterogeneity in treatment effect between first-line and second-line therapy.

Rhythm control was also reported in two retrospective studies.[29,30] One found a statistically significant improved AF-free survival for RFA (n=589) compared to medical treatment (n=582) with a mean followup of 30 months (hazard ratio (HR) 0.30, 95% CI 0.24-0.37, P<0.001).[29] The other study also found that patients who underwent RFA had improved rhythm control (82%) compared to patients who were on medical treatment (40%) (P value not reported).[30]

Rates of Congestive Heart Failure (Table 3)

No RCT examined the incidence of congestive heart failure in RFA versus medical treatment of AF.

One retrospective study evaluated congestive heart failure as part of adverse events during followup (mean, 30 months) in patients who had RFA compared to patients who had medical treatment. This study found that congestive heart failure developed in 5% of patients who had RFA compared to 10% of patients who had medical treatment although no formal statistical test was performed.[29]

Left Atrial and Ventricular Size Changes (Table 4)

One RCT[28] evaluated changes in left atrial diameter (LAD), left ventricular end-diastolic diameter (LVED), and left ventricular ejection fraction (EF) in patients with AF treated with RFA versus medical therapy. No statistically significant differences in changes in LAD, LVED, or EF were observed at 1 year followup between RFA and medical treatment.

A retrospective study reported improvement in LAD in patients who had undergone RFA according to subsequent recurrence following the procedure (no recurrence: -1.1 cm (P<0.01); recurrence: -0.5 cm (P value not reported)) and in patients who had received medical treatment (no recurrence: -0.3 cm (P<0.01); recurrence: -0.2 cm (P value not reported)).[29] However, direct statistical comparison between RFA and medical treatment was not performed.

Rates of Stroke (Table 5)

All six RCTs evaluated stroke as an adverse event. We performed a metaanalysis on the six RCTs (Figure 4).[23-27] Two RCTs[26,28] allowed multiple ablations for patients who relapsed after the first procedure. In our metaanalysis, we considered each patient who underwent at least one RFA (regardless of multiple procedures) to be the unit of analysis. There were no statistically significant differences in stroke rates at 12 months between RFA and medical treatment (range: 0 to +7.1%). All three stroke events in the RFA arm occurred during or just after the procedure. Three studies observed no strokes in both arms.[24,26,28] The summary risk difference of stroke was 0.6% (95% CI –1.2 to 2.3%; favoring AAD); the RCTs had statistically homogeneous results. The summary risk difference was similar in subgroup analyses of four studies that used RFA as a second-line therapy: 0.7% (95% CI –1.1 to 2.4%; favoring AAD). There was no statistical heterogeneity in risk difference of stroke between first- and second-line therapy. The results were similar when three RCTs with no events in both arms were excluded in sensitivity analysis (Peto odds ratio (OR) 2.80, 95% CI 0.39-19.9; favoring AAD).

Two observational studies reported higher stroke rates in medical treatment than RFA. During the 30 month followup in one study, 14 patients (2%) in the RFA arm versus 49 patients (8%) in the AAD arm developed stroke (statistical test not performed).[29] Similarly, Rossillo et al. found a lower stroke rate in patients who underwent RFA than in patients who had medical treatment (1% vs. 6%, P=0.09) at 16 months.[30] Neither study explored the impact of anticoagulation therapy on stroke events.

Quality of Life (Table 6)

Three RCTs measured quality of life (QoL) using the 36-Item Short-Form General Health Survey (SF-36), which has a range of scores from 0 (worst) to 100 (best). One study found that patients treated with RFA as a second-line therapy had a statistically significant improvement in general health score at 6 and 12 months (+15 and +20, respectively) compared to medical treatment (+6 and +3 respectively, P=0.048).[23] It also found a statistically nonsignificant improvement in physical fitness score at 6 and 12 months (+11 and +23, respectively) in the RFA arm compared to the medical treatment arm (+2 and -2 respectively). The RCT that used RFA as a first-line treatment also found that patients in the RFA arm had a statistically significant improvement in general health functioning score and physical functioning score at 6 months (+22 and +26, respectively) compared to patients in the medical treatment arm (+11 and +6, P<0.001 and P=0.001, respectively) while no statistically significant improvement was reported in mental health score.[24] Another RCT that used RFA as a second-line therapy also reported patients treated with RFA had better physical component score at 12 months than patients who had medical treatment (within-subject improvement from baseline, +7.2 vs. +6.0, P=0.015), whereas improvement was not significantly different in mental component score between RFA and medical treatment (within-subject improvement from baseline, +9.7 and +9.1, respectively, P=0.09).[28]

Improvement in both physical and mental component summary score at 12 months was larger in patients who had RFA (+10 and +8) compared to patients who had medical treatment (+1 and +1) in one retrospective study, but no statistical comparisons were provided.[29]

Avoiding anticoagulation. One study evaluated the rates of avoiding anticoagulation between RFA and medical treatment. Jais et al.[28] found a higher proportion of patients reported freedom from anticoagulation at 12 months, comparing RFA with medical therapy (60% vs. 34%, P=0.02).

Readmissions (Table 7)

Two RCTs evaluated readmission. One found that patients treated with RFA as a first-line treatment had a statistically significant lower readmission rate during the 12 months of followup (9%) compared to medical treatment (54%, P<0.001).[24] The other reported a statistically nonsignificant lower median number of readmissions in the RFA arm compared to the medical treatment arm (1 vs. 2 readmissions, respectively).[25] None of the studies provided the specific reasons for readmissions.

A retrospective study reported mean change in readmission rates in patients treated by RFA according to subsequent recurrence following the procedure (no recurrence: -1.8 times/year (P<0.001), recurrence: -0.7 times/year (P=0.04)) and in those patients who had received medical treatment (no recurrence: -1.2 times/year (P=0.01), recurrence: +0.5 times/year (P=0.43)).[29] However, comparison between RFA and medical treatment was not performed. The patients were readmitted mostly due to drug-related side effects.

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

For this question, we evaluated only direct comparisons within studies. We did not attempt to make indirect, cross-study comparisons (such as comparing a study of patients with PAF only to a study of patients with persistent AF only). Patient-level characteristics are those that describe a patient's pre-procedure physical characteristics, AF characteristics, cardiac status, and other comorbid conditions. Intervention-level characteristics are those that describe the setting and the features of the team performing the RFA. Differences specific to the intervention (e.g., catheter tip, ablation technique) are evaluated in Key Question 3.

As described in the Methods chapter, for most patient-level characteristics, we included only studies that reported multivariable analyses. These studies are presented first. For the association between pre-procedure AF type and rhythm control during followup, AF recurrence, we also included studies that reported AF recurrence rates for subgroups of patients with different types of AF (paroxysmal, persistent, chronic/permanent, or nonparoxysmal). We also included any information we found regarding intervention-level characteristics.

Patient-Level Characteristics: Multivariable Analyses

Twenty-five studies reported multivariable analyses of the association between patient-level characteristics and AF recurrence.[25,27-29,31-51] The studies were highly heterogeneous in terms of study design, patient population, RFA technique used, and definition of AF recurrence. **Table 8 (parts A and B)** presents a summary of the findings for each of the studies, with the

summarized associations between predictors and AF recurrence in part A and the reported details in part B. The studies are ordered by sample size.

Atrial fibrillation type. Seventeen studies tested AF type (paroxysmal versus nonparoxysmal, persistent, or chronic).[25,29,31-34,37,38,40,42-46,48,49,51] Eleven of these reported (or implied) no statistically significant association between AF type and AF recurrence. Only three of the nonsignificant studies reported HRs for AF type, with HRs for persistent, chronic, or nonparoxysmal AF that ranged from 1.1 to 1.6 for AF recurrence, suggesting higher recurrence rates with nonparoxysmal AF.[29,32,42] Six studies found that nonparoxysmal (i.e., chronic or persistent) AF statistically significantly independently predicted higher rates of recurrent AF,[31,33,38,40,45,49] with HR ranging from 1.8 to 22 (among the five studies that reported data), favoring PAF. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Ejection fraction (EF). Among the studies, 17 evaluated EF in multivariable analysis for AF recurrence.[25,27-29,32,34-36,38,40-43,47,48,50,51] Across these studies there was a variable range of EFs among patients receiving RFA. The mean EFs ranged from 50% to 70% with standard deviations (approximately one-quarter of the size of the distribution) ranging from 4% to 13%. Most studies did not report excluding potential participants due to low EF, though four studies excluded patients with EFs less than 35%[25,27,48] or 45%.[36] Thus, overall, the majority (and often the large majority) of included patients had normal EFs. The reported data suggest that very few patients in any study had EFs below about 40%. Furthermore, the majority of studies failed to define how the EF variable was parameterized (as a continuous variable or dichotomized at a particular threshold); this was particularly true for studies that found no significant association. Among the 17 studies, only five[28,34,35,42,51] reported statistically significant independent associations between lower EF and AF recurrence. Only eight of the studies reported estimates of the association between EF and recurrence; these ranged from 0.90 to 5.2 (with a median value of 1.07), favoring an association between lower EF and more frequent AF recurrence. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Left atrial diameter (LAD). Twenty studies analyzed LAD as a predictor of AF recurrence in multivariable models.[25,27-29,31,32,34-38,40-43,46-48,50,51] Across studies (that reported data) the mean LAD ranged from 39 to 51 mm with standard deviations ranging from 4 to 9 mm. Most studies did not report excluding potential participants due to large LADs, though five studies excluded patients with LADs greater than 55 mm,[43,46,48] 60 mm,[25] or 65 mm.[27] Thus, overall, the majority (and often the large majority) of included patients had LADs less than 55 mm. The reported data suggest that very few patients in any study had LADs above about 60 mm. Furthermore, the majority of studies failed to define how the LAD variable was parameterized (as a continuous variable or dichotomized at a particular threshold). Among the 20 studies, only four found statistically significant independent associations between larger LAD and AF recurrence.[29,37,43,50] Only nine of the studies reported estimates of the association between larger LAD and more frequent recurrence; these ranged from 0.87 to 2.1 (with a median value of 1.11) There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Structural heart disease. Among 21 studies that evaluated the presence of structural (or valvular) heart disease as a predictor of AF recurrence in multivariable models,[25,27,28,31-34,36-43,45-48,50,51] one reported a statistically significant association at 12 months (HR 2.05, 95% CI 1.18-3.6),[46] one reported a statistically significant association at 6 months (HR 4.0, 95% CI 1.0-16) but no association at 12 months (no data),[45] and one reported a trend (HR 2.4, 95% CI 0.9-6.3, P=.08).[48] Among the remaining studies that found no association, six reported HRs ranging from 0.6 to 2.4. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

AF duration. Sixteen studies evaluated AF duration as a predictor of AF recurrence.[25,27,29,31,32,34-36,40-43,46-48,50] Only three studies found a statistically significant independent association between AF duration and recurrence. Themistoclakis et al. and Cha et al. reported similar associations between longer duration and recurrence (HR 1.03, 95% CI 1.00-1.06, per additional year; and 1.04, 95% CI 1.01-1.08, per additional year; respectively); Oral et al (2004) reported only that AF duration was significantly associated with recurrence.[31,34,41] There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Hypertension. Eleven studies evaluated hypertension as a predictor,[25,27-29,31,34,37,39,42,43,45] two of which found independent associations with AF recurrence. Themistoclakis et al. reported a HR of 1.65 (95% CI 1.14-2.39)[31] and Berruezo et al. reported a HR of 2.8 (95% CI 1.5-5.4).[43] Two studies reported nonsignificant HRs of 1.2 and 1.8 for recurrence, favoring more frequent recurrence in patients with hypertension. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Age and sex. Almost all the studies evaluated age and sex. Three studies did not evaluate age, two studies did not evaluate sex. Mean ages ranged from 49 to 65 years with standard deviations ranging from 7 to 13 years. Six studies excluded older patients (over 70 years,[27,33] 75 years,[37,43] or 80 years[25,48]). It is likely that there were relatively few patients under age 40 or over age 70. Furthermore, the majority of studies failed to define how the age variable was parameterized (as a continuous variable or dichotomized at a particular threshold). Only one of 22 studies found a statistically significant independent association between age and recurrence; older age was associated with *lower* rates of AF recurrence (HR 0.97, 95% CI 0.95-0.99).[34] All of 23 studies found no independent association between sex and recurrence rate.

Other potential predictors. In two studies, frequency of AF episodes pre-procedure was not associated with rate of recurrence.[41,50] Duration of AF episodes was also no associated with recurrence in one study.[28] Other echocardiographic parameters (left ventricular end diastolic and end systolic diameters, interventricular septal thickness, and left ventricular posterior wall thickness) were not associated with recurrence in three studies.[28,43,48] History of coronary artery or cardiac disease were not associated with recurrence in two studies.[25,29] Use of a variety of pre-procedure medications, including AAD did not predict recurrence in three studies.[25,35,42] Two studies reported no association with body mass index.[34,38] Two other studies found no association with diabetes history[28,34] One study each reported no association between AF recurrence and left ventricular mass, stroke or TIA history, typical atrial flutter, AAD treatment failure, number of cardioversions, sleep apnea, or other comorbidities. One study reported a statistically significant association between AF recurrence and pre-procedure vagal-mediated AF.[41]

Atrial Fibrillation Type: Unadjusted, Univariable Analyses

Thirty-one studies **(Table 9, Figures 5-7)** reported rates of AF recurrence for different subgroups of patients based on their type of AF (paroxysmal, persistent, chronic, or nonparoxysmal). [31,32,34,38-40,44-46,48,49,52-71] The studies were highly heterogeneous in terms of study design, patient population, RFA technique used, and definition of AF recurrence. While acknowledging the clinical heterogeneity, we performed meta-analyses (using random effects model of RR) to explore the associations between AF types and AF recurrence. Separate meta-analyses were performed for the three comparisons reported in the studies: persistent versus paroxysmal AF; chronic versus paroxysmal AF; and nonparoxysmal versus paroxysmal (combined persistent and chronic). We calculated RRs for all studies based on the data provided and estimated P values of these RRs, regardless of how the data were analyzed in the original studies.

Paroxysmal versus persistent atrial fibrillation. Sixteen studies with 3,545 patients reported AF recurrence rates for both patients with paroxysmal and persistent AF. [31,38,39,46,52-54,56-60,66,67,69,71] The 16 studies included 21 cohorts of patients (based on specific RFA intervention), as shown in **Figure 5**. Among patients with PAF, most studies reported PAF recurrence rates between 13% and 39%. Compared to other eligible studies, Zhou et al. reported an atypically low recurrence rate of 5%[71] and Nilsson et al. reported a particularly high recurrence rate of about 73%.[46] The range of RRs for AF recurrence (paroxysmal versus persistent AF) was 0.90 to 3.05, with a median value of 1.50. Eight of the associations were statistically significant. Only three of the studies also included AF type in a multivariable analysis. Themistoclakis et al. and Richter et al. found that PAF was associated with a lower risk of recurrence in both univariable and multivariable analyses.[31,38] In contrast, Nilsson et al. found that AF type was associated with recurrence in a univariable analysis, but not in a multivariable analysis.[46] In addition to the clinical heterogeneity across the studies, including a variety of RFA techniques used and a wide range of rates of AF recurrence, the studies were statistically heterogeneous. The summary RR was 1.55 (95% CI 1.35-2.79, P<.001), suggesting that patients with persistent AF were about twice as likely to have recurrence as patients with PAF.

Chronic versus paroxysmal atrial fibrillation. Five studies with 2,448 patients reported AF recurrence rates for both patients with paroxysmal and chronic AF **(Figure 6)**.[31,54,62-64] PAF recurrence rates ranged from 13% to 37%. The RRs for AF recurrence (chronic versus paroxysmal AF) varied from 1.04 to 2.19, with a median value of 1.88; three of the studies found a statistically significant difference. The one study that also performed multivariable analysis found statistical significance in both analyses.[31] By metaanalysis, the five studies had statistically heterogeneous results. The summary RR was 1.69 (95% CI 1.29-2.21, P<.001), suggesting that patients with chronic AF had a 69% increased risk of recurrent AF as patients with PAF.

Nonparoxysmal versus paroxysmal atrial fibrillation. Fourteen studies with 4,394 patients reported AF recurrence rates for both patients with paroxysmal and nonparoxysmal (both persistent and chronic) AF. [31,32,34,40,44,45,48,49,54,55,61,65,68,70] The 14 studies included 17 cohorts of patients (based on specific RFA intervention), as shown in **Figure 7**. Most studies reported PAF recurrence rates between 13% and 37%. Compared to the other eligible studies, Cheema et al. reported an atypically high recurrence rate of 63%.[40] The range of RRs for AF recurrence (paroxysmal versus nonparoxysmal AF) varied from 0.91 to 2.9, with a median value of 1.76.

Nine of the 17 associations were statistically significant. Three studies found that recurrence was significantly less common in patients with PAF than nonparoxysmal AF in both unadjusted and multivariable analyses;[40,45,49] two found that the association was statistically significant by univariable analysis, but not in a multivariable model;[32,44] and two studies found that there was no significant association between AF type and recurrence in both univariable and multivariable models.[34,48] By metaanalysis, the studies had statistically heterogeneous results. The summary RR was 1.59 (95% CI 1.38-1.82, P<.001), suggesting that patients with nonparoxysmal AF were 59% more likely to have AF recurrence than patients with PAF.

Heterogeneity. Across the studies that analyzed AF type as a predictor of AF recurrence by either univariable or multivariable analysis, there was no clear factor that explained any heterogeneity in results.

Intervention-Level Characteristics

We found no studies that reported analyses of operator or center ("intervention-level") characteristics as predictors of AF recurrence.

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

Approaches to RFA (Tables 10 and 11)

There are a number of different approaches to catheter-based RFA for AF. One major approach is based on the technique developed by Haissaguerre et al. to electrically isolate the PVs.[12] This involved the identification and ablation of triggering potentials in the PV myocardial sleeves. Studies that employed this technique have used the term segmental, focal, or ostial pulmonary vein isolation (PVI). For simplicity, all such studies were classified as ostial PVI in this review. After recognizing PV stenosis as a complication from this technique, other ablation approaches were developed to deliver lesions outside the PV itself. These include antral PVI (ablation within the PV antrum, not the ostium) and continuous circumferential ablation encircling the right and left PVs (wide-area circumferential ablation (WACA)). Additional techniques have also been employed to target the substrate thought responsible for the propagation of AF (substrate modification) by creating linear ablation lines in the left atrium (LA) (e.g., a roof line connecting the superior aspect of the PV encircling lesions, a posterior line connecting the posterior aspect of the encircling lesions (posterior LA line), a mitral line from the left inferior pulmonary vein or a septal line from the right inferior pulmonary vein to the mitral isthmus line (MIL), or a linear lesion at the inferior aspect of the left atrium which runs parallel to the coronary sinus). In patients with a history of atrial flutter, a cavotricuspid isthmus ablation line (CTI) is also recommended.[1]

Sixteen RCTs,[33,46,48,50,52,56,72-81] two nonrandomized comparative trials,[82,83] two prospective cohort,[84,85] and seventeen retrospective cohort studies[36,38,40,47,70,86-98] reported outcomes of RFA for AF using different techniques. Sample size in these studies ranged from 43 to 560. Eleven RCTs compared PVI within and around the PV ostia with either WACA or additional ablation lines (CTI, MIL, roof line, posterior LA line or WACA) with respect to AF recurrence. One nonrandomized comparative trial compared PVI using antral ablation with

versus without additional ablation dependent on residual potentials. Two RCTs excluded patients with PAF.[77,80] Six RCTs included only patients with PAF.[48,50,73,76,78,81] The rest of the RCTs included a mixture of patients with either paroxysmal or persistent/permanent AF. The comparisons in retrospective studies were similarly diverse. Methodological quality of eleven RCTs was rated fair. The rest of the studies were rated poor.

Randomized Controlled Trials

PVI versus WACA. Five RCTs compared the efficacy of ostial PVI to WACA with or without additional ablation lines in maintaining sinus rhythm, randomizing a total of 500 patients with followup ranging from 6 to 15 months.[46,50,52,74,75] The proportion of patients with PAF in the studies ranged from 51% to 100%. Only two studies reported results after one procedure and off AADs. Both found that patients who had WACA had a higher rate of success (freedom from AF recurrence) than patients who had ostial PVI (67% vs. 49%, P≤0.05;[52] 88% vs. 67%, P=0.02;[50]). Two[46,75] of three studies[46,74,75] that included patients who had reablation during followup also reported similar findings.

RFA with or without additional left sided ablation lines. Six RCTs (total enrolled 1,069, followup ranging from 7 to 17 months) directly compared the efficacy of one RFA technique with versus without the addition of left-sided ablation lines (e.g., mitral-isthmus, roof or posterior LA lines).[33,56,72,73,78,80] One study included only patients with persistent AF.[80] The proportion of patients with PAF in the rest of the studies ranged from 63% to 100%. The majority of the studies reported AF recurrence rates including patients who had reablation or were continued on AADs. The one study that included only patients with persistent AF found that the addition of LA linear lines to PVI and CTI improved the rate of freedom from AF (69% vs. 20%, P=0.0001). Three of five studies of 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% vs. 53%, P=0.01;[56] roof line: 87% vs. 69%, P=0.04;[73] MIL: 74% vs. 83%, no P value;[72] Two studies did not find a significant difference in AF recurrence with the addition of left-sided ablation lines.[33,78]

PVI versus PVI with right sided lines. While several RCTs (as described above) included CTI in all randomized patients, only one directly examined the incremental benefit of adding CTI in patients undergoing RFA for AF.[79] This study of 108 patients with AF (59% PAF) and at least one episode of atrial flutter found no significant difference in AF recurrence between the group that had ostial-antral PVI and the group that had ostial-antral PVI with CTI ablation at 12 months followup. This finding included some patients who had repeat procedure and some who were on AADs. It should be noted that at 2 months postprocedure, no patients in the CTI group had atrial flutter, while 5% of the patients in the group without CTI had recurrent sustained atrial flutter.

Another RCT compared WACA with versus without superior vena cava ablation.[81] This study of 106 patients with PAF found no significant difference in recurrence of atrial tachyarrhythmia between the patients who had WACA with superior vena cava ablation and the patients who only had WACA at 12 months followup.

Miscellaneous comparisons. One study randomized 100 patients with AF (75% PAF) to either modified WACA (WACA, then PVI inside circular lines in patients with residual PV

conduction) or aggressive WACA (WACA, then closure of gaps in patients with residual intraoperative PV conduction).[48] At 13 months followup, 58% of patients in the former versus 82% in the latter had no atrial tachyarrhythmia after the initial procedure and did not need AADs (P=0.01).

One study randomized 60 patients whose AF were not terminated or inducible after WACA and MIL and posterior lines into either no further treatment or additional ablation on the LA septum and roof and posterior mitral annulus and/or anterior wall based on fractionated or rapid atrial activity.[76] At 6 months, 67% of patients in the former compared to 86% in the latter were free of AF without AADs (P=0.05). There were no additional reablations in these patients during followup.

One study randomized 80 patients with chronic AF (present for ≥6 months without SR and recurred within 1 month after cardioversion) to either WACA and posterior LA (or roof line) and MIL or nonencircling LA roof, septum, anterior wall, mitral isthmus and annulus lines.[77] At 10 months followup, 48% of patients in the former versus 33% in the latter had no AF or atrial flutter after the initial procedure and did not need AADs (P=0.20).

Nonrandomized Comparative Trial

PV ablation with or without assessment of electrical isolation. One study assigned 60 patients to either antral PV ablation without checking for electrical isolation or antral PV ablation with assessment of electrical isolation and additional ablation for residual potentials.[82] At 15 months followup, 13% of patients in the former versus 53% in the latter had stable sinus rhythm and did not need AADs (P=0.002). This analysis included patients who had repeat procedures (13%).

Selective PVI versus PVI in all 4 PVs. One study on patients with PAF compared 42 subjects who had selective PVI (only in PVs with triggering AF) with 35 subjects who had PVI in all 4 PVs.[83] Followup duration was 39 months; there was no significant difference in AF recurrence between the two groups (62% vs. 74%). It was unclear how the patients were assigned to the respective study group.

Prospective Cohort

PVI with or without superior vena cava isolation. One study followed 407 patients who had either antral PVI or antral PVI with superior vena cava isolation.[84] No overall comparative data between the two groups were provided. Sixty-six patients had recurrence of AF at a mean followup of 15 months. A repeat ablation procedure was performed in 25 of the 66 patients who had recurrent AF. Five of these 25 patients (20%) were found to have AF initiated by superior vena cava triggers, of whom four were in the group that had only antral PVI (4/190, 2%) and one was from the group that had antral PVI with superior vena cava isolation (1/217; 0.4%), P<0.05.

PVI with or without additional right sided ablation lines. One study compared 113 patients who had ostial PVI and additional posterior LA line and/or MIL when required (in patients who failed PVI or had persistent or permanent AF) to 75 patients who also had additional CTI (these patients had either a history of atrial flutter or atrial flutter during ablation).

There was no significant difference in the rate of stable sinus rhythm at 30 months followup (79% vs. 82%, respectively).[85]

Retrospective Cohort

Retrospective studies compared many different approaches to RFA. These observational studies have limitations in the comparability between groups. Historical controls were used in half of the studies. In some of the studies, proportions of patients with different types of AF were different between groups, and followup results from different time points were compared between groups. None of the studies adjusted for potential confounders. It is difficult to draw conclusions from this group of studies.

Ostial versus antral PVI. Three studies compared ostial versus antral PVI.[91,92,95] Sample size ranged from 77 to 187. Followup ranged from 6 months to 2.8 years. Two of three studies found that patients who had antral PVI had less AF recurrence than patients who had ostial PVI (89% vs. 50%, P<0.001;[91] 69% vs. 47%, P<0.05[c];[92]). One study did not find a difference in AF recurrence rates between the two groups, although the recurrence rates were measured at different time intervals between the two groups.[95]

Ostial PVI versus WACA. Seven studies compared ostial PVI with WACA.[38,40,86,89,92,93,96,97] Sample sizes ranged from 73 to 234. Followup ranged from 6 to 26 months. While four[40,86,89,92] of six studies reported that patients who had WACA had less AF recurrence than patients who had ostial PVI, only one of them provided a statistical comparison (87% vs. 47%, P<0.05[d];[92]). Three studies did not report significant differences in AF recurrence rates between the two groups.[38,93,96,97]

PVI with or without additional left sided ablation lines. One study compared 100 patients who had ostial PVI, CTI, and MIL with a historical cohort of 100 patients who had PVI and CTI.[47] All patients had PAF. At 12 months followup, freedom from atrial arrhythmia without the use of AADs was 87% in the former versus 69% in the latter (P=0.002).

RFA with or without ablations of complex fractionated atrial electrograms (CFAE). Two studies compared RFA with or without CFAE ablations.[70,88] The sample size was 84[88] and 200,[70] respectively. Followup were at 9[88] and 12 months,[70] respectively. The studies did not find a significant difference in freedom from AF between those who did and those who did not have CFAE ablations (71% vs. 67%;[88] 85% vs. 80%;[70]). One study compared the subgroup of patients with persistent/permanent AF with additional CFAE ablations to the subgroup without additional CFAE ablations and found that the freedom from AF recurrence was 82% versus 72% (P=0.047), respectively.[70]

RFA with or without adenosine infusion. Two studies compared RFA with or without ablation of adenosine-induced potentials.[87,90] Both studies used historical cohorts for comparisons. Sample size was 202;[90] and 252;[87] respectively. Followup were at 20;[90] and 6

[c] P value from three way comparison of ostial vs. antral vs. WACA (Bonferroni)
[d] P value from three way comparison of ostial vs. antral vs. WACA (Bonferroni)

months;[87] respectively. Both studies found that patients who had additional ablation of adenosine-induced potentials had less AF recurrence than patients who did not (80% vs. 60%, P<0.05;[90] 73% vs. 60%, P=0.04;[87]).

Miscellaneous comparisons. One study compared 102 patients who had RFA with additional ablation at sites that induced vagal reflexes[e] to 195 patients who had RFA only.[36] At 12 months followup, freedom from AF was 99% in the former compared to 85% in the latter (P<0.001).

One study compared 60 patients who had ablations of 0 to 3 PVs (i.e., single focal isolations elsewhere besides the PV were counted as zero PV ablation) with 20 patients who had ablations of 4 to 5 PVs.[94] At 17 months followup, 90% of patients in the former versus 80% in the latter were free from atrial tachyarrhythmia (no P value reported).

One study compared 21 patients with segmental PVI with 22 patients who had segmental PVI with exclusion of sites adjacent to the esophagus if such sites were identified (16/22 patients had this modified procedure).[98] At 6 months followup, 81% of patients in the former versus 82% in the latter were free from recurrent AF (P=1.0).

Technical Issues Related to RFA (Tables 12 and 13)

In this section, we evaluated only findings from direct comparisons. We did not make indirect comparisons across studies (such as comparing a study of PVI via an 8 mm tip catheter with a different study of PVI via an irrigated-tip catheter).

Ten RCTs,[44,49,67,68,99-104] five nonrandomized comparative trials,[37,61,105-107] and five retrospective cohort studies[97,108-111] reported outcomes of PVI for AF comparing catheter tips, energy outputs, imaging guidance, or postprocedure duration of observation in the electrophysiology (EP) laboratory. Sample sizes in these studies ranged from 50 to 335 subjects. Patient characteristics were heterogeneous across studies, including proportion of patients with PAF (51% to 100%), percent male (52% to 90%), mean left atrial diameter (3.5 to 4.8 cm), and mean ejection fraction (33% to 66%).

Randomized Controlled Trials

8 mm versus irrigated (closed or open) tip catheter. Overall, data from four RCTs [44,49,99,101] 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. Methodological quality of two studies were rated good;[44,49] and two were rated fair.[99,101]

Using a 2x2 factorial design, one study randomized 42 patients with drug refractory AF into either electrical isolation of all PVs or electrical isolation of only arrhythmogenic PVs using an 8 mm tip versus a closed irrigated tip catheter.[49] The primary outcome, long-term rhythm control of AF, was defined as complete freedom or more than 90% reduction in AF burden either off or on previously ineffective AAD at 6 months following a single ablation procedure. The primary outcome was achieved in 32 patients (78%) in the 8 mm tip catheter arm versus 28 patients (70%) in the irrigated tip catheter arm (OR 1.52, 95% CI 0.56-4.15). A subsequent study by the same group with 1 year followup data including slightly more patients (but overlapped

[e] RF energy was delivered for up to 30 seconds or until vagal reflexes were abolished); vagal reflexes were defined as sinus bradycardia (40 bpm), asystole, AV block, or hypotension that occurred within a few seconds of the onset of RF application (P<0.001).

with the previous study) reported the same findings.[44] A total of 91 patients with drug refractory AF were randomized to PVI using an 8 mm tip or a closed irrigated tip catheter. Long-term rhythm control of AF was achieved in 32 patients (78%) in the 8 mm tip catheter arm versus 35 patients (70%) in the irrigated tip catheter arm (OR 1.18, 95% CI 0.47-2.99).

Two RCTs compared the outcomes of PVI using an 8 mm versus open irrigated tip catheter for treatment of AF.[99,101] The first RCT randomized 180 patients (mean followup 6 months) into three groups using different tips and settings: 8 mm tip catheter; open irrigated tip catheter with a higher power (50 W) and higher irrigation flow rate (30 mL/min); or open irrigated tip catheter with a lower power (35 W) and lower irrigation flow rate (17 to 30 mL/min).[99] The second RCT randomized 53 patients (mean followup 14 months) to either an 8 mm tip catheter or an open irrigated tip catheter, both set to a maximum power of 50 W ablation.[101] In both RCTs, there was no significant difference in rhythm control between patients who underwent PVI with an 8 mm tip catheter and those who underwent PVI with an open irrigated tip catheter using a higher power (50 W). However, in the second RCT, more patients who underwent PVI using an 8 mm tip catheter were free from atrial arrhythmia off AADs compared to those patients who underwent PVI using an open irrigated tip catheter with a lower power (35 W) (79% vs. 68%, respectively). Formal statistical testing was only done for differences among the three arms of this RCT (P=0.04), but no pairwise statistical testing was reported.

Different energy outputs. One fair quality RCT compared the outcomes of PVI in 121 patients with drug refractory AF using an open irrigated tip catheter with a higher power (50 W) and irrigation flow rate (30 mL/min) with the same catheter but using a lower power (35 W) and irrigation flow rate (17 to 30 mL/min).[99] More patients who underwent PVI using an open irrigated tip catheter with a higher power (50 W) were free from atrial arrhythmia off AADs than patients who underwent RFA with a lower power (35 W) (82% vs. 68%, respectively). As described previously, statistical testing was only done for differences among all three arms of this RCT without pairwise testing. Thus, the reported P value cannot be extrapolated to any of the two arm comparisons.

Different postprocedure duration of observation in the electrophysiology (EP) laboratory. One fair quality RCT examined the impact of postprocedure duration of observation in the EP laboratory on outcomes of PVI in 90 patients with PAF.[104] Patients were randomized into three groups of different observation time after PVI: no additional observation time; 30 minutes of observation; and an additional 60 minutes of observation. Patients were monitored and underwent additional ablation if recovery of PV was detected. At 6 months followup, 7/18 patients (39%) with no additional observation time, 3/21 patients (14%) with 30 minutes observation, and 1/21 patients (5%) with an additional 60 minutes observation had atrial tachyarrhythmia lasting >30 seconds. The differences between the three groups were statistically significant (P=0.03).

Different imaging modalities. Five RCTs, three fair quality[68,100,102] and two poor quality,[67,103] compared different imaging modalities used during RFA. Two RCTs compared a 3-dimensional mapping system with conventional fluoroscopic guidance. The other three RCTs examined the impacts of computed tomographic (CT) integration with either 3-dimensional mapping system or conventional fluoroscopic guidance. Each of the five RCTs enrolled fewer

than 100 patients. Overall, data from the fair quality RCTs did not show significant differences in the outcomes of PVI in patients with drug refractory AF up to 1 year followup.

One fair quality RCT[102] and one poor quality RCT[103] compared the outcomes of PVI guided by a 3-dimensional mapping system versus the same ablation technique using only conventional fluoroscopic guidance in 72 and 60 patients with drug refractory AF, respectively. The fair quality RCT used a closed irrigated tip catheter and the results showed that, after a mean followup of 6.5 months, there was no significant difference in the rate of freedom from arrhythmia between patients who received PVI guided by a 3-dimensional mapping system and those who received PVI guided by conventional fluoroscopic guidance (74% vs. 78%, respectively). Seven patients in each arm were on AADs after ablation. The poor quality RCT used an open irrigated tip catheter. Over a mean followup of 7 months, fewer patients in the 3-dimensional mapping arm had recurrence of AF compared to those patients in the conventional fluoroscopic guidance arm (10% vs. 20%, respectively). No statistical testing was reported for this analysis. In the 3-dimensional mapping system arm, all three patients who had recurrence of AF had the event within 3 months of the ablation and required titration of their medications. In the conventional fluoroscopic arm, there was recurrence of AF in six patients; the timing of the recurrence was not reported, and in four patients the arrhythmias self-terminated.

One fair quality RCT compared the outcomes of PVI guided by a 3-dimensional mapping system with CT integration versus the same ablation technique using PVI guided by fluoroscopy (2-dimensional) with CT registration in 77 patients with drug refractory AF.[100] The results showed no significant difference in single procedure success (freedom from AF) between the two groups after 6 months of followup (50% vs. 56%, respectively).

One fair quality RCT compared CT integration versus the same ablation technique using an older version of a 3-dimensional mapping system without CT integration in 81 patients with drug refractory PAF.[68] After a mean followup duration of 1 year, there was no significant difference in the rate of ablation success (no recurrence of symptomatic and asymptomatic AT) between the two groups (79% vs. 74%, respectively).

One poor quality RCT compared the outcomes of PVI guided by fluoroscopy (2-dimensional) with CT registration versus the same ablation technique using only conventional fluoroscopic guidance in 50 patients with drug refractory AF.[67] Eight patients (five in the CT-fluoro-guided group) had undergone one prior catheter ablation procedure for AF. The results showed that more patients in the CT-fluoro-guided group were free from arrhythmia than those in the conventional fluoroscopic guidance group (84% vs. 64%). No statistical testing was reported for this analysis. The study did not provide information on the use of AADs first month post-ablation.

Nonrandomized Comparative Trials

8 mm versus closed irrigated tip catheter. One poor quality nonrandomized comparative trial of PVI compared an 8 mm to opened irrigated tip catheter with two different energy settings (30 or 40 W) in 221 patients with symptomatic AF.[37] The first 90 patients received RFA using an 8-mm tip catheter and the next 131 patients received RFA using a closed irrigated tip catheter. At 1 year followup, the probability of being arrhythmia-free after a single procedure was 53% and 49%, respectively (no statistical analysis was done for the difference between groups).

Different energy outputs. The same nonrandomized comparative trial of PVI, described above, also compared the outcomes of PVI using a closed irrigated tip catheter with two different energy settings (30 or 40 W).[37] Among the 131 patients, 42 patients received RFA at 45°C and 30 W power output, and the remaining 89 patients received RFA at 45°C and 40 W power output. At 1 year followup, ablation with a closed irrigated-tip catheter at 30 W led to a lower arrhythmia-free rate compared to ablation with a closed irrigated-tip catheter at 40 W (35% vs. 55%).

Another poor quality nonrandomized comparative trial of PVI using a 5 mm open irrigated tip catheter compared the outcomes of higher power (45 W) versus lower power (30 W) settings in 90 patients with AF who had undergone segmental PVI before the study.[107] After a mean followup of 15 months, there was no significant difference in the proportion of patients with stable sinus rhythm without symptomatic recurrent AF between groups (76% vs. 74%, respectively; not statistically significant).

Different imaging modalities. In the first study, the first half of 100 consecutive patients with drug refractory AF underwent PVI guided by conventional 3-dimensional electroanatomic mapping were compared to the second half of patients who underwent PVI using the same 3-dimensional electroanatomic mapping with the addition of CT image integration technology. The addition of CT image integration technology was associated with an improvement in rhythm control with or without AADs as compared to conventional 3-dimensional electroanatomic mapping used in the historical controls (85% vs. 68% P=0.02).[61]

In the second study, the first half of 64 patients with drug refractory AF who underwent PVI with conventional fluoroscopic guidance were compared to the second half of patients who underwent PVI guided by a 3-dimensional mapping system. Patients in the two groups had similar rates of rhythm control over a mean followup of 10 months (74% vs. 68%, not statistically significant).[106]

The third study described AF mapping and ablation using manually controlled steerable sheath catheter navigation and compared it to an ablation approach with a nonsteerable sheath. Patients (controls) treated with PVI in 2004 and 2005 using a conventional nonsteerable transseptal sheath were matched with subsequent patients (cases) ablated in 2006 with a similar line concept but mapping and ablation performed with a manually controlled steerable sheath. A total of 166 patients were included in the analyses. Patients ablated with the steerable sheath showed an increase in the success rate (freedom from AF) from 56% to 77% (P=0.0009) after a single procedure and 6 months of followup.

Retrospective Cohorts

Several retrospective studies compared different techniques of PVI. None of these analyses controlled for differences in RFA operators' experience or variations in RFA techniques. In some studies, there was no explicit definition of rhythm control, and different durations of followup were reported between groups. It is difficult to draw conclusions from this group of studies. Methodological quality of all five retrospective studies in this section was rated poor.

8 mm versus conventional 4 mm tip catheter. One retrospective study reported improved rhythm control (at 6 months) in patients who underwent PVI with an 8 mm tip catheter

compared to those who underwent RFA with a conventional 4 mm tip catheter.[110] However, repeat RFA was performed only in patients who underwent RFA with an 8 mm tip catheter.

Different imaging or mapping techniques for PVI. Three studies compared the outcomes between different imaging and mapping techniques for PVI. The comparisons were different across studies, including circular mapping alone versus circular mapping enhanced with intracardiac echocardiogram (ICE) with or without monitoring for microbubble formation (which can indicate overheating of atrial tissue with RFA),[108] mapping the earliest PV potential alone versus additional mapping by electrogram polarity reversal approach,[111] and circular mapping versus electroanatomic mapping.[109] A total of 1,149 patients with drug refractory AF who had undergone PVI were analyzed.

In one study, rhythm control was significantly better in patients who underwent ICE-guided PVI compared to circular mapping guided PVI (87% vs. 80%, P=0.01). The difference was more pronounced in those patients in whom ICE guided PVI included the titration of RFA energy based on microbubble formation as compared to circular mapping alone (90% vs. 80%, P=0.009). Among the patients who underwent ICE guided PVI, rhythm control in patients in whom RFA energy was titrated based on microbubble formation was not statistically different compared to ICE guidance without microbubble monitoring (90% vs. 83%, P=0.08).[108] In another study, PVI guided by circular mapping had better rhythm control without the use of AADs in 92% (243/264) of patients (including 35 patients with second procedure), compared with the electroanatomically guided technique, in which only 30% (21 of 71) of patients were free of arrhythmia while not on AADs.[109] No other significant differences in the patients' outcome were reported in the remaining studies.

Different ablation time. One study reported outcomes of PVI in 90 patients with PAF.[97] Of these, 41 patients received ostial–antral PVI (32 patients had purely ostial and 9 patients antral ablation) while 49 patients underwent circumferential ablation. When all patients were analyzed together, it was found that 1 minute increase in RFA time was associated with 16% reduction in the risk for recurrence of AF (HR 0.84, 95% CI 0.77–0.90, P<0.001). This inverse relationship between RFA time and recurrence of AF remained after adjustment for potential confounders such as age, sex, cause of AF, LA size, and type of ablation technique (ostial–antral or circumferential) (HR 0.80, 95% CI 0.72–0.87, P<0.001), even. It is unclear what proportion of patients was on AADs at the time of followup.

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

Technologies and techniques of RFA of AF have evolved over the last decade. Because the risk of adverse events of RFA may theoretically depend on the specific ablation approach or catheter tip used, the studies were categorized according to ablation approach and catheter tip. For this section, ablation approaches were broadly classified into two groups: ostial (including focal and segmental approaches) and extra-ostial (all other approaches external to the pulmonary vein (PV) ostia including wide area circumferential ablation (WACA)) PV ablation.

A total of 116 cohorts from 100 studies[23-30,33-35,37,39,40,43-56,58,59,61,63,65,68-71,73-75,77-83,85,87,89-95,97-140] involving 22,344 patients reported adverse events: extraostial RFA with irrigated tip catheters (37 cohorts, **Table 14**), conventional 8 mm tip catheters (22 cohorts, **Table 15**), or

other catheters (10 cohorts, **Table 16**), ostial PVI with irrigated tip catheter (18 cohorts, **Table 17**), conventional 8 mm tip (8 studies, **Table 18**), or other tips (10 cohorts, **Table 19**), and various ablation approaches (11 cohorts, **Table 20**).

In general, the definition and monitoring of adverse events was not uniform among studies, and there were variations in the durations of followup. For example, not all studies evaluated asymptomatic PV stenosis at 3 months by computed tomography, and in those that did, different definitions of severe, moderate, or mild PV stenosis were used. Few studies provided detailed data on the exact timing of an adverse event, or explicitly defined the time frames of short- versus long-term complications. Thus, direct comparisons across studies or different ablation approaches were not possible.

There were 84 studies that reported at least one adverse event associated with RFA. Adverse events included PV stenosis,[24,28,34,35,39,40,46,48,52,54,58,61,68,73-75,79,82,83,85,90-95,98,100,108,109,113,114,117,123,127,129,132-134,136,138-140] cardiac tamponade,[25,28,29,33-35,37,39,40,45,47,48,52,54,56,58,65,68,73,78,80,82,83,85,87,89,90,97,99,100,105,112-122,124,131,133,134,136-140] stroke or transient ischemic attach (TIA),[23,25,27,29,34,35,37,39,40,43-46,48,49,54,56,58,61,63,68,69,71,74,78,80,81,83,89,99,106-108,112-114,116,123-127,131,133,134,136-140] bleeding or hematoma,[40,48,51,69,75,92,124,134,136,139] pseudoaneurysm,[40,81,92,104,112,116,124,138,139] femoral vein thrombosis,[39,117,139] or arteriovenous fistula.[39,92,112,120,121,138,139] **(see Tables 14-20)**

There were 78 studies that assessed the rates of asymptomatic or symptomatic PV stenosis.[23-26,28-30,33-35,37,39,40,43-50,52-55,58,59,61,68-70,73-75,77-79,81,83,85,89-95,97-103,105-111,113,114,117,119,122,123,127,128,130,132-136,138-140] The majority of these papers reported rates of asymptomatic PV stenosis between 0% and 19% (median 0.3%); of which, 36 studies did not identify a single case of PV stenosis.[23,25,26,29,33,37,43-45,47,49,50,53,55,59,69,70,77,78,81,89,97-99,101-103,105-107,110,111,119,122,128,130] Symptomatic PV stenosis requiring interventions occurred in 0.07% to 0.9% of patients in six studies.[28,39,134,136,138,139] Cardiac tamponade occurred in 0% to 5% (median 1%) of patients in 70 studies.[23,25,26,28,29,33-35,37,39,40,44,45,47-49,52,54-56,58,59,65,68-70,73,74,77,78,80,82,83,85,87,89,90,97,99,100,102-106,110,112-122,124,126,128,129,131,133-140] Cerebrovascular events were reported in 0% to 7% (median 0.9%) of patients in 72 studies,[23-30,33-35,37,39,40,43-46,48,49,54-56,58,59,61,63,65,68-71,74,77-81,83,89,89,99,102-104,106-108,110,112-114,116,117,119-127,130,131,133-140] of which 19 studies reported no cerebrovascular events.[24,26,28,29,33,55,59,65,70,77,79,102-104,110,119,120,122,130] Atrioesophageal fistula was assessed in 26 studies;[23,26,28,44,45,49,55,59,69,77,78,97,99,101-103,105,106,119,122,126,128,134,135,139,140] four of these reported one case each in 0.07% to 1.2% of patients.[44,49,134,139] The remaining studies did not identify any cases. In 16 studies,[25,26,28,30,44,45,49,65,69,71,99,119,122,138,140,141] five deaths were reported within 30 days postprocedure: one died from pulmonary infection,[71] one died from anaphylaxis after the procedure,[139] and three died from atrioesophageal fistula (three publications from the same group of investigators each reported one death from atrioesophageal fistula).[44,49,139]

Patient Characteristics Associated with Adverse Events

Eleven studies evaluated patient characteristics as predictors of certain procedure-related adverse events. Nine studies used univariate analysis to compare risk of adverse events in patients with or without a single predictor of interest;[35,54,68,103,114,123,127,131,134] whereas two large patient surveys assessed multiple patient-level predictors of various complications.[138,140] In general, studies failed to identify specific patient characteristics that would reliably predict particular adverse events. **(Table 21)**

Operator- or Hospital-Level Characteristics Associated with Adverse Events

Only one study examined the relationship between operator-level characteristics and adverse events of RFA. Spragg et al.[140] reported no statistically significant difference of complication rates between operators who had performed fewer than 50 total cases and those who had performed more than 50 cases (P=0.32).

Two studies reported data on the relationship between a center's learning curve for the procedure and adverse event rates. From a data registry of 1,011 consecutive patients with AF who underwent PV ablation at 10 electrophysiology laboratories, Bertaglia et al. evaluated multiple clinical and procedure-related characteristics to predict PV stenosis, hemorrhagic events, vascular events, and cerebral embolism.[138] In univariate analyses, none of these adverse event rates were statistically different between the first 50 procedures in a center and those performed thereafter. Another single center study[140] reported higher overall complication rates of 9% in the first 100 cases (9 major complications) compared to 4% in 541 cases thereafter (23 major complications; P values not reported), although no global temporal trends were observed in specific adverse event rates including PV stenosis, cardiac tamponade, stroke, or vascular complications.

Conclusions

Key Question 1. What is the effect of RFA on short- (6 to 12 months) and long- (>12 months) term 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 who had failed AADs. 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.

Rhythm Control

There is a moderate level of evidence to show that patients with AF who received RFA as a second-line therapy (i.e., in patients who did not respond to medical therapy) had a higher chance of maintaining sinus rhythm compared to those treated with medical therapy alone (relative risk (RR) 3.46, 95% confidence interval (CI)1.97-6.09) at 12 months postprocedure. The summary estimate was derived from metaanalysis of three RCTs that assessed the rhythm control of patients exclusively after single procedure.

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

It should be noted that the majority (70%) of the patients enrolled in RCTs of RFA versus medical therapy had paroxysmal AF. Therefore, a reliable estimate of the efficacy of RFA for maintenance of sinus rhythm in patients with non-paroxysmal AF (i.e., persistent and longstanding persistent AF) will require further study.

Rates of Congestive Heart Failure

There is insufficient evidence comparing the rate of congestive heart failure between RFA and medical treatment. Only one observational study reported that patients who underwent RFA had a lower risk of developing congestive heart failure compared to those treated with medical therapy (5% vs. 10%, 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%, 95% CI –1.1 to 2.3%; favoring AAD)). The summary estimate was derived from a metaanalysis of six RCTs.

Quality of Life

There is a low level of evidence to suggest that RFA improves QoL compared to medical treatment. Three RCTs and one observational study reported more improvement in general or physical functioning score of the SF-36 health survey in patients who underwent RFA compared to patients who had medical treatment alone (net difference between 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. Only one RCT found a higher proportion of patients reported freedom from anticoagulation at 12 months, comparing RFA with medical therapy (60% vs. 34%, 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% vs. 54%, P<0.001), while the other RCT reported that there was no statistically significant difference in the median number of readmissions between RFA and medical treatment (one readmission vs. two 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 versus other types of AF were clinically and statistically heterogeneous, but metaanalysis found statistically significant higher rates of recurrence in patients with nonparoxysmal AF, with RRs 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, only 6 found statistically significant independent associations between AF type and recurrence rates. In the eight (of 25) studies that reported hazard ratios, these ranged from 1.1 to 22, suggesting

lower recurrence rates in patients with PAF; 16 of the remaining 17 studies reported only that no significant association was found (one reported only that there was a significant association). Among 11 comparisons that reported both univariable and multivariable analyses, six found statistically significant crude and adjusted higher recurrence rates in patients with nonparoxysmal AF, three found significant crude but nonsignificant adjusted associations, and two found nonsignificant crude and adjusted associations. In both the studies that reported univariable or multivariable analyses, 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, five of 17 studies found an association between lower EF and AF recurrence, and four of 20 found an association between larger LAD and AF recurrence. However, the reported data suggest that only a few percent of patients included in the analyses had EFs below about 40% 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. All of 23 studies found no independent association of sex with AF recurrence. Only one of 21 studies found a consistent association between structural heart disease and AF recurrence. Only three 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 one 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 few percent 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, two nonrandomized comparative trials, two 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) within and around PV ostia, a wide-area circumferential ablation (WACA), or additional ablation lines. The majority of the studies included a mixture of patients with either PAF or persistent/permanent AF.

PVI versus 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 versus WACA with or without additional ablation lines compared the 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% vs. 49%, $P \leq 0.05$; 88% vs. 67%, 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 among the studies as to the value of the addition of left-sided ablation lines during RFA. Six RCTs compared the efficacy of one RFA technique with versus 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 including 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% vs. 53%, P=0.01; roof line 87% vs. 69%, P=0.04; MIL 74% vs. 83%, no P value reported). Two studies did not find a significant difference in AF recurrence with the addition of left-sided ablation lines.

PVI versus PVI with right sided lines. There is insufficient evidence concerning the effects on AF recurrence by adding right sided lines in 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 between the group that had ostial-antral PVI and the group that had ostial-antral PVI with cavotricuspid isthmus ablation at 12 months followup. Another RCT compared WACA with versus without superior vena cava ablation. 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 only had WACA.

Different approaches in retrospective studies. There is insufficient evidence to draw meaningful 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 followup results from different time points were compared between groups. None of the studies adjusted for potential confounders.

Technical Issues

There is a moderate level of evidence to suggest that there was no difference in using the 8 mm tip catheter or an irrigated tip catheter for RFA in long-term rhythm control in patients with AF. Furthermore, there is a low level of evidence suggesting no differences in rhythm

control in patients with drug refractory AF comparing different imaging modalities used during RFA.

There is insufficient evidence to draw conclusions in 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, postprocedure durations of observation in the EP laboratory, various mapping techniques (e.g., circular mapping alone versus circular mapping enhanced with intracardiac echocardiogram with or without monitoring of microbubbles) or different ablation time.

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, with sample sizes generally less than 100, and incomplete reporting. 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 time frame 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 TIA, peripheral vascular complications such as bleeding/hematoma, pseudoaneurysm, femoral vein thrombosis, or arteriovenous fistula. There were 78 studies that assessed the rates of asymptomatic or symptomatic PV stenosis. These studies reported asymptomatic PV stenosis rates that ranged from 0% to 19% (median 0.3%); 36 studies did not identify a single case of PV stenosis. Symptomatic PV stenosis requiring interventions occurred in less than 1% of patients in six studies. Cardiac tamponade occurred between 0% and 5% (median 1%) in the 70 studies that evaluated this adverse event. Rates of cerebrovascular events ranged from 0% to 7% (median 0.9%) in the 72 studies that evaluated stroke and/or TIA. Twenty-six studies assessed for atrioesophageal fistula. Among these, four studies reported one case each with an event rate ranged from 0.1 to 0.9%; the rest of the studies 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; it is unclear whether these are three separate incidents or a single incident reported multiple times).

Discussion

A summary of the studies reviewed for this report is given in Table 22.

Key Question 1: Medical Treatment Versus Radiofrequency Ablation (RFA)

There is a moderate level of evidence to show that patients who received RFA as a second-line therapy (i.e., in patients who did not respond to medical therapy) had a higher chance of maintaining sinus rhythm compared to those treated with medical therapy alone (relative risk (RR) 3.46, 95% CI 1.97-6.09) at 12 months postprocedure. This finding is in general agreement with a previously published metaanalysis.[142] We did not find a statistically significant difference in the risk of cerebrovascular events in patients who were treated with RFA compared to those treated with medical therapy. However, clinically meaningful differences could not be excluded because the event rates were small and studies were not powered to detect such small differences.

There were insufficient data to draw meaningful conclusions concerning RFA use as a first-line therapy for rhythm control (i.e., in patients who have never been treated with antiarrhythmic drugs (AADs)).

Key Question 2: Patient- and Intervention-Level Characteristics Associated with Rhythm Control

There is low level of evidence to show that atrial fibrillation (AF) type, namely nonparoxysmal AF, is predictive of a higher rate of AF recurrence. Although metaanalyses of univariable analyses support an association (RR about 1.6 suggesting more recurrence with nonparoxysmal AF), the studies were clinically and statistically heterogeneous, and more importantly, only six of 17 multivariable analyses bear this out, with hazard ratios ranging from 1.1 to 22 (favoring paroxysmal AF).

There is a moderate level of evidence to show that among patients with approximately normal ejection fraction (EF) or left atrial diameter (LAD), these parameters are not independent predictors of AF recurrence; however, there is insufficient evidence to estimate the predictive value of abnormal EF or LAD on recurrence rates. There is a high level of evidence to show that sex, AF duration, and the presence of structural heart disease are not associated with AF recurrence. Among patients between approximately 40 and 70 years of age, there is a high level of evidence to show that age is not associated with AF recurrence; however, 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.

Key Question 3: Approaches and Technical Issues Concerning RFA

Approaches to RFA

There is a moderate level of evidence to show that wide-area circumferential ablation (WACA) resulted in a higher rate of freedom from AF recurrence compared to ostial pulmonary

vein isolation (PVI) (absolute difference: ~20%) in patients with either paroxysmal AF or persistent AF.

It is unclear whether the addition of left sided ablation lines to PVI increases the freedom from AF recurrence compared to PVI alone. Three studies found that the addition of left sided lines in RFA increased the freedom from AF recurrence compared to RFA alone, and two studies did not find significant differences. The heterogeneity of the different types of additional left sided ablation lines may have precluded meaningful comparisons among the studies.

One study found that adding a cavotricuspid isthmus ablation line to PVI in patients with persistent or permanent AF and a history of atrial flutter did not result in a significantly lower recurrence of AF. The limited evidence does not allow us to draw definitive conclusions.

Retrospective studies have limitations in the comparability among groups. The majority of the studies used historical (non-concurrent) controls. The proportions of patients with different types of AF were different between groups in many comparisons. None of the studies adjusted for potential confounders. It is not possible to draw conclusions from this group of studies.

Technical Issues Related to RFA

There is a moderate level of evidence suggesting no differences in using the 8 mm tip catheter or an irrigated tip catheter for RFA in long-term rhythm control in patients with AF. Furthermore, there is a low level of evidence suggesting no differences in rhythm control in patients with drug refractory AF comparing different imaging modalities used during RFA.

There were insufficient data to draw conclusions regarding the outcomes of PVI for AF comparing different energy outputs, mapping techniques, or ablation times.

Key Question 4: Adverse Events Associated with RFA

There is a low level of evidence suggesting major 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, with sample sizes generally less than 100, and incomplete reporting. While there is no doubt that certain adverse events are uniquely associated with the use of RFA (e.g., atrioesophageal fistula), the limitations cited precluded accurate estimates of those adverse event rates. Asymptomatic PV stenosis, cardiac tamponade, and cerebrovascular events were reported at rates of 4% or less in the majority of the studies. Symptomatic PV stenosis was reported at rates of 1% or less. Four studies reported rates of atrioesophageal fistula ranging from 0.1% to 0.9%. A total of five deaths were reported in all the studies reviewed (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). 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. For example, even though the presence of PV stenosis was generally evaluated at around 3 months post-RFA, severe and moderate PV stenoses were defined differently across studies. Some clearly reported stroke as periprocedural, and some reported stroke without stating a time of occurrence. Also, it was not always made clear whether the lack of information on a particular adverse event meant zero events (i.e., the researchers systematically ascertained for it and found none) or it was simply not spontaneously reported. In addition, the sample sizes in most RCTs and comparative studies were generally small, precluding reliable risk estimates of the adverse events. Furthermore, many of the studies had a mean followup of no more than 12 months, any long term events like late AF recurrence or

mortality or delayed adverse effects from radiation exposure could not be properly assessed from this group of studies.

Remaining Issues and Future Research

RFA was superior to medical treatments at maintaining sinus rhythm in patients with PAF who failed first-line medical treatment over 1 year of followup. It should be noted that the primary endpoint in all published RCTs to date has been the recurrence of AF and no RCT 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 and patients who were off AADs (but did not segregate the data respectively). 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 including taking advantage of modalities that would be 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 could be made concerning 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 the 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 uncommonly 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 efficacies and minimize complications should be undertaken. Furthermore, adverse events should be uniformly defined so that informative comparative analyses could be performed.

Further investigations are also needed on the effect of RFA for AF on quality of life, including in patient population under-represented 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).

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Abbreviations

AAD	anti-arrhythmic Drug
ACE-I*	angiotensin converting enzyme inhibitor
AF	atrial fibrillation
AFL*	atrial flutter
ARB*	angiotensin II receptor blocker
AT	atrial tachyarrhythmia
BMI*	body mass index
bpm	beats per minute
CAD*	coronary artery disease
CFAE	complex fractionated atrial electrogram
CS	coronary sinus
CTI	cavotricuspid isthmus line
CVA*	cerebrovascular accident (stroke)
c/w*	consistent with
EF	left ventricular ejection fraction
EP	electrophysiology
HR	hazard ratio
HRS	Heart Rhythm Society
HTN	hypertension
ICE	intracardiac echocardiogram
LA	left atrium
LACA	left atrial circumferential (or catheter) ablation
LAD	left atrial diameter
LV*	left ventricle
LVD	Left ventricular diameter
MI	myocardial infarction
MIL	mitral isthmus line
nd*	no data (not described)
nonParox*	nonparoxysmal (atrial fibrillation)
NS*	(statistically) nonsignificant
PAF	paroxysmal atrial fibrillation
Parox*	paroxysmal (atrial fibrillation)
Perm*	permanent
Persist*	persistent (atrial fibrillation)
PV	pulmonary vein
PVAI	pulmonary vein antrum isolation
PVI	pulmonary vein isolation
QoL	quality of life
RCT	randomized controlled trial
RF	radiofrequency
RFA	radiofrequency ablation
RR	relative risk
SF-36	the 36-Item Short-Form General health Survey

SR	sinus rhythm
TEE	transesophageal echocardiography
TEP	technical expert panel
TIA	transient ischemic attack
WACA	wide area circumferential ablation

* Used in tables only

Tables

Table 1. Characteristics of comparative studies of RFA vs. AAD

Author Year Country UI	Intervention(s)	Ancillary Ablations	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	N enrolled	Enrollment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Mean Symptom Duration, yr
Randomized controlled trials													
First-line therapy													
Wazni 2005[24] Germany & Italy 15928285	AAD (flecainide, sotalol, or propafenone)[a]					37	2001-2002	96	54	nd	nd	54	0.4
	RFA (PVI)	None	8 mm	Yes	No	33							
Second-line therapy													
Krittayaphong 2003[23] Thailand 12866763	Amiodarone[b]					15	nd	67	52	63	3.9	63	4.7
	RFA (WACA)[c]	• WACA + mitral line (LA) • Cavotricuspid isthmus line, SVC-IVC, and mid RA horizontal line (RA)	8 mm	No	No	15							
Stabile 2006[25] Italy 16214831	AAD (amiodarone, flecainide, propafenone, or etc.)[d]					69	2002-2003	67	62	57	4.6	58	6.1
	RFA (CPVA) plus AAD[e]	• Circumferential lines around each PV and mitral isthmus line (LA) • Cavotricuspid isthmus line (RA)[f]	8 mm or 3.5 mm cooled[g]	Yes	No	68							

Author Year Country UI	Intervention(s)	Ancillary Ablations	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	N enrolled	Enrollment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Mean Symptom Duration, yr
Oral 2006[26] US & Italy 16510747	Amiodarone[h]					69	2002-2004	0[i]	56	65	4.5	55	4.5
	RFA (LACA)[j]	• Encircling lesions of PVs, Roof line, and mitral isthmus line (LA) • Cavotricuspid isthmus line (RA)[k]	8 mm	Yes	No	77							
Pappone 2006[27] Italy 17161267	AAD (Flecainide, sotalol, or amiodarone)[l]					99	2005	100	56	67	3.9	61	6
	RFA (CPVA)[m]	• Circumferential lines around each PV (LA) • Cavotricuspid isthmus line (RA)	8 mm or 3.5 mm irrigated[n]	No	No	99							
Jais 2008[28] France, US, & Canada 19029470	AAD (Amiodarone, quinidine, disopyramide, or etc.)[o]					53	nd	100	51	84	4.0	64	5.5 (median)
	RFA (CPVA)[p]	• Roof and Mitral isthmus lines (LA) • Cavo-Tricuspid Isthmus line (RA) • Targeted Foci	3.5- or 5-mm irrigated	Yes	No	59							

Author Year Country UI	Intervention(s)	Ancillary Ablations	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	N enrolled	Enrollment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Mean Symptom Duration, yr
Nonrandomized comparative trials													
Second-line therapy													
Pappone 2003[29] Italy 12875749	AAD					582	1998-2001	70	65	58	4.6	54	4.6[q]
	RFA (CPVA)[r]	nd	nd	Yes	No	589							
Rossillo 2008[30] Italy 18268419	AAD					85	2002-2004	16[s]	62	84	4.3	57	8[t]
	RFA (PVI)	• SVC isolation (RA)	8 mm	Yes	No	85							

AAD, anti-arrhythmic drug; CPVA, Circumferential pulmonary vein ablation; IVC, inferior vena cava; LA, LACA, left atrial catheter ablation; left atrium; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; nd, no data; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RFA, radiofrequency ablation; SVC, superior vena cava; WACA, wide area circumferential ablation

a. Maximum tolerable dose was set as follows: flecainide 100-150 mg, sotalol 120-160 mg bid, and propafeonone 225-300 mg tid.
b. Loading dose: 1200 mg everyday for 1 week and then 600 mg everyday for 2 weeks. Maintenance dose: 200 mg everyday.
c. Amiodarone 200mg everyday was prescribed for 3 months after the procedure.
d. Amiodarone. A class IC anti-arrhythmic was used if patients had a history of side effects or intolerance to amiodarone. Dosing schedule not provided in detail; mean daily dose was as follows: amiodarone 209 mg, flecainide 191 mg, propafenone 750mg, sotalol 184 mg, and disopyramide 500mg.
e. AAD was prescribed concurrently and continued during the entire study period as combined modality therapy.
f. Only if the conduction in this region was detected.
g. 8 mm tip catheter was used in the first 17 patients, and was replaced with 3.5 mm cooled-tip catheter in the remaining patients.
h. Amiodarone 200 mg everyday was terminated at 3 months.
i. All patients had chronic AF, which was defined as AF that had been present for more than six months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion.
j. Amiodarone 200 mg everyday was prescribed for 3 mos after the procedure.
k. Performed in 55 patients at the discretion of the operators.
l. Flecainide 100 mg bid; sotalol 80 mg tid; or amiodarone 200 mg/day (maintenance dose)
m. AAD was prescribed for 6 weeks after the procedure.
n. 8 mm tip catheter was used in the first 50 patients, and was replaced with 3.5 mm cooled-tip catheter in the remaining patients.
o. Amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, and sotalol. Up to 3 attempts for alterations or modifications of pharmacologic therapy were allowed until 90 days from randomization.
p. Up to 2 repeat ablations were allowed until 90 days from randomization. Also, additional ablations were performed at the discretion of the treating physicians: roof line (17%), mitral isthmus line (30%), cavo-tricuspid Isthmus line (64%), and targeted foci (23%).
q. 5.5 years for RFA group and 3.6 years for AAD group (P<0.001).
r. AAD was prescribed for 3 months in 115 patients (20%) who had in-hospital AF and/or needed cardioversion to terminate AF after the procedure.
s. No patients in AAD group had paroxysmal AF.
t. No data available for AAD group.

Table 2. Rhythm control in patients who received RFA vs. AAD

Study Year UI	Description		No. Analyzed		Outcome	Metric/ Units	Results			Quality
	Interv	Cont	Interv	Cont			Interv	Cont	P Between	
Randomized controlled trials										
First-line therapy										
Wazni 2005[24] Germany & Italy 15928285	RFA (PVI)	AAD	32[a]	35[b]	Freedom from AF recurrence at 12 mo	Crude %	88	37	<0.001 (χ^2)	Fair
Second-line therapy										
Krittayaphong 2003[23] Thailand 12866763	RFA (WACA)	Amiodarone	14[c]	15	Freedom from AF recurrence at 12 mo	KM %	79	40	0.018 (Log-rank)	Poor
Stabile 2006[25] Italy 16214831	RFA (CPVA) plus AAD	AAD	68	69	Freedom from atrial arrhythmias recurrence at 12 mo	Crude %	56	9	<0.001 (Fisher)	Fair
					Atrial arrhythmias-free survival	KM	nd	nd	<0.001	
						Adj HR	3.2[d]		<0.05	
Oral 2006[26] US & Italy 16510747	RFA (LACA)	Amiodarone	77	69	Maintaining sinus rhythm at 12 mo[e]	Crude %	74	4[f]	<0.001 (χ^2)	Fair
								58[g]	0.05 (χ^2)	
Pappone 2006[27] Italy 17161267	RFA (CPVA)	AAD	99	99	Atrial tachyarrhythmias-free survival at 12 mo	KM %	86	22	<0.001 (Log-rank)	Fair
Jais 2008[28] France, US, & Canada 19029470	RFA (CPVA)	AAD	52[h]	55	Freedom from AF recurrence beyond d 90 until 12 mo	KM %	89	23	<0.0001 (Log-rank)	Fair
Retrospective										
Second-line therapy										
Pappone 2003[29] Italy 12875749	RFA (CPVA)	AAD	589	582	AF-free survival at 12 mo	KM %	84	61	<0.001 (Log-rank)	Poor
					AF-free survival at 24 mo		79	47		
					AF-free survival at 36 mo		78	37		
					AF-free survival	HR	0.30[i]		<0.05	
Rossillo 2008[30] Italy 18268419	RFA (PVI)	AAD	85	85	Stable sinus rhythm[j]	Crude %	82	40	nd	Poor

a. One patient was excluded from analysis due to lost to follow-up.

b. Two patients were excluded from analysis due to lost to follow-up.
c. One patient was excluded from analysis due to procedure-related adverse effects.
d. 95%CI, 2.0-5.1.
e. Patients who maintained sinus rhythm at 12 months regardless of relapse until this time point.
f. For only patients who did not resume AAD or cross over to RFA.
g. For patients allocated to AAD (i.e., intention-to-treat analysis).
h. These patients underwent a mean of 1.8 (standard deviation of 0.8) procedures (1 to 3; median, 2).
i. 95% CI, 0.24-0.37
j. At last follow-up: 15 mo for PVI group and 16 mo for AAD group.

AAD, anti-arrhythmic drug; Adj, adjusted; AF, atrial fibrillation; CI, confidence interval; CPVA, circumferential pulmonary vein ablation; HR, hazard ratio; KM, Kaplan-Meier; LACA, left atrial catheter ablation; nd, no data; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; WACA, wide area circumferential ablation

Table 3. Congestive heart failure in patients who received RFA vs. AAD

Study Year UI	Description		No. Analyzed		Outcome	Metric/ Units	Results			Quality
	Interv	Cont	Interv	Cont			Interv	Cont	P Between	
Retrospective										
Second-line therapy										
Pappone 2003[29] Italy 12875749	RFA (CPVA)	AAD	589	582	Developing CHF	Crude %a	5	10	nd	Poor

AAD, anti-arrhythmic drug; CHF, congestive heart failure; CPVA, circumferential pulmonary vein ablation; RFA, radiofrequency ablation

a. The number of patients who developed CHF was originally reported in the literature.

Table 4. Change in LAD or LVD or LV function in patients who received RFA vs. AAD

Study Year UI	Description		No. Analyzed		Outcome	Metric/ Units	Results			Quality
	Interv	Cont	Interv	Cont			Interv	Cont	P Between	
Randomized controlled trials										
Second-line therapy										
Jais 2008[28] France, US, & Canada 19029470	RFA (CPVA)	AAD	53	59	LAD at 12 mo	cm	3.9	3.9	0.92[a] (t-test)	Fair
Jais 2008[28] France, US, & Canada 19029470	RFA (CPVA)	AAD	53	59	LVED at 12 mo	cm	5.0	5.1	0.35[a] (t-test)	Fair
Jais 2008[28] France, US, & Canada 19029470	RFA (CPVA)	AAD	53	59	LVEF at 12 mo	%	65	65	0.99[b] (t-test)	Fair
Retrospective										
Second-line therapy										
Pappone, 2003[29] Italy 12875749	RFA (CPVA)	AAD	nd[c] nd[d]	nd[c] nd[d]	Change in LAD	cm	-0.5 -1.1	-0.2 -0.3	nd	Poor

AAD, anti-arrhythmic drug; AF, atrial fibrillation; CPVA, circumferential pulmonary vein ablation; LACA, left atrial catheter ablation; LAD, left atrial diameter; LVD, left ventricular diameter; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; nd, no data; RFA, radiofrequency ablation

a. Difference in size between groups at 12 months was considered. Not net difference between before procedure (baseline) and after 12 months (final) between groups.
b. Difference in % between groups at 12 months was considered. Not net difference between before procedure (baseline) and after 12 months (final) between groups.
c. Only patients with recurrent AF.
d. Only patients without recurrent AF.

Table 5. Stroke in patients who received RFA vs. AAD

Study Year UI	Description		No. Analyzed		Outcome	Metric/ Units	Results			Quality
	Interv	Cont	Interv	Cont			Interv	Cont	P Between	
Randomized controlled trials										
First-line therapy										
Wazni 2005[24] Germany & Italy 15928285	RFA (PVI)	AAD	32[a]	35[b]	Stroke	Crude %	0	0	nd	Fair
Second-line therapy										
Krittayaphong 2003[23] Thailand 12866763	RFA (WACA)	Amiodarone	14[c]	15	Stroke	Crude %	7	0	nd	Poor
Stabile 2006[25] Italy 16214831	RFA (CPVA) plus AAD	AAD	68	69	Stroke	Crude %	1	1	nd	Fair
Oral 2006[26] US & Italy 16510747	RFA (LACA)	Amiodarone	77	69	Stroke	Crude %	0	0	nd	Fair
Pappone 2006[27] Italy 17161267	RFA (CPVA)	AAD	99	99	Stroke	Crude %	1	0	nd	Fair
Jais 2008[28] France, US, & Canada 19029470	RFA (CPVA)	AAD	53[d]	59	Stroke	Crude %	0	0	nd	Fair
Retrospective										
Second-line therapy										
Pappone 2003[29] Italy 12875749	RFA (CPVA)	AAD	589	582	Stroke	Crude %	2	8	nd	Poor
Rossillo 2008[30] Italy 18268419	RFA (PVI)	AAD	85	85	Stroke	Crude %	1	6	0.059 (Fisher)	Poor

AAD, anti-arrhythmic drug;CPVA, circumferential pulmonary vein ablation; LACA, left atrial catheter ablation; nd, no data; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; WACA, wide area circumferential ablation

a. One patient was excluded from analysis due to lost to follow-up.
b. Two patients were excluded from analysis due to lost to follow-up.
c. One patient was excluded from analysis due to procedure-related adverse effects.
d. These patients underwent a mean of 1.8 (standard deviation of 0.8) procedures (1 to 3; median, 2).

Table 6. Quality of life in patients who received RFA vs. AAD

Study Year UI	Description		No. Analyzed		Outcome	Metric/ Units	Results			Quality
	Interv	Cont	Interv	Cont			Interv	Cont	P Between	
Randomized controlled trials										
First-line therapy										
Wazni 2005[24] Germany & Italy 15928285	RFA (PVI)	AAD	32[a]	35[b]	SF-36 general health functioning score at 6 mo	ΔScore[b]	NetΔ = 11		<0.001 (ANOVA)	Fair
							+22	+11		
					SF-36 physical functioning score at 6 mo		NetΔ = 20		0.001 (ANOVA)	
							+26	+6		
					SF-36 mental health score at 6 mo		NetΔ = -4		0.62 (ANOVA)	
							0	+4		
Second-line therapy										
Krittayaphong 2003[23] Thailand 12866763	RFA (WACA)	Amiodarone	14[c]	15	SF-36, general health score at 6 mo	ΔScore[d]	+15	+6	0.048 (ANOVA)	Poor
					SF-36, general health score at 12 mo		+20	+3		
					SF-36, physical fitness score at 6 mo		+11	+2		
					SF-36, physical fitness score at 12 mo		+23	-2	0.69 (ANOVA)	
Jais 2008[28] France, US, & Canada 19029470	RFA (CPVA)	AAD	53	59	SF36 physical component summary at 12 mo	ΔScore[d]	+7.2	+5.9	0.01 (t-test)[e]	Fair
						ΔScore[f]	+7.2	+6.0	0.015 (GLM)	
					SF36 mental component summary at 12 mo	ΔScore[d]	+10.5	+7.9	0.01 (t-test)[e]	
						ΔScore[f]	+9.7	+9.1	0.09 (GLM)	
Retrospective										
Second-line therapy										
Pappone 2003[29] Italy 12875749	RFA (CPVA)	AAD	589	582	SF-36, physical component summary score at 6 mo	ΔScore[b]	+9	+1	nd	Poor
					SF-36, physical component summary score at 12 mo		+10	+1		
					SF-36, mental component summary score at 6 mo		+8	+1	nd	
					SF-36, mental component summary score at 12 mo		+8	+1		

AAD, anti-arrhythmic drug; ANOVA, analysis of variance; CPVA, circumferential pulmonary vein ablation; GLM, generalized linear models; nd, no data; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; SF-36, the 36-Item Short-Form General health Survey; WACA, wide area circumferential ablation

a. One patient was excluded from analysis due to lost to follow-up.
b. Two patients were excluded from analysis due to lost to follow-up.
c. One patient was excluded from analysis due to failure to complete the procedure.
d. Difference of the mean score between baseline and at the particular point.
e. The mean summary scores at 12 mo were compared.
f. Within-subject increase based-on repeated measures were presented.

Table 7. Readmission in patients who received RFA vs. AAD

Study Year UI	Description		No. Analyzed		Outcome	Metric/ Units	Results			Quality
	Interv	Cont	Interv	Cont			Interv	Cont	P Between	
Randomized controlled trials										
First-line therapy										
Wazni 2005[24] Germany & Italy 15928285	RFA (PVI)	AAD	32	35[a]	Re-admission	Crude %[b]	9	54	<0.001 (Fisher)	Fair
Second-line therapy										
Stabile 2006[25] Italy 16214831	RFA (CPVA) plus AAD	AAD	68	69	Re-admission	Time/patient-year	1[c]	2[c]	0.34 (t-test)	Fair
Retrospective										
Second-line therapy										
Pappone 2003[29] Italy 12875749	RFA (CPVA)	AAD	nd[d] nd[f]	nd[d] nd[f]	Change in re-admission[e]	Time/patient-year	-0.7 -1.8	+0.5 -1.2	nd	Poor

AAD, anti-arrhythmic drug; CPVA, circumferential pulmonary vein ablation; PVI, pulmonary vein isolation; RFA, radiofrequency ablation

a. Two patient s were excluded due to lost to follow-up.
b. The number of patients who needed re-admission was originally reported.
c. Median
d. Only patients with recurrent AF.
e. Change in hospitalization from 2 years prior to the entry of the study.
f. Only patients without recurrent AF.

Table 8A. Predictors of AF recurrence in multivariable analyses

Study Year	Time, mo	AF Type	N	Association with Outcome, HR (95% CI), P value										Comments
				AF Type	↑AF Duration	↓EF	↑LAD	Male	↑Age	Structural Disease	HTN	Other		
Themistoclakis 2008[31]	41	Mixed	1298	**++ Persist 2.2 Chronic 2.3**	**++ 1.03/yr**		0			0	**++ 1.7**			Model included early tachyarrhythmia and SVC isolation
Verma 2005[32]	16	Mixed	700	0	0	0	0		0	0				
Pappone 2003[29]	30	Mixed	589	0	0	0	**++ 2.1**	0	0		0	CAD	0	
												LV mass	0	
												CVA / TIA	0	
Pappone 2004[33]	12	Parox Chronic	560	**++ Chronic 22**				0	0	0				
Cha 2008[34]	12	Mixed	432	0	**++ 1.04/yr**	**++ 1.02**	0	0	**- - 0.97**	0	0	BMI	0	Similar model at 24 months
												AAD treatment failure	0	
												DM	0	
												Sleep apnea	0	
Chen 2004[35]	14	Mixed	377		0	**++ nd**	0	0	0			No. of AAD	0	Model included PV ostial size
Pappone 2004[36]	12	Parox	297		0	0	0	0	0	0				
Matiello 2008[37]	14	Mixed	247	0?†			**++ 1.1**	0?†	0?†	0?†	0?†			Model included catheter type
Richter 2006[38]	6	Parox Persist	234	**++ Persist 1.8**		0	0	0	0	0		BMI	0	Model included AF inducibility
Della Bella 2005[39]	12	Parox Persist	234					0	0	0	0			
Cheema 2006[40]	26	Mixed	200	**++ NonParox 2.8**	0	0	0	0	0	0				
Pappone 2006[27]	12	Parox	198		0	0	0	0	0	0	0			
Oral 2004[41]	15	Parox	188		**+ nd**	0	0	0	0	0		Vagotonic AF	**++ nd**	
												Frequency of AF episodes	0	
Al Chekakie 2007[42]	14	Mixed	177	0	0	**++ 2.7**	0	0	0	0	0	ACE-I, ARB, or statins (individually / collectively)	0	
Berruezo 2007[43]	13	Mixed	148	0	0	0	**++ 1.1**	0	0	0	**++ 2.8**	Other echo parameters	0	
Dixit 2008[44]	12	Mixed	103	0				0						Model included early AF recurrence
Essebag 2005[45]	6/12*	Mixed	102	**++ / ++* NonParox 3.2/4.8**				0	0	**++ / 0* 4.0 / NS**	0			Model included AF inducibility
Nilsson 2006[46]	12	Parox Persist	100	0	0		0	0	0	**++ 2.05**				
Jais 2004[47]	12	Parox	100		0?†	0?†	0?†	0?†	0?†	0				
Liu 2006[48]	13	Mixed	100	0	0	0	0	0	0	+		Typical AFlutter	0	

Study Year	Time, mo	AF Type	N	Association with Outcome, HR (95% CI), P value										Comments
				AF Type	↑AF Duration	↓EF	↑LAD	Male	↑Age	Structural Disease	HTN	Other		
										2.4		Other echo parameters	0	
Dixit 2006[49]	6	Mixed	82	**++ NonParox nd**				0			0	Comorbidities	0	
Oral 2003[50]	6	Parox	80		0	0	**++ nd**	0	0	0		Frequency of AF episodes	0	
Calò 2006[51]	14	Persist Perm	80	0?‡		**++ 5.2**	0?‡	0?‡	0?‡	0?‡				Model included continuation of AAD
Stabile 2006[25]	12	Parox Persist	68	0	0	0	0	0	0	0	0	Heart disease	0	
												Various drugs	0	
Jais 2008[28]	12	Parox	53			**++ 1.1**	0?§	0?§	0?§	0?§	0?§	Duration of AF episodes	0	
												Number of cardioversions	0	
												DM	0?§	
												Other echo parameters	0?§	

0, no statistically significant association (P>.1 if adequate data are available to estimate P value or reported as nonsignificant)
+, "trend" for positive association between predictor and (poor) outcome, .05<P≤.10
++, positive association between predictor and (poor) outcome, P<.05
- -, negative association between predictor and (poor) outcome (predicts better outcome), P<.05

* 6 months/12 months.
† Unclear if this variable was tested in the multivariable model.
‡ Adjusted for in model. Unclear if these variables were nonsignificant.
§ Article implied that this variable was not statistically significant by univariable analysis and thus was not tested in multivariable model.

Table 8B. Details of multivariable models predicting AF recurrence

Study, Year	Predictor Association with Outcome, HR (95% CI)
Themistoclakis 2008[31]	Persistent AF 2.17 (1.33-3.53); Permanent AF 2.28 (1.51-3.46); AF duration 1.03 (1.00-1.06) per year; LAD >4 cm 1.39 (0.90-2.15); Hypertension 1.65 (1.14-2.39); Structural heart disease 1.09 (0.74-1.65).
Verma 2005[32]	Nonparoxysmal AF 1.6 (0.80, 2.7); AF duration 1.0 (0.9, 1.2; estimated from figure); EF 1.3 (0.7, 2.3; estimated from figure), per 10% decrease; LA size 0.96 (0.50, 1.8; estimated from figure), per cm; Age 1.3 (0.86, 2.1), per decade; Structural heart disease 1.7 (0.7, 3.6, estimated from figure).
Pappone 2003[29]	Chronic AF 1.2 (0.8, 1.5); AF duration >2 years 1.0 (0.7, 1.5); EF <45% 0.9 (0.5, 1.3); LA size >4.5 cm 2.1 (1.8, 2.7); Male 1.0 (0.8, 1.3); Age >65 years 1.0 (0.8, 1.4); HTN 1.2 (0.8, 1.9); Prior stroke or TIA 1.1 (0.7, 1.6); LV mass >125 g/m^2 1.0 (0.2, 1.6); CAD 0.9 (0.4, 1.4). Values estimated from figure.
Pappone 2004A[33]	Chronic AF (vs paroxysmal) 22 (6.7, 74); Age, Sex, and Heart disease were nonsignificant.
Cha 2008[34]	AF duration 1.04 (1.01, 1.08); higher EF 0.98 (0.96, 1.00); older age 0.97 (0.95, 0.99); HTN NS.
Chen 2004[35]	AF duration, LA size, Age, Gender, Number of AAD were not predictive. EF was. No further data.
Pappone 2004B[36]	AF duration 0.92 (0.78, 1.07), implied per year; EF 1.04 (0.94, 1.14), implied per % decrease; LAD 1.11 (0.98, 1.27), implied per mm; Male 0.93 (0.44, 1.97); Age 1.04 (0.98, 1.10), implied per year; Structural heart disease 0.61 (0.27, 1.37).
Matiello 2008[37]	Anteroposterior atrial diameter 1.105 (1.05-1.19), implied per mm. Other analyzed variables not an "independent predictor". Variables taken from Table 1 patient characteristics.
Richter 2006[38]	Persistent AF (vs. paroxysmal) 1.77 (1.17, 2.7) for AF recurrence. Other predictors not significant in multivariable analysis that also included inducibility of AF exceeding 1 minute of duration. [Other predictors not explicitly defined.]
Della Bella 2005[39]	Sex, Age >50 years, structural heart disease, mitral valve disease, and HTN not predictive.
Cheema 2006[40]	Non-paroxysmal AF 2.83 (1.23, 6.0); AF duration 1.02 (0.94, 1.10); EF 0.97 (0.92, 1.02); LA size 1.2 (0.74, 1.9); Gender 1.6 (0.68, 3.7); Age 1.02 (0.97, 1.04); Structural heart disease 1.03 (0.51, 3.1). [Individual predictors not explicitly defined. Implied that predictors were analyzed as continuous variables, when possible.]
Pappone 2006[27]	No independent predictors of AF recurrences were found in the ablation group. [Individual predictors not explicitly defined. Implied that predictors were analyzed as continuous variables, when possible.]
Oral 2004[41]	AF duration P=.05; Age, Gender, EF, LAD, Structural heart disease, and Frequency of episodes of AF were nonsignificant (P>.1); Vagotonic AF P=.03. Hazard ratios not reported.
Al Chekakie 2007[42]	Persistent AF 1.1 (0.55, 2.2); AF duration 0.95 (0.89, 1.02), per year; EF <50% 2.7 (1.13, 6.5); LAD >4.2 cm 0.87 (0.47, 1.6); Male 1.25 (0.63, 2.5); Age >65 years 1.4 (0.72, 2.8); Structural heart disease 0.91 (0.45, 1.9); HTN 1.8 (0.87, 3.8); ACE-I 1.3 (0.57, 2.9); ARB 0.17 (0.02, 1.3); Statins 1.10 (0.55, 2.3); ACE-I or ARB 0.94 (0.46, 1.9); ACE-I or ARB and statins 1.02 (0.54, 1.9).
Berruezo 2007[43]	Final model included only LAD (mm) 1.1 (1.06, 1.2), per mm; HTN 2.8 (1.5, 5.4). [Definitions of other analyzed parameters included: Permanent AF, AF duration, per month; EF, per percentage point.
Dixit 2008[44]	No variables (of interest) that were tested in univariable analysis significantly affected long term AF control.
Essebag 2005[45]	At 12 months: Nonparoxysmal AF (vs. paroxysmal) 4.8 (1.42, 16) for AF recurrence; moderate to severe valve regurgitation or stenosis nonsignificant. At 6 months: Nonparoxysmal AF 3.2 (1.05, 10); Valvular heart disease 4.0 (1.00, 16). Noninducibility after ablation included in both models. Sex, age and hypertension tested but not included in final models.
Nilsson 2006[46]	Structural heart disease 2.05 (1.18, 3.6). Other predictors nonsignificant. Only LAD variable defined, >4.0 cm.
Jais 2004[47]	Structural heart disease was analyzed in univariable analysis. Variables (of interest) were not significant on multivariable analysis. No list of included variables was provided.
Liu 2006[48]	Among the variables analyzed, RR reported only for Structural heart disease 2.39 (0.90, 6.3), P=.08; LAD 1.06 (0.97, 1.17), implicitly on a continuous scale.
Dixit 2006[49]	Presence of paroxysmal AF was the only variable that affected (complete freedom from AF at 6 months off AADs])
Oral 2003[50]	Among included variables, only LAD was an independent predictor or recurrent paroxysmal AF, P<.01. No other data. Definitions of variables not reported.
Calò 2006[51]	After adjustment for age, gender, LAD, structural heart disease, type of AF (persistent vs. permanent) and continuation of AAD after 6 months, EF <45% 5.2 (2.0, 13).
Stabile 2006[25]	None of the clinical factors was significant. No other data reported.
Jais 2008[28]	Higher baseline EF only independent predictor of lack of recurrent AF after ablation OR 1.10 (1.01, 1.19).

Table 9. Association between types of AF and recurrence of AF in univariable (unadjusted) analyses

Study	Time, mo	Total N	Paroxysmal, % n/N		Persistent, % n/N		Chronic* % n/N		Comparison	OR (95% CI)	P value
Themistoclakis 2008[31]	41	1298	37%	107/699	22%	65/230	41%	120/369	Persist vs Parox	1.85 (1.41, 2.42)	<.001 (c/w multivariable)
									Chronic vs Parox	2.12 (1.69, 2.67)	<.001 (c/w multivariable)
									Nonparox vs Parox	2.02 (1.64, 2.50)	<.001
Bhargava 2004[54]	15	323	13%	22/174	20%	7/35	22%	25/114	Persist vs Parox	1.58 (0.73, 3.41)	NS
									Chronic vs Parox	1.04 (0.56, 1.92)	NS
									Nonparox vs Parox	1.17 (0.67, 2.02)	NS
Tao 2008[69]	18	249	33%	58/175	30%	22/74			Persist vs Parox	0.85 (0.47, 4.54)	NS
Della Bella 2005[39]	13	234	24%	49/204	42%	25/59			Persist vs Parox	1.76 (1.20, 2.59)	.004
Richter 2006[38]	6	234	33%	54/165	52%	36/69			Persist vs Parox	1.59 (1.16, 2.18)	.004 (c/w multivariable)
Fiala 2008[57]	28	194	34%	20/59	47%	63/135			Persist vs Parox	1.38 (0.92, 2.05)	NS
Fassini 2005[56]	12	187	~31%	~39/126	~44%	~27/61			Persist vs Parox	1.43 (0.97, 2.10)	.07
Zhou 2007[71]	7	148	5%	4/84	11%	7/64			Persist vs Parox	2.30 (0.70, 7.51)	NS
Arentz 2007[52]	15	110	37%	25/67	49%	21/43			Persist vs Parox	1.31 (0.85, 2.02)	NS
Beukema 2005[53]	15	105	25%	13/52	40%	21/53			Persist vs Parox	1.58 (0.89, 2.82)	NS
Nilsson 2006[46]	12	100	~73%	~37/51	~92%	~45/49			Persist vs Parox	1.27 (1.05, 1.53)	.01 (NS multivariable)
Kottkamp 2004[59]	12	100	26%	~21/80	78%	~16/20			Persist vs Parox	3.05 (1.99, 4.67)	<.001
Kistler 2006[58]	6	94	39%	18/46	48%	23/48			Persist vs Parox	1.22 (0.77, 1.95)	NS
Shimano 2008[66]	25	62	21%	9/43	32%	6/19			Persist vs Parox	1.51 (0.63, 3.64)	NS
Marsan 2008[60]	8	57	24%	11/45	67%	8/12			Persist vs Parox	2.73 (1.42, 5.23)	.003
Sra 2007[67]	9	50	22%	7/32	33%	6/18			Persist vs Parox	1.52 (0.60, 3.84)	NS
Metaanalysis		**3545**							**Persist vs Parox**	**1.55 (1.35, 1.79) heterogeneous**	**<.001**
Oral 2006[63]	24	755	23%	~113/490			32%	~85/265	Chronic vs Parox	1.39 (1.10, 1.77)	.007
Pappone 2001[64]	10	251	15%	27/179			32%	23/72	Chronic vs Parox	2.12 (1.30, 3.44)	.002
Miyazaki 2008[62]	6	86	21%	13/61			40%	10/25	Chronic vs Parox	1.88 (0.95, 3.71)	.07
Metaanalysis		**2448**							**Chronic vs Parox**	**1.69 (1.29, 2.21) heterogeneous**	**<.001**
Verma 2005[32]	16	700	14%	38/274		27%	114/426		Nonparox vs Parox	1.93 (1.38, 2.70)	<.001 (NS multivariable)
Cha 2008[34]	12	432	26%	65/247		30%	56/185		Nonparox vs Parox	1.15 (0.85, 1.56)	NS (c/w multivariable)
Chugh 2005[55]	13	349	13%	30/227		25%	31/122		Nonparox vs Parox	1.92 (1.22, 3.02)	.005
Tang 2006[68]	13	263	23%	45/199		27%	17/64		Nonparox vs Parox	1.17 (0.73, 1.90)	NS
Cheema 2006[40]	26	200	63%	58/92		80%	86/108		Nonparox vs Parox	1.26 (1.05, 1.52)	.01 (c/w multivariable)
Verma 2007[70]	12	200	14%	17/120		23%	18/80		Nonparox vs Parox	1.59 (0.87, 2.89)	NS
Proclemer 2008[65]	25	144	13%	12/93		37%	19/51		Nonparox vs Parox	2.89 (1.53, 5.46)	.001
Dixit 2008[44]	12	103	21%	16/75		43%	12/28		Nonparox vs Parox	2.01 (1.09, 3.70)	.02 (NS multivariable)

Study	Time, mo	Total N	Paroxysmal, % n/N		Persistent, % n/N		Chronic* % n/N	Comparison	OR (95% CI)	P value
Essebag 2005[45]	12	102	26%	~16/60	55%	~23/42		Nonparox vs Parox	2.05 (1.24, 3.39)	.005 (c/w multivariable)
Martinek 2007[61]	6	100	31%	18/59	49%	20/41		Nonparox vs Parox	1.60 (0.97, 2.63)	.06
Liu 2006[48]	13	100	31%	23/75	28%	7/25		Nonparox vs Parox	0.91 (0.45, 1.87)	NS (c/w multivariable)
Dixit 2006[49]	6	82	34%	20/58	70%	16/23		Nonparox vs Parox	2.02 (1.29, 3.15)	.002 (c/w multivariable)
Metaanalysis		**4394**						**Nonparox vs Parox**	**1.59 (1.38, 1.82) heterogeneous**	**<.001**

*or permanent

Table 10. Study characteristics of approaches to RFA

Author Year Country UI	Group 1	Group 2	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Randomized controlled trials													
Arentz 2007[52] Germany 17562956	PVI (ostia)	WACA	irrigated	yes	no	110	2004-2006	61	56	75	4.0	nd	5.5
Oral 2003[50] US 14557355	PVI (ostia)	WACA + MIL + posterior line	4 or 8 mm	yes	no	80	nd	100	52	78	4.0	56	7
Nilsson 2006[46] Denmark 16923426	PVI (ostia)	WACA	5 mm irrigated (ostia); 3.5 mm irrigated (WACA)	yes	yes	100	2002-2004	51	56	71	nd	nd	4.1
Karch 2005[74] Germany 15927974	PVI (ostia)	WACA	4 mm cooled; 8 mm; irrigated	yes (not in WACA)	no	100	2002-2003	89	60	64	4.7	63	4.5
Liu 2006 China 17062959[75]	Stepwise PVI (add roof line if inducible; then add MIL if inducible)	WACA	Both irrigated: 4 mm in stepwise; 3.5 mm in WACA	yes	yes in stepwise	110	nd	100	58	66	3.8	64	5
Willems 2006[80] Germany 16782716	PVI (antrum?) + CTI	PVI (antrum?) + CTI + LA linear lines	open irrigated	yes	no	62	nd	0	59	nd	4.8	≥40	6
Pappone 2004[33] Italy 15520310	WACA	WACA + posterior LA lines + MIL	8 mm	yes (?)	no	560	2002-2003	63	56	52	3.95	nd	7.2
Fassini 2005[56] Italy 1630289	PVI	PVI + mitral isthmus line (MIL)	irrigated	yes	no	187	nd	67	55	80	4.26	56	nd

Author Year Country UI	Group 1	Group 2	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Haissaguerre 2004[72] France 15184286	PVI + (CTI)	PVI + CTI + MIL	4 mm irrigated	yes	yes	70	nd	nd	53	74	4.3	67	5.1
Sheikh 2006[78] US 17318445	PVI (ostia)	PVI + superior PV line + LIPV to MV annulus line	nd	yes	no	100	nd	100	59	63	4.1	54	nd
Hocini 2005[73] France 16344401	PVI (antrum) + Cavotricuspid isthmus ablation (CTI)	PVI (antrum) + CTI + roof line	4 mm irrigated	yes	yes	90	2003	100	55	79	4.1	67	5.25
Wazni 2003[79] US; Germany; Italy 14610012	PVI (ostia-antrum)	PVI (ostia-antrum) + CTI	4 mm cooled	yes	no	108	2000-2002	59 (must have had 1 AFL episode)	55	81	4.2	53	5.5
Wang 2008[81] China 18442966	WACA	WACA + SVC	3.5 mm irrigated	yes	no	106	2006	100	66	55	3.7	54	3.6
Liu 2006[48] China 17239094	WACA, then closing gaps in pts with residual PV conduction (aggressive)	WACA, then PVI inside circular lines in pts with residual PV conduction (modified)	3.5 mm irrigated	yes	no	100	2004-2005	75	57	69	3.9	65	6.7

Author Year Country UI	Group 1	Group 2	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Oral 2004[76] US 15505091	WACA + posterior LA lines + MIL	WACA + posterior LA lines + MIL + additional lines	8 mm	yes	yes	60	nd	100 (AF not terminated or inducible after WACA + posterior LA lines + MIL)	55	83	4.3	59	7
Oral 2005[77] US 16253904	WACA + posterior LA (or roof line) + MIL + within the circles but outside the PV	non-encircling LA roof, septum, anterior wall, MIL	8 mm	yes in WACA	yes	80	nd	0	54	84	4.8	53	4.5
Non-randomized comparative trials													
Mantovan 2005[82] Italy 16403059	PV antrum ablation (PVI not checked)	PV antrum ablation + assessment of PVI with further ablation for residual potentials	3.5 mm irrigated	see previous cells	no	60	nd	65	54	85	4.3	60	4.2
Pak 2008[83] Korea 18284506	Selective PVI (in PV with triggering AF)	4-PV PVI	5 mm	yes	yes	77	nd	100	52	74	3.9	57	5
Prospective cohorts													
Arruda, 2007[84] US 17850288	PVI (antrum) or PVI (antrum) + SVC isolation		4 mm, 8 mm or irrigated	yes	yes	407	nd	51	55	79	nd	nd	6

Author Year Country UI	Group 1	Group 2	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Shah 2007[85] Switzerland 17655668	PVI (ostia) + posterior LA line and/or MIL as needed (persistent or permanent AF; failed PVI)	techniques in group 2 + CTI as needed in pts with hx of AFL or AFL during ablation	irrigated	yes	no	188	nd	72	56	81	4.2	nd	6
Retrospective cohorts													
Okada 2007[91] Japan 17397672	PVI (ostia)	circumferential PV antrum ablation	8 mm	yes	yes	77	nd	100	58	84	3.41	67	5
Schwartzman 2003[92] US 14574043	PVI (ostia)	PVI (antrum); WACA	nd	yes	yes	112	nd	100	55	81	4.0	56	nd
Yamane 2007[95] Japan 17457004	PVI (ostia)	PVI (antrum)	8 mm	yes	yes	187	nd	66	53	77	3.9	nd	nd
Richter 2008[96] 2006[38] Austria 18328850 17038349	PVI	WACA	8 mm; 4 mm	yes	yes	234	2002-04 (group 1); 2004 (group 2)	70	57	72	4.5	61	6.1
Cheema 2006[40] USA 17019636	PVI (ostia) + Cavotricuspid isthmus ablation (CTI)	WACA+ CTI + mitral isthmus line + posterior LA line + “figure of 8”	irrigated 4 mm (ostia); 8 mm (WACA)	yes in ostial PVI	no	200	nd	46	56	66	4.4	59	6.4
Dong 2005[86] China 16117858	PVI (ostia)	WACA	irrigated tip in WACA	yes	no	151	nd	86	57	72	3.78	67	6.9

Author Year Country UI	Group 1	Group 2	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Mansour, 2004[89] USA 15149421	PVI (ostia)	WACA	nd	yes	no	80	2000-2002	81	54	85	4.0	nd	nd
Tamborero 2005[93] Spain 16311935	PVI (ostia)	WACA	4 mm in PVI; 8 mm in CPVA	yes in PVI	no	73	nd	74	51	78	4.0	55	5.6
Katritsis 2008[97] Greece 18363086	PVI (ostia or antrum)	WACA	4 mm in PVI; irrigated in WACA	yes	no	90	nd	100	55	83	4.1	nd	nd
Jais 2004[47] France 15520313	PVI (ostia) + CTI	PVI (ostia) + CTI+MIL	4 mm irrigated	yes	no	200	2001 (group 1); 2002 (group 2)	100	55	87	4.6	71	6
Verma 2007[70] USA 17338763	PVI (antrum) + SVC isolation	PVI (antrum)+ SVC isolation + CFAE ablation in anterior LA/septum	8 mm	yes	yes	200	nd	40	57	63	4.3	53	5.2
Lemola 2006[88] US 16843185	WACA+ roof line + MIL	CFAE ablation	8 mm	no	yes in CFAE ablation	84	nd	58	57	83	4.3	57	6.5
Hachiya 2007[87] Japan 17286569	WACA	WACA + ablation of adenosine induced potentials	8 mm	yes	yes	252	2003-2005	78	55	83	4.14	nd	nd
Matsuo 2007[90] Japan 17506857	PVI (ostia or antrum)	PVI + ablation of adenosine induced potentials	8 mm	yes	yes	148	2003-2006	65	53	86	3.8	66	4.7

Author Year Country UI	Group 1	Group 2	Catheter Tip	PVI (yes/no)	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Walczak 2006[94] Poland 16444625	Selective PVI (0-3 PVs)	non-selective PVI (4 or 5 PVs)	nd	yes	yes	80	nd	70	48	64	3.8	64	nd
Pappone 2004[36] Italy 14707026	WACA + posterior LA lines + MIL	WACA + posterior LA lines + MIL + vagal denervation	nd	nd	nd	297	1999-2002	100	49	nd	3.9	58	7.0
Kettering 2008[98] Germany 18507536	PVI	PVI (exclude areas near esophagus)	3.5 mm irrigated	yes	no	43	2004-2007	100	62	65	nd	59	nd

*WACA, CFAE, other lines, ganglionic plexi, etc.

Table 11. Outcomes comparing different ablation approaches and study quality

Author Year Country UI	Group 1	Group 2	N Analyzed Group 1	N Analyzed Group 2	Outcome	Followup	Results Group 1	Results Group 2	P Between	Quality
Randomized controlled trials										
Arentz 2007[52] Germany 17562956	PVI (ostia)	WACA	55	55	freedom from AF (no AAD, after 1 ablation)	15 mo	49%	67%	≤0.05	Fair
Oral 2003[50] US 14557355	PVI (ostia)	WACA + MIL + posterior line	40	40	absence of symptomatic AF off AAD (no repeat procedure)	6 mo	67%	88%	0.02 (log rank)	Fair
					repeat ablation		17.5%	0%	nd	
Nilsson 2006[46] Denmark 16923426	PVI (ostia)	WACA	54	46	freedom from symptomatic AF or left AT (not on AADs; 74 pts had 1 reablation)	12 mo	31%	57%	0.02	Fair
Karch 2005[74] Germany 15927974	PVI (ostia)	WACA	50	50	freedom from atrial tachyarrhythmia (AT) (no repeat procedure)	6 mo	54%	34%	nd	Fair
					freedom from AT (with repeat procedure)	6 mo	66%	42%	0.02	
					repeat ablation procedure within	6 mo	16%	24%	NS	
Liu 2006 China 17062959[75]	Stepwise PVI (add roof line if inducible; then add MIL if inducible)	WACA	55	55	no AT 3-9 mo after the last procedure (no AADs)	9 mo	78%	84%	0.63	Poor
					repeat ablation	3-5 mo of initial procedure	13%	9%	nd	
Willems 2006[80] Germany 16782716	PVI (antrum) + CTI	PVI (antrum) + CTI + LA linear lines	30	32	SR (Lack of any symptomatic or asymptomatic AF episode (>30 s); some pts on AADs(?))	17 mo	20%	69%	0.0001	Fair

Author Year Country UI	Group 1	Group 2	N Analyzed Group 1	N Analyzed Group 2	Outcome	Followup	Results Group 1	Results Group 2	P Between	Quality
Pappone 2004[33] Italy 15520310	WACA	WACA + posterior LA lines + MIL	280	280	freedom from symptomatic incessant AT (39 pts had reablation for AT)	12 mo	90%	96%	0.005	Fair
					freedom from recurrent AF (3 pts had reablation for AF)	12 mo	87% (est.)	88% (est.)	0.57	
Fassini 2005[56] Italy 1630289	PVI	PVI + mitral isthmus line (MIL)	92	95	stable SR (after this procedure)	12 mo	53 ± 5%	71 ± 5%	0.01	Fair
					continual use of AAD	12 mo	56%	50%	NS	
Haissaguerre 2004[72] France 15184286	PVI + CTI	PVI + CTI + MIL	35	35	freedom from AF or flutter (no AAD; included reablation)	7 mo	74%	83%	nd	Fair
Sheikh 2006[78] US 17318445	PVI (ostia)	PVI + superior PV line + LIPV to MV annulus line	50	50	SR (no AAD; 3 had AFL ablation)	9 mo	28%	28%	NS	Poor
Hocini 2005[73] France 16344401	PVI (antrum) + Cavotricuspid isthmus ablation (CTI)	PVI (antrum) + Cavotricuspid isthmus ablation (CTI) + roof line	45	45	no atrial arrhythmia and off AAD	14 mo	69%	87%	0.04	Poor
Wazni 2003[79] US; Germany; Italy 14610012	PVI (ostia-antrum)	PVI (ostia-antrum) + CTI	59	49	no AF recurrence	>8 wk	90%	86%	NS	Fair
			53	42	no AF recurrence (9% had repeat procedure; 3% on AADs)	12 mo	100%	100%	NS	
Wang 2008 China 18442966	WACA	WACA + SVC	54	52	freedom from recurrent AT (after 1 procedure; ? some on AADs)	4.6 mo (12 mo?)	78%	81%	0.75	Poor

Author Year Country UI	Group 1	Group 2	N Analyzed Group 1	N Analyzed Group 2	Outcome	Followup	Results Group 1	Results Group 2	P Between	Quality
			54	52	freedom from recurrent AT (included reablation; some on AADs)	12 mo	93%	94%	0.73	
Liu 2006[48] China 17239094	WACA, then closing gaps in pts with residual PV conduction (aggressive)	WACA, then PVI inside circular lines in pts with residual PV conduction (modified)	50	50	no AT beyond 3 mo after initial procedure (no AADs)	13 mo (?)	82%	58%	0.01	Fair
Oral 2004[76] US 15505091	WACA + posterior LA lines + MIL	WACA + posterior LA lines + MIL + additional lines	30	30	freedom from AF (no AADs; no additional reablation)	6 mo	67%	86%	0.05	Fair
Oral 2005[77] US 16253904	WACA + posterior LA (or roof line) + MIL + ablation of amplitude >0.2 mv within the circles but outside the PV	non-encircling LA roof, septum, anterior wall, mitral isthmus and annulus lines	40	40	freedom from AF or AFL, no AAD, single procedure	10 mo	48%	33%	0.20	Poor
Nonrandomized comparative trials										
Mantovan 2005[82] Italy 16403059	PV antrum ablation (PVI not checked)	PV antrum ablation + assessment of PVI with further ablation for residual potentials	30	30	stable SR	15.4 mo	57%	83%	0.024	Poor
					SR (no AADs; 8 pts had reablation)	15.4 mo	13%	53%	0.002	
Pak 2008 Korea 18284506	Selective PVI (in PV with triggering AF)	4-PV PVI	42	35	freedom from recurrent AF (after 1 ablation, not on AAD?)	39 mo	62%	74%	NS	Poor
			42	35	reablation		31%	23%	nd	

Author Year Country UI	Group 1	Group 2	N Analyzed Group 1	N Analyzed Group 2	Outcome	Followup	Results Group 1	Results Group 2	P Between	Quality
Prospective cohort										
Arruda, 2007[84] US 17850288	PVI (antrum) or PVI (antrum) + SVC isolation		407		AF recurrence	14.8 mo	16%			Poor
Shah 2007[85] Switzerland 17655668	PVI (ostia) + posterior LA line and/or MIL as needed (persistent or permanent AF; failed PVI)	techniques in group 2 + CTI as needed in pts with hx of AFL or AFL during ablation	113	75	stable SR, no AF or AFL, no AAD; 62 pts had reablation for AF or AFL	30	79%	82%	NS	Poor
Retrospective cohort										
Okada 2007[91] Japan 17397672	PVI (ostia)	circumferential PV antrum ablation	50	27	AF free (no AAD)	6 mo	50%	89%	<0.001	Poor
Schwartzman 2003[92] US 14574043	PVI (ostia)	PVI (antrum); WACA	47	42; 23	no detectable AF (not on type 1 or III AAD)	6 mo	47%	69%; 87%	<0.05	Poor
Yamane 2007[95] Japan 17457004	PVI (ostia)	PVI (antrum)	44	80	freedom from AF after 3 mo in pts with PAF after initial procedure (? on AADs)	2.8 yes (ostia); 1.8 yes (antrum)	58.7%	61.4%	NS	Poor
			26	37	freedom from AF after 3 mo in pts with persistent AF after initial procedure	2.8 yes; 1.8 yes	32.4%	36.2%	NS	
			44	80	freedom from AF after 3 mo in pts with PAF after final procedure	2.8 yes; 1.8 yes	76%	93%	0.015	
			26	37	freedom from AF after 3 mo in pts with persistent AF after final procedure	2.8 yes; 1.8 yes	48%	78%	0.032	

Author Year Country UI	Group 1	Group 2	N Analyzed Group 1	N Analyzed Group 2	Outcome	Followup	Results Group 1	Results Group 2	P Between	Quality
Richter 2008[96] 2006[38] Austria 18328850 17038349	PVI	WACA ± CTI (?)	83	151	freedom from AF (?AADs)	6 mo (median)	64%	60%	nd	Poor
Cheema 2006[40] USA 17019636	PVI (ostia) + (CTI)	WACA+ CTI + other lines	87	113	no symptomatic AF 6 mo prior to last f/u, exclude 3 mo of blanking period (single procedure; no AAD)	26 mo	22%	32%	nd	Poor
Dong 2005[86] China 16117858	PVI (ostia)	WACA	68	83	stable SR (no AAD)	12.7 mo (ostia); 7.2 mo (WACA)	60%	82%	<0.001	Poor
Mansour, 2004[89] USA 15149421	PVI (ostia)	WACA	40	40	freedom from AF at 21 mo (PVI group) and 11 mo (CPVA group)		60%	75%		Poor
			40	40	repeat ablation		15%	10%		
Tamborero 2005[93] Spain 16311935	PVI (ostia)	WACA	32	41	freedom from AF recurrence	15 mo	72%	76%	NS	Poor
Katritsis 2008 Greece 18363086	PVI (ostia or antrum)	WACA	41	49	Freedom from AF; symptom improvement	12 mo	61%	67%	0.5	Poor
Jais 2004[47] France 15520313	PVI (ostia) + CTI	PVI (ostia) + CTI+MIL	100	100	arrhythmia free, no AAD (included pts with repeat ablations)	12 mo	69%	87%	0.002	Poor

Author Year Country UI	Group 1	Group 2	N Analyzed Group 1	N Analyzed Group 2	Outcome	Followup	Results Group 1	Results Group 2	P Between	Quality
Verma 2007[70] USA 17338763	PVI (antrum) + SVC isolation	PVI (antrum)+ SVC isolation + CFAE ablation in anterior LA/septum	100	100	no AF or atypical AFL 2 mo post procedure (no AAD)	12 mo	80%	85%	0.054	Poor
Lemola 2006[88] US 16843185	WACA+ roof line + MIL	CFAE ablation	42	42	no AF (no AAD, single ablation)	9 mo	67%	71%	0.6	Poor
Hachiya 2007[87] Japan 17286569	WACA	WACA + ablation of potentials induced by adenosine	170	82	no AF (no AAD)	6 mo	60%	73%	0.04	Poor
Matsuo 2007[90] Japan 17506857	PVI (ostia or antrum)	PVI + ablation of potentials induced by adenosine	94	54	freedom from AF after single procedure (no AAD)	20 mo	60%	80%	<0.05	Poor
			94	54	maintenance of NSR (no AAD) after last procedure	20 mo (?)	90%	91%		
			94	54	repeat ablation	5.6 mo	38%	17%	<0.05	
Walczak 2006[94] Poland 16444625	Selective PVI (0-3 PVs)	non-selective PVI (4 or 5 PVs)	60	20	effective rhythm control (no AT lasting >30 s) (31 on AADs)	17 mo	90%	80%	nd	Poor
Pappone 2004[36] Italy 14707026	WACA + posterior LA lines + MIL	WACA + posterior LA lines + MIL + vagal denervation	195	102	freedom from recurrent AF	12 mo	85%	99%	<0.001	Poor
Kettering 2008 Germany 18507536	PVI	PVI (exclude areas near esophagus)	21	22	freedom from recurrent AF	6 mo	81%	82%	1.00	Poor

Table 12. Study characteristics of technical issues related to RFA

Author Year Country UI	Group 1	Group 2	Additional RFA	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Randomized controlled trials												
Dixit 2006[49] 16879626	PVI - 8 mm	PVI – Closed irrigated tip	No	yes	82	2003-2005	72	57	73	nd	nd	5.2
Dixit 2008 US[44a] 18242535	PVI - 8 mm	PVI – Closed irrigated tip	Simulation protocol to elicit non-PV triggers, which also were targeted	yes	91	2003-2005	73	57	72	nd	nd	5.2
Marrouche 2007[101] Germany 17490437	PVI – 8 mm with ICE and monitoring of microbubbles	PVI – Open irrigated tip with ICE and monitoring of microbubbles	Electrical isolation of the SVC	no	53	nd	62	54	75	4.3	nd	5.0
Kanj 2007[99] USA and Italy 17433955	PVI - 8 mm	Group 2: PVI – Open irrigated tip 30-50 W Group 3: PVI - Open irrigated tip 10-35 W	Electrical isolation of the SVC	no	180	nd	nd	60	81	4.2	54	6.0
Wang, 2007[104] China 17522081	PVI - no intraoperative post procedure observation (Obs) time	Group 2: PVI – 30 min Obs time Group 3: PVI – 60 min Obs time	Circumferential RFA of PV antra	no	90	2006	100	56	57	3.8	nd	4.2

Author Year Country UI	Group 1	Group 2	Additional RFA	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Rotter 2005[102] France 15741228	PVI guided by 3D electroanatomic mapping	PVI guided by conventional fluoroscopy	Roof-line (LA) if persistent or inducible sustained AF	yes	72	nd	nd	52	88	4.3	66	nd
Tondo, 2005[103] Italy 15683472	PVI guided by 3D electroanatomic mapping	PVI guided by conventional fluoroscopy	WACA; CTI	no	60	nd	63	56	52	4.0	57	nd
Kistler 2008[100] UK 18931059	PVI guided by a 3D electroanatomic mapping + CT integration	PVI guided by fluoroscopy + CT registration	WACA	no	80	2006	59	56	nd	nd	nd	6.3
Tang 2008[122] China 18364135	PVI guided by a 3D electroanatomic mapping + CT integration	PVI guided by a 3D electroanatomic mapping	Linear ablation of the cavotricuspid isthmus	no	81	nd	100	59.8	67	3.8	61	3.1
Sra 2007[67] US 17284262	PVI guided by fluoroscopy + CT registration	PVI guided by conventional fluoroscopy	WACA	no	50	nd	64	55	82	4.5	47	3.5
Nonrandomized comparative trials												
Matiello 2008[37] Spain 18515285	Group 1: PVI – 8 mm	Group 2: PVI – Closed irrigated tip (30 W) Group 3: PVI – Closed irrigated tip (40 W)	Mitral isthmus ablation	no	221	nd	62	52	76	4.1	nd	nd
Nilsson 2006[107] Denmark 17043070	PVI – 5mm Open irrigated tip 45 W	PVI – 5mm Open irrigated tip 30 W	No	no	90	nd	57 (45 W) vs. 71 (30 W)	55 (45 W) vs. 51 (30 W)	67 (45 W) vs. 80 (30 W)	nd	nd[c]	4.6 (45 W) vs. 6.4 (30 W)

Author Year Country UI	Group 1	Group 2	Additional RFA	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Martinek 2007[61] Austria 17897124	PVI - conventional electro-anatomic mapping	PVI - multislice CT integration with electroanatomic mapping	WACA or RFA of CFAEs	no	100	2005	59	56	85	4.8	55	6.5
Estner 2006[106] Germany 16831837	PVI guided by conventional fluoroscopy	PVI guided by 3D electroanatomic mapping (without 3D geometric reconstruction)	No	no	64	nd	94 (PVI) vs. 88	59	75	4.7	33	5.6
Piorkowski 2008[105] Germany 18684284	PVI using a manually controlled steerable sheath	PVI using a conventional nonsteerable transseptal sheath	Roof line and mitral line	no	166	Group 1: Jan 2006 and October 2006 Group 2: October 2004 and December 2005	80	55	73	3.7	61	4.4
Retrospective cohorts												
Yamada, 2006[110] Japan 16607049	PVI – 8 mm	PVI – 4 mm (nd)	Gaps between peri-ostial ablation sites (only for 8 mm catheter)	no	108	nd	100	57	90	3.5	66	4.0
Marrouche, 2003[108] USA 12756153	PVI with no ICE	Group 2: PVI with ICE but no monitoring of micro-bubble Group 3: PVI with ICE and monitoring of micro-bubble	No	no	315	2000-2002	51	54	78	4.2	nd	6.0

Author Year Country UI	Group 1	Group 2	Additional RFA	Checked inducibility (yes/no)	Total $N_{enrolled}$	Enroll-ment Years	% PAF	Mean Age, yr	Male, %	Mean LAD, cm	Mean LVEF, %	Symptom duration, year
Yamane, 2002[111] France 11955852	PVI guided by mapping the earliest PV potential	PVI guided additionally by electrogram polarity reversal	No	yes	157	nd	100	54	60	3.7	nd	4.7
Saad 2003[109] USA 12693885	PVI guided by a circular mapping catheter	PVI guided by a 3D electroanatomic mapping system	No	no	335	nd	52	54	78	4.2	53	5.2
Katritsis 2008[97] Greece 18363086	Ostial or antral PVI ; Ablation time < median	Ostial or antral PVI ; Ablation time > median	WACA	nd	90	nd	100	55	83	4.1	nd	nd

a. Dixit 2008 is a subsequent study of Dixit 2006 with 1 year followup data and including slightly more patients. The patients were largely overlapped between these two studies.
b. CHF: 4.4% (45 W) vs. 9% (30 W)
c. No breakdown patient characteristics by groups was reported

Table 13. Outcomes comparing different technical issues related to RFA

Study, Year UI	Description		No. Analyzed		Outcome	Mean Follow-up, mo	Metric/ Units	Results			Quality
	Group 1	Group 2	Group 1	Group 2				Group 1	Group 2	P Between	
Randomized controlled trials of 8mm vs. irrigated tip											
Dixit 2006[49] 16879626	PVI - 8 mm	PVI – Closed Irrigated tip	41[a]	40	Complete freedom and/or >90% reduction in AF burden on or off previously ineffective AADs	6	rate	78%	70%	NS	Good
Dixit 2008 US[44] 18242535	PVI - 8 mm	PVI – Closed irrigated tip	41[a]	50	Complete freedom and/or >90% reduction in AF burden on or off previously ineffective AADs	12	rate	78%	70%	NS	Good
Kanj 2007[99] (comparison 1) USA and Italy 17433955	PVI - 8 mm	PVI – Open Irrigated tip 30-50 W	59	61	Freedom from atrial arrhythmia off AAD	6	rate	79%	82%	0.04[c]	Fair
Kanj 2007[99] (comparison 2) USA and Italy 17433955	PVI - 8 mm	PVI – Open Irrigated tip 10-35 W	59	60	Freedom from atrial arrhythmia off AAD	6	rate	79%	68%	0.04[c]	Fair
Marrouche 2007[101] Germany 17490437	PVI – 8 mm	PVI – Open Irrigated tip	27	26	Recurrence of atrial arrhythmia[d]	14	rate	19%	22%	NS	Fair

Study, Year UI	Description		No. Analyzed		Outcome	Mean Follow-up, mo	Metric/ Units	Results			Quality
	Group 1	Group 2	Group 1	Group 2				Group 1	Group 2	P Between	
Randomized controlled trials of different tip outputs											
Kanj 2007[99] (comparison 3) USA and Italy 17433955	PVI - Open Irrigated tip 30-50 W	PVI – Open Irrigated tip 10-35 W	61	60	Freedom from atrial arrhythmia off AAD	6	rate	82%	68%	0.04[c]	Fair
Randomized controlled trials of different imaging Modalities											
Rotter 2005[102] France 15741228	PVI guided by 3D electroanatomic mapping	PVI guided by conventional fluoroscopy	35	37	Freedom from arrhythmia	6.5	rate	74%	78%	NS	Fair
Tondo, 2005[103] Italy 15683472	PVI guided by 3D electroanatomic mapping	PVI guided by conventional fluoroscopy	30	30	AF recurrence	7	rate	10%	20%	nd	Poor
Kistler 2008[100] UK 18931059	PVI guided by a 3D electroanatomic mapping + CT integration	PVI guided by fluoroscopy + CT registration	38	39	Freedom from AF or AT	6	rate	50%	56%	NS	Fair
					Recurrent AF or AT	12	rate	58%	51%	NS	
Tang 2008[122] China 18364135	PVI guided by a 3D electroanatomic mapping + CT integration	PVI guided by a 3D electroanatomic mapping	42	39	No recurrence of symptomatic and asymptomatic AT	12	rate	79%	74%	NS	Fair
Sra 2007[67] US 17284262	PVI guided by fluoroscopy + CT registration	PVI guided by conventional fluoroscopy	25	25	Freedom from arrhythmia	9	rate	84%	64%	nd	Poor
Randomized controlled trials of different Observation times											
Wang, 2007[104] (comparison 1) China 17522081	PVI - no intraoperative post procedure observation (Obs) time	PVI – 30 min Obs time	18	21	Any AT (symptomatic or asymptomatic) lasting >30 secs (documented)	6	rate	39%	14%	.03[g]	Fair

Study, Year UI	Description		No. Analyzed		Outcome	Mean Follow-up, mo	Metric/ Units	Results			Quality
	Group 1	Group 2	Group 1	Group 2				Group 1	Group 2	P Between	
Wang, 2007[104] (comparison 2) China 17522081	PVI - no intraoperative post procedure observation (Obs) time	PVI – 60 min Obs time	18	21	Any AT (symptomatic or asymptomatic) lasting >30 secs (documented)	6	rate	39%	5%	.03[g]	Fair
Nonrandomized comparative trials											
Matiello 2008[37] Spain 18515285	Group 1: PVI – 8 mm	PVI – Closed irrigated tip (30-40 W)	90	131	Arrhythmia free after a single procedure, on or off AADs.	12	rate	53%	49%	nd	Poor
Matiello 2008[37] Spain 18515285	Group 2: PVI – Closed irrigated tip (30 W)	Group 3: PVI – Closed irrigated tip (40 W)	42	89	Arrhythmia free after a single procedure, on or off AADs.	12	rate	35%	55%	nd	Poor
Nilsson 2006[107] Denmark 17043070	PVI – 5 mm irrigated tip 45 W	PVI – 5 mm irrigated tip 30 W	45	45	Stable SR with no symptomatic recurrent AF	15	rate	76%	74%	NS	Poor
					No need additional AAD	15	rate	56%	54%	NS	
Martinek 2007[61] Austria 17897124	PVI - conventional electro-anatomic mapping	PVI - multislice CT integration with electroanatomic mapping	53	47	Full success: free of arrhythmias without class IC or class III AAD	6	rate	49%	77%	nd	Poor
					No symptomatic recurrences, on AAD	6	rate	19%	9%	nd	
					Full success + success on AAD	6	rate	68%	85%	.02[h]	
Estner 2006[106] Germany 16831837	PVI guided by conventional fluoroscopy	PVI guided by 3D electroanatomic mapping (without 3D geometric reconstruction)	32	32	Freedom from recurrence of symptomatic AF	10.0 (fluoroscopy) vs. 9.5 (3D)	rate	87%	90%	nd	Poor
					Sinus rhythm	10.0 (fluoroscopy) vs. 9.5 (3D)	rate	68%	74%	NS	
					Asymptomatic AF	10.0 (fluoroscopy) vs. 9.5 (3D)	rate	19%	16%	NS	

Study, Year UI	Description		No. Analyzed		Outcome	Mean Follow-up, mo	Metric/ Units	Results			Quality
	Group 1	Group 2	Group 1	Group 2				Group 1	Group 2	P Between	
Piorkowski 2008[105] Germany 18684284	PVI using a manually controlled steerable sheath	PVI using a conventional nonsteerable transseptal sheath	79	83	AF recurrence (on or off AAD)	6	rate	24%	42%	0.0009	Poor
Retrospective cohorts											
Yamada, 2006[110] Japan 16607049	PVI – 8 mm	PVI – 4 mm (nd)	61	47	Freedom from recurrence (no explicit definition; after multiple procedure)	6	rate	84%	66%	<.05	Poor
Marrouche, 2003[108] USA (comparison 1) 12756153	PVI guided by circular mapping alone with no ICE	PVI with ICE (with or without monitoring of microbubbles) (group 2+3)	56	259	Freedom from recurrent AF	21 (no ICE) vs. 11 (ICE)	rate	80%	87%	.01	Poor
Marrouche, 2003[108] USA (comparison 2) 12756153	PVI with ICE but no micro-bubble	PVI with ICE and micro-bubble	107	152	Chronic success (not defined)	14 (no micro-bubble) vs. 9 (micro-bubble)	rate	80%	90%	.01	Poor
Yamane, 2002[111] France 11955852	PVI guided by mapping the earliest PV potential	PVI guided additionally by electrogram polarity reversal mapping	113	44	Free from AF (not explicitly defined)	9	rate	42%	39%	NS[j]	Poor
Saad 2003[109] USA 12693885	PVI guided by a circular mapping catheter	PVI guided by electroanatomic mapping	264	71	Cure of AF after the last procedure without AAD (not explicitly defined)	6	rate	92%	30%	nd	Poor
Katritsis 2008[97] Greece 18363086	Ostial or antral PVI ; Ablation time < median	Ostial or antral PVI ; Ablation time > median	45	45	Freedom from AF	12	rate	49%	80%	0.002	Poor

a. Excluding patient who died from atrio-esophageal fistula. Dixit 2008 is a subsequent study of Dixit 2006 with 1 year followup data and including slightly more patients. The patients largely overlapped between these two studies.
b. Patients with recurrent AF during the 2-mon period were cardioverted
c. P-value from chi-square test comparing 3 groups (8mm, irrigated 30-50 W, and irrigated 10-35 W)
d. 2 patients in each groups had 2nd procedure
e. Implied blanking period based on late recurrence (14 mo) rates were lower than early recurrence (8 wk) rates.
f. Patients with recurrent AF during the 2-mo period were cardioverted
g. P-value from chi-square test comparing 3 groups (no observational time, 30-min, and 60-min observational time)
h. Non-concurrent comparison (first 53 patients compared with second 47 patients)
i. Non-concurrent comparison (patients enrolled 2002-2004 compared with patients enrolled after 2004)
j. Non-concurrent comparison (first 113 patients compared with second 44 patients)

Table 14. Adverse events (extraostial PVI, cooled- or irrigated-tip)

Author Year UI	F/up, mo	PV Stenosis, no/N (%)	Cardiac Tamponade[a], no/N (%)	Stroke or [TIA], no/N (%)	Atrio-esophageal Fistula, no/N (%)	Peripheral Vascular Complication, no/N (%)	30-Day Mortality, no/N (%)	Other Major AE, no/N (%)	
Wang 2008[112] 18256124	nd		4/452 (0.9%)	2/452 (0.4%)		2/452 (0.4%)[b] 2/452 (0.4%)[c]			
Khaykin 2004[113] 15851113	18	3/336 (0.9%)[d]	4/336 (1%)	1/336 (0.3%) [1/336 (0.3%)]					
Tang 2006[68] 17235682	13	2/263 (0.8%)[e]	4/263 (2%)	3/263 (1%)				Pneumothorax	1/31 (3%)
								Cardiac arrest	1/232 (0.4%)
Tao 2008[69] 18855350	18.2	0/249	0/249	[2/249 (0.8%)	0/249	1/249 (0.4%)[f]	0/249		
Forleo 2007[114] I7636302	23	2/221 (0.9%)[e]	4/221 (2%)	2/221 (0.9%) [2/221 (0.9%)]					
Shah 2007[85] 17655668	30	3/188 (2%)[g]	3/188 (2%)					Embolic events	1/188 (0.5%)
Rotter 2005[115] 16403060	nd		2/181 (1%)						
Piorkowski 2008[105] 18684284	6	0/166	2/166 (1%)		0/166	3/166 (2%)		Embolic event	1/166 (0.6%)
Matiello 2008[37] 18515285	Intra-procedual	0/159	0/159	[3/159 (2%)]				Pericarditis	4/159 (3%)
								Transient ST elevation	3/159 (2%)
Jais 2008[28] 19029470	12	1/155 (0.6%)[hi]	2/155 (1%)[i]	0/155[i]	0/155[i]	0/155[i]	0/155[i]		
Bertaglia 2005[116] 15869666	19		2/143 (1%)	[1/143 (0.7%)]		1/143 (0.7%)[c]		Phrenic nerve paralysis	1/143 (0.7%)
								AV block	1/143 (0.7%)
Jais 2004[47] 15520313	12	0/136[j]	4/100 (4%)					Embolic events	0/136[f]
								Coronary artery events	0/136[f]

Author Year UI	F/up, mo	PV Stenosis, no/N (%)	Cardiac Tamponade[a], no/N (%)	Stroke or [TIA], no/N (%)	Atrio-esophageal Fistula, no/N (%)	Peripheral Vascular Complication, no/N (%)	30-Day Mortality, no/N (%)	Other Major AE, no/N (%)	
Liu 2005[117] 16336813	6	1/130 (0.8%)[c]	1/130 (0.8%)	1/130 (0.8%)		1/232 (0.4%)[g]			
Kanj 2007[99] 17433955	6	0/121	2/121 (2%)	0/121	0/121	0/121	0/121	Pulmonary edema	2/121 (2%)
Tondo 2005[103] 15683472	7	No adverse events (no=120)							
Liu 2006[75] 17062959	9	2/110 (2%)[g]				1/110 (1%)[f]			
Wazni 2003[79] 14610012	12	2/108 (2%)[l]		0/108					
Turco 2007[118] 17302684	Periprocedural		1/107 (0.9%)						
Ma 2006[119] 17199954	12	0/106	2/106 (2%)	0/106	0/106		0/106		
Wang 2008[81] 18442966	12	0/106		1/106 (0.9%)		3/106 (3%)[c]			
Tondo 2006[120] 16981920	14		1/105 (1%)	0/105		5/105 (5%)[b]			
Kistler 2007[121] 17916142	nd		1/101 (1%)	[1/101 (1%)]					
Liu 2006[48] 17239094	13	2/100 (2%)[g]	1/100 (1%)	1/100 (1%)		1/100 (1%)[f]			
Martinek 2007[61] 17897124	6	3/100 (3%)[g]		1/100 (1%) [2/100 (2%)]				Phrenic nerve paralysis	1/100 (1%)
Kistler 2006[58] 16989651	6	1/94 (1%)[m]	1/94 (1%)	[1/94 (1%)]					
Hocini 2005[73] 16344401	15	1/90 (1%)[n]	1/90 (1%)					Phrenic nerve paralysis	1/90 (1%)
Wang 2007[104] 17522081	7		0/90	0/90		2/90 (2%)[c]			

Author Year UI	F/up, mo	PV Stenosis, no/N (%)	Cardiac Tamponade[a], no/N (%)	Stroke or [TIA], no/N (%)	Atrio-esophageal Fistula, no/N (%)	Peripheral Vascular Complication, no/N (%)	30-Day Mortality, no/N (%)	Other Major AE, no/N (%)	
Tang 2008[122] 18364135	12	0/81	2/81 (2%)	0/81	0/81		0/81		
Kistler 2008[100] 18931059	13.6	1/79 (1%)	2/79 (3%)						
Rotter 2005[102] 15741228	6.7	No adverse events (no=72)							
Estner 2006[106] 16831837	10	0/64	0/64	1/64 (2%)	0/64	0/64			
Mantovan 2005[82] 16403059	16		1/60 (2%)						
Arentz 2007[52] 17562956	15	1/55 (1%)[o]	1/55 (1%)					Pulmonary edema	1/55 (1%)
Nilsson 2006[46] 16923426	12	1/46 (2%)[p]		1/46 (2%) [1/46 (2%)]					
Oral 2003[50] 14557355	6	0/40						Atrial Flutter	1/40 (3%)
Oral 2005[77] 16253904	10	No adverse events (no=40)							
Marrouche 2007[101] 17490437	3	0/26			0/26				

AE, adverse events; LA, left atrium: nd, no data; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
b. AV fistula
c. Pseudoaneurysm.
d. Asymptomatic PV stenosis with >70% reduction in diameter.
e. Asymptomatic PV stenosis with 50% reduction in diameter.
f. Catheter insertion site-related bleeding or hematoma requiring interventions (e.g., transfusion).
g. Asymptomatic PV stenosis with >50% reduction in diameter.
h. Symptomatic PV stenosis requiring interventions (e.g., stent placement).
i. Fifty-three patients underwent in total 155 ablation procedures.
j. The data were based on total number of procedures. Some patients underwent repeated ablations due to recurrent arrhythmias.
k. Femoral vein thrombosis.
l. Asymptomatic PV stenosis with 50-70% reduction in diameter.
m. No explicit definition of PV stenosis reported.
n. Asymptomatic PV stenosis with >70% reduction in diameter.
o. Asymptomatic PV with 40% reduction in diameter.
p. Asymptomatic PV stenosis with >30% reduction in diameter.

Table 15. Adverse events (extraostial PVI, conventional tip)

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[a], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Kilicaslan 2005[123] 15734612	18	4/1125 (0.4%)[b]		7/1125 (0.6%)					
Pappone 2004[33] 15520310	12	0/560	4/560 (0.7%)	0/560				AT	8/560 (1%)
Wazni 2007[124] 17998456	nd		2/355 (0.6%)	3/355 (0.8%)		31/355 (9%)[c] 5/355 (1%)[d]			
Chugh 2005[55]15840468	13	No adverse events (no=349)							
Hachiya 2007[87] 17286569	6		1/252 (0.4%)						
Kilicaslan 2006[125] 16684021	nd			4/202 (2%)					
Verma 2007[70] 17338763	12	0/200	0/200	0/200					
Corrado 2008[126] 18363688	20		0/194[e]	1/194 (0.5%)[e]	0/194[e]	0/194[e]		Hemothorax	1/194 (0.5%)[e]
Yamane 2007[95] 17457004	22	0/117						Atrial flutter	4/117 (3%)
Essebag 2005[45] 16183686	14	0/102	3/102 (3%)	[1/102 (1%)]	0/102	4/102 (4%)	0/102		
Kottkamp 2004[59] 15312874	12	No adverse events (no=100)							
Matiello 2008[37] 18515285	Intra-procedural	0/88[f]	1/88 (1%)	[1/88 (1%)]				Pericarditis	4/88 (4%)
Rossillo 2008[30] 18268419	15	6/85 (7%)[g]		1/85 (1%)					
Calò 2006[51] 16781381	13					1/80 (1%)[c]		Hemothorax	1/80 (1%)
Oral 2006[26] 16510747	12	0/77	0/77	0/77	0/77	0/77	0/77	Atrial Flutter	5/77 (6%)
								Sick sinus syndrome	1/77 (1%)
								Pneumonia	1/77 (1%)

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[a], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Pak 2008[83] 18284506	39	1/77 (1%)[f]	2/77 (3%)	[1/77 (1%)]					
Kanj 2007[99] 17433955	6	0/59	0/59	[1/59 (2%)]	0/59	0/59	0/59		
Tamborero 2005[93] 16311935	4	0/41[h]							
Wazni 2005[24] 15928285	12	1/32 (3%)[g]		0/32				Bleeding[i]	2/32 (6%)
Marrouche 2007[101] 17490437	3	0/27							
Okada 2007[91] 17397672	6	1/27 (4%)[f]							
Krittayaphong 2003[23] 12866763	12	0/14	0/14	1/14 (7%)	0/14	0/14		Gastrointestinal[j]	2/14 (14%)
								Sinus node dysfunction[j]	1 (7%)
								Dizziness[j]	1 (7%)
								Pre-syncope[j]	1 (7%)

AT, atrial tachyarrhythmia; AAD, antiarrhythmic drug; AE, adverse event; nd, no data; adverse events; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
b. "Moderate to severe" PV stenosis.
c. Catheter insertion site-related bleeding or hematoma requiring interventions (e.g., transfusion).
d. Pseudoaneurysm.
e. The data are based on the total number of procedures. Some patients underwent repeated procedures due to recurrent arrhythmias.
f. Asymptomatic PV stenosis with >50% reduction in diameter.
g. Asymptomatic PV stenosis with 50-70% reduction in diameter.
h. Asymptomatic PV stenosis with >70% reduction in diameter.
i. No details reported.
j. Details were not reported. This might have been associated with concurrent AAD.

Table 16. Adverse events (extraostial PVI, various tips or no information on tip)

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[a], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Lakkireddy 2005[127] 16360082	12	(2%)[b]		(1%)				Pulmonary edema	(0.5%)
Berruezo 2007[43] 17395676	13	0/148		[2/148 (1%)]				Pericarditis	6/148 (4%)
								Dressler's syndrome	2/148 (1%)
Zhou 2007[71] 17624261	7			1/148 (0.7%) [2/148 (1%)]			1/148 (0.7%)[c]		
Beukema 2005[53] 16203925	15	0/105							
Sheikh 2006[78] 17318445	9	0/100	1/100 (1%)	[1/100 (1%)]	0/100	0/100	0/100		
Pappone 2006[27] 17161267	12			[1/99 (1%)]					
Li 2008[128] 18577822	Intra-procedual	0/92	0/92		0/92				
Stabile 2006[25] 16214831	12	0/68	1/68 (1%)	1/68 (1%)				Phrenic nerve paralysis	1/68 (1%)
								Coronary artery events	1/68 (1%)
Karch 2005[74] 15927974	6	3/50 (6%)[d]	0/50	1/50 (2%) [2/50 (4%)]					
Mansour 2004[89] 15149421	11	0/40	1/40 (3%)	1/40 (3%)		2/40 (5%)			

AE, adverse events; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
b. Asymptomatic PV stenosis with >70% reduction in diameter.
c. Died from pulmonary infection.
d. Asymptomatic PV stenosis with >50% reduction in diameter.

Table 17. Adverse events (ostial PVI, cooled- or irrigated-tip)

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[a], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Hsu 2005[129] 15683473	nd		14/746 (2%)						
Chen 2004[35] 15028358	14	6/377 (2%)[b]	2/377 (1%)	5/377 (1%)				Pulmonary edema	1/377 (0.3%)
Bhargava 2004[54] 15028066	15	6/323 (2%)[b]	3/323 (1%)	3/323 (1%)					
Marrouche 2003[108] 12756153	13	5/315 (2%)[b]		2/315 (0.6%) [3/315 (1%)]					
Della Bella 2005[39] 15763523	12	2/234 (0.9%)[c] 1/234 (0.4%)[b]	3/234 (1%)	1/234 (0.4%)		4/234 (2%)[d] 2/234 (0.9%)[e]			
Fassini 2005[56] 1630289	Intra-procedural		1/187 (0.5%)	[1/187 (0.5%)]					
Macle 2002[130] 12475093	9	0/136		0/136					
Hsu 2004[131] 15575053	12		2/116 (2%)	1/116 (0.9%)				Death at 3 mo[f]	1/116 (0.9%)
Berkowitsch 2005[132] 15683534	12	16/104 (15%)[b]							
Nilsson 2006[107] 17043070	15	0/90		[2/90 (2%)]					
Arentz 2007[52] 17562956	15	1/55 (1%)[g]	1/55 (1%)						
Nilsson 2006[46] 16923426	12			1/54 (2%) [1/54 (2%)]					
Karch 2005[74] 15927974	6	6/50 (12%)[h]	0/50	0/50 [1/50 (2%)]					
Thomas 2004[133] 15172657	nd	2/158 (1%)[i]		1/48					

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[a], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Kettering 2008 18507536[98]	6	0/43[h]							
Dixit 2006[49] 16879626	6	0/40[b]	0/40	[1/40 (3%)]	0/40		0/40		
Oral 2003[50] 14557355	6	0/40							
Willems 2006[80] 16782716	17[j]		1/32 (3%)	[1/32 (3%)]					

AE, adverse events; nd, no data; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
b. Asymptomatic PV stenosis with >70% reduction in diameter.
c. Symptomatic PV stenosis requiring interventions (e.g., stent placement).
d. Arteriovenous fistula.
e. Venous thrombosis.
f. Died from underlying congestive heart failure.
g. Asymptomatic PV stenosis with 40% reduction in diameter.
h. Asymptomatic PV stenosis with >50% reduction in diameter.
i. The unit of analysis was each PV.
j. Median.

Table 18. Adverse events (ostial PVI, conventional tip)

Author Year UI	F/up, mo	Cardiac Tamponade[a], n/N (%)	Cardiac Tamponade, n/N (%) [effusion]	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Matsuo 2007[90] 17506857	20	2/148 (1%)[b]	1/148 (1%)						
Yamada 2006[110] 16607049	6	0/108	0/108	0/108					
Yamane 2007[95] 17457004	34	3/70 (4%)[c]						Atrial flutter	1/70 (1%)
Okada 2007[91] 17397672	6	2/50 (4%)[d]							
Dixit 2006[49] 16879626	6	0/42[e]	0/42	0/42	1/42 (2%)		1/42 (2%)[f]		
Oral 2005[77] 16253904	10	No adverse events (n=40)							
Tamborero 2005[93] 16311935	4	6/32 (19%)[e]							
Thomas 2004[133] 15172657	nd	4/81 (5%)[b,g]	1/31 (3%)						

AE, adverse events; nd, no data; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
b. Asymptomatic PV stenosis with 50-70% reduction in diameter.
c. No explicit definition of PV stenosis reported.
d. Asymptomatic PV stenosis with >50% reduction in diameter.
e. Asymptomatic PV stenosis with >70% reduction in diameter.
f. Died from LA-esophageal fistula at 2 weeks.
g. The unit of analysis was each PV.

Table 19. Adverse events (ostial PVI, various tips or no information on tip)

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[a], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Zado 2008[134] 18462325	28	1/1506 (0.07%)[b,c] 5/1506 (0.3%)[b,d]	12/1506 (0.8%)[b]	6/1506 (0.4%)[b,e]	1/1506 (0.07%)[b]	1/1506 (0.07)[b,f]		Phrenic nerve injury	2/1506 (0.1%)[b]
								Anaphylaxis	2/1506 (0.1%)[b]
Sauer 2006[135] 16831982	21	"Major complications" (3%, no=629)							
Gerstenfeld 2006[136] 16443531	16	1/449 (0.2%)[c] 2/449 (0.4%)[g]	6/449 (1%)	4/449 (0.9%)[d]		1/449 (0.2%)[e]			
Saad 2003[109] 12693885	5	18/335 (5%)[h]							
Walczak 2006[94] 16444625	17	5/183 (3%)[c]							
Yamane 2002[111] 11955852	9	0/157							
Proclemer 2008[65] 18667447	25 mo (median)		5/144 (3%)	0/144			0/144		
Dixit 2008[44] 18242535	12	0/105[c]	0/105	1/105 (2%)	1/105 (1%)		1/105 (1%)		
Schwartzman 2003[92] 14574043	6	2/42 (5%)[i]							
Mansour 2004[89] 15149421	21	0/40	2/40 (5%)	1/40 (3%)		0/40			

AE, adverse events; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
b. The data are based on the total number of procedures. Some underwent repeated procedures due to recurrent arrhythmia.
c. Symptomatic PV stenosis requiring interventions (e.g., stent placement).
d. Asymptomatic PV stenosis with >70% reduction in diameter.
e. Both strokes and TIAs were combined.
f. Catheter insertion site-related bleeding or hematoma requiring intervention (e.g., transfusion)
g. No explicit definition of PV stenosis reported.
h. Asymptomatic PV stenosis with 50-70% reduction in diameter.
i. Asymptomatic PV stenosis with >50% reduction in diameter.

Table 20. Adverse events (miscellaneous)[a]

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[b], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
Irrigated tip									
Nilsson 2006[46] 16923426	12							Embolic events	4/173 (2%)[c]
Conventional tip									
Cha 2008[34] 18474813	12	7/523 (1.3%)[d]	12/523 (2.3%)	4/523 (0.8%)				hemi-diaphragm paralysis	4/523 (0.8%)
Cheema 2006[40] 17019636	26	3/264 (1%)[e]	6/264 (2%)	3/264 (1%)		21/264 (8%)[f,g]		Heart block	1/264 (0.3%)
								Valve injury	1/264 (0.3%)
Oral 2006[137] 16606789	11		2/180 (1%)[c]	[2/180 (1%)[c]]					
Various tips or no information on tip									
Bertaglia 2007[138] 17905330	nd	1/1011 (0.1%)[h] 3/1011 (0.3%)[d]	7/1011 (0.7%)	4/1011 (0.4%) [1/1011 (0.1%)]		10/1011 (10%)[g] 3/1011 (0.3%)[l]	0/1011	Aortic root puncture	1/1011 (0.1%)
								AV block	1/1011 (0.1%)
								Phrenic nerve paralysis	1/1011 (0.1%)
								Pneumothorax	1/1011 (0.1%)
Gerstenfeld 2007[139] 17081205	35	(0.1%)[h] (0.6%)[j]	(0.9%)	(0.5%) [(0.2%)]	1/1058 (0.1%)	(0.8%)[f] (0.6%)[g] (0.7%)[i] (0.1%)[k]	2/1058 (0.2%)[l]	Cardiogenic shock	(0.1%)
								Radiation burn	(0.1%)
								Coronary air embolism	(0.4%)
								Anaphylaxis	1/1058 (0.1%)
Oral 2006[63] 16908760	25			10/755 (1%)					
Spragg 2008[140] 18462327	< 30 days	1/641 (0.2%)[c,m]	8/641 (1%)[c]	7/641 (1%)[c]	0/641[c]	11/641 (2%)[c]	0/641[c]	Hemothorax	1/641 (0.2%)[c]
								Heart block	1/641 (0.2%)[c]

Author Year UI	F/up, mo	PV Stenosis, n/N (%)	Cardiac Tamponade[b], n/N (%)	Stroke or [TIA], n/N (%)	Atrio-esophageal Fistula, n/N (%)	Peripheral Vascular Complication, n/N (%)	30-Day Mortality, n/N (%)	Other Major AE, n/N (%)	
								Lung injury	1/641 (0.2%)[c]
								MV injury	1/641 (0.2%)[c]
Pappone 2003[29] 12875749	30	0/589	4/589 (1%)	0/589					
Schwartzman, 2003[92] 14574043	6	4/112 (4%)[d]				1/112 (1%)[f] 3/112 (3%)[g] 2/112 (2%)[l]		Non-cardiogenic pulmonary edema	1/112 (0.9%)
Katritsis 2008[97] 18363086	12	0/90	2/90 (2.2%)		0/90				

AE, adverse events; AV, atrio-ventricular; MV, mitral valve; nd, no data; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

a. Various different ablation techniques were employed (e.g., extraostial PVI and ostial PVI).
b. Pericardial effusion that required pericardiocentesis was considered cardiac tamponade.
c. The data were based on total number of procedures. Some patients underwent repeated ablations due to recurrent arrhythmias.
d. Asymptomatic PV stenosis with >50% reduction in diameter.
e. Asymptomatic PV stenosis with >70% reduction in diameter.
f. Catheter insertion site-related bleeding or hematoma requiring interventions (e.g., transfusion).
g. Pseudoaneurysm.
h. Symptomatic PV stenosis requiring interventions (e.g., stent placement).
i. AV fistula.
j. PV stenosis with >75% reduction in diameter regardless of symptoms.
k. Femoral vein thrombosis.
l. One died from anaphylactic shock after the procedure and the other died from left atrio-esophageal fistula at 3 weeks.
m. "Occlusion" of PV

Table 21. Studies associating patient characteristics with adverse events[a]

Predictor	PV Stenosis	Cardiac Tamponade[b]	Stroke or TIA,	Peripheral Vascular Complication	Pulmonary edema	General	Total Studies, n
Gender	NS (H,I)	NS (H,I)	NS (H,I)	NS (I)		NS (H,J[c])	3
Age	NS (B,I)	NS (B,I)	P<0.05 (B) NS (I)	NS (I)		P=0.04[d] (J) NS (B,J[e],K)	4
Duration of AF	NS (I)	NS (I)	NS (I)				1
Left atrial size	NS (I)	NS (I)	NS (I)			NS (J)	2
EF	NS (A,I)	NS (A,I)	NS (A,I)			NS (J)	3
CHF		NS (G)		P<0.01 (G)		P<0.01 (G) NS (C)	2
Paroxysmal AF	NS (I)	NS (I)	NS (I)	NS (I)		NS (J)	2
History of CVD	NS (I)		NS (I)				1
Valvular HD	NS (I)	P<0.003 (I)	NS (I)	NS (I)			1
CAD	NS (I)	P<0.005[f] (I)	NS (I)	NS (I)			1
DCM	NS (I)	NS (I)	NS (I)	NS (I)			1
Hypertension	NS (I)	NS (I)	NS (I)	NS (I)		NS (J)	2
Diabetes						P=0.002[g] (F)	1
Pacemaker or ICD	NS (E)		NS (E)		NS (E)		1
History of cardiac surgery	NS (D)		NS (D)				1
Total studies, *n*	6	5	6	2	1	6	11

AF, atrial fibrillation; CAD, coronary artery disease; CHD, congestive heart failure; CVD, cerebrovascular disease; DCM, dilated cardiomyopathy; HD, heart disease; ICD, intracardiac device; NS, not significant; TIA, transient ischemic attack.

a. P-values are estimated by univariate analysis. Studies are coded as follows: A, Chen 200435 (no=377); B, Bhargava 200454 (no=323); C, Hsu 2004131 (no=116); D, Kilicaslan 2005123 (no=1125); E, Lakkireddy 2005127 (no=172); F, Tang 200668 (no=263); G, Tondo 2005103 (no=105); H, Forleo 2007114 (no=221); I, Bertaglia 2007138 (no=1015); J, Spragg 2008140 (no=640); K, Zado 2008134 (no=1165).

b. One study (Bertaglia 2007138) assessed both cardiac tamponade and pericardial effusion requiring prolongation of hospital stay.

c. P=0.014 in multivariate analysis. Female gender was significantly predictive of major complications (OR=3.0 [95% CI, 1.3-7.2]).

d. P=0.002 in multivariate analysis. Age >70 was significantly predictive of major complications (OR=6.0 [95% CI, 1.9-19.1]).

e. P=0.02 in multivariate analysis (the mean age of patients with or without complications was evaluated).

f. P<0.008 in multivariate analysis.

g. P=0.001 in multivariate analysis.

Table 22. Summary of reviewed studies: radiofrequency catheter ablation for atrial fibrillation

Comparisons	Study type	Studies, n (references)	Number of studies by quality[a]			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	1	214
8 mm vs. closed irrigated tip catheter	RCT	2	2			91
8 mm vs. open irrigated tip catheter	RCT	2		2		233
	nonRCS	1			1	221
Different imaging modalities	RCT	5		3	2	340
	nonRCS	3			3	330
Miscellaneous comparisons	RCT, nonRCS, 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						
	[b]Cohort	100	Quality not rated			[c]≤20,000

[a]**Quality ratings:**

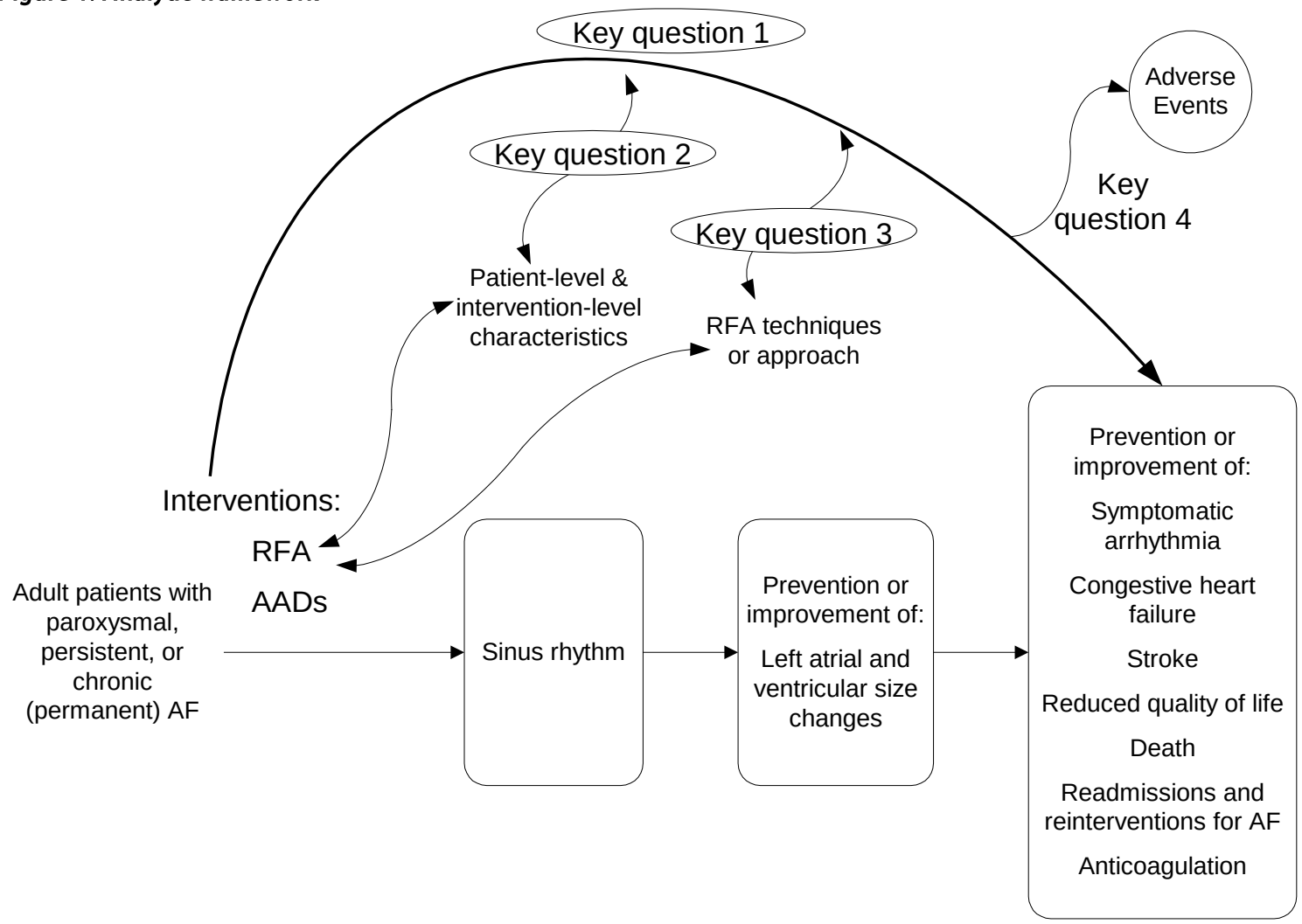
Good	Studies that have the least bias and results that are considered valid. Studies that mostly adhere to the commonly held concepts of high quality including the following: a formal randomized controlled design; clear description of the sample, setting, interventions, and comparison groups; appropriate 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."

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

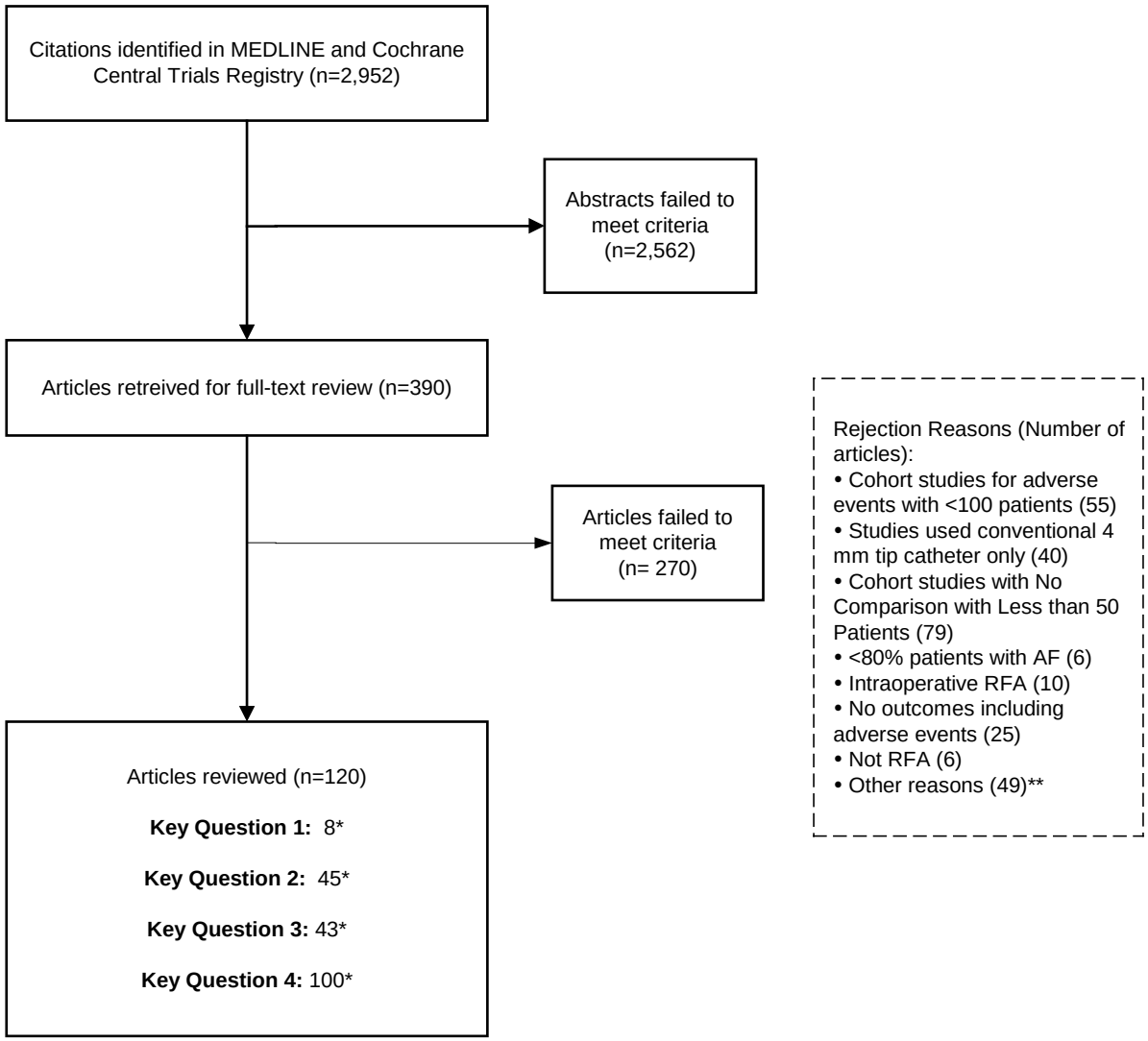
Figures

Figure 1. Analytic framework



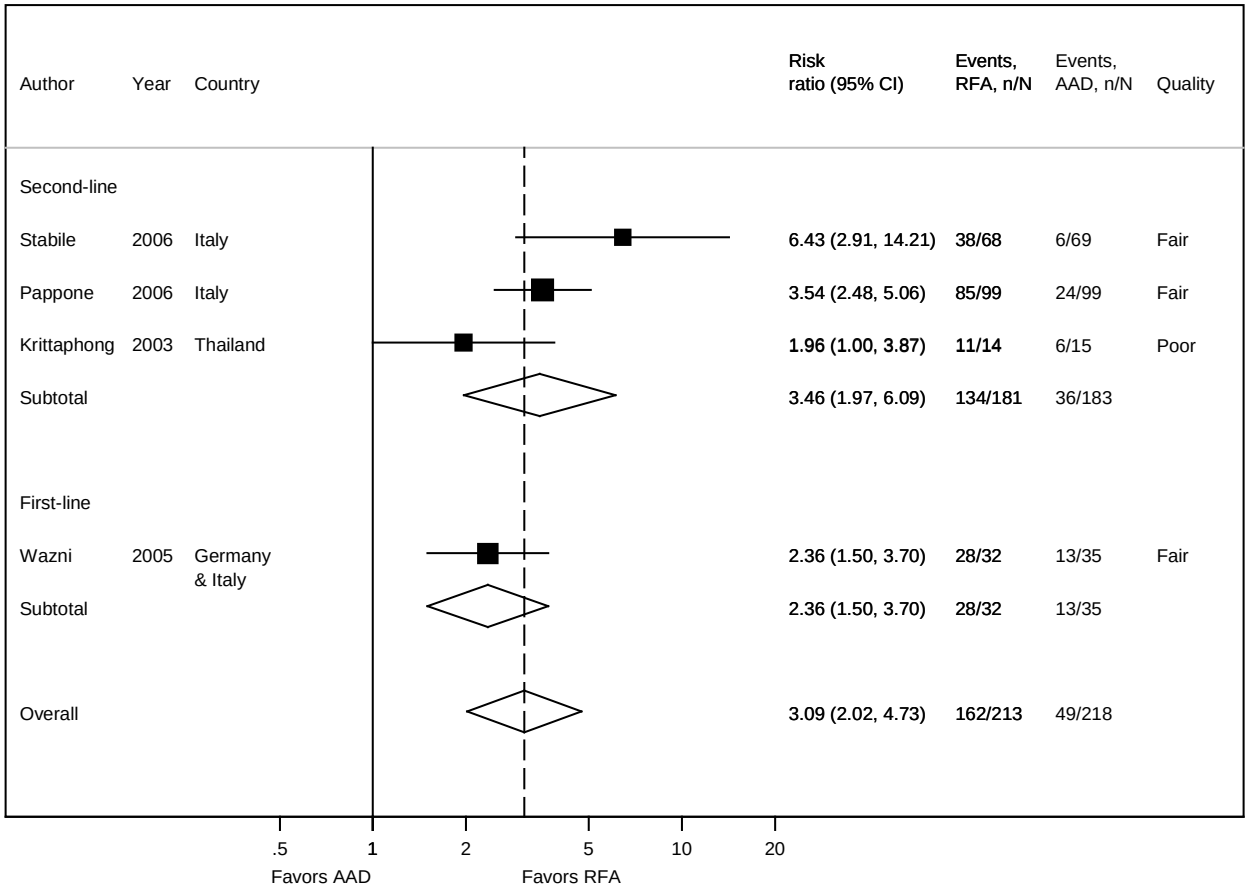
AF, atrial fibrillation; AADs, antiarrhythmic drugs; RFA, radiofrequency ablation.

Figure 2. Literature flow diagram



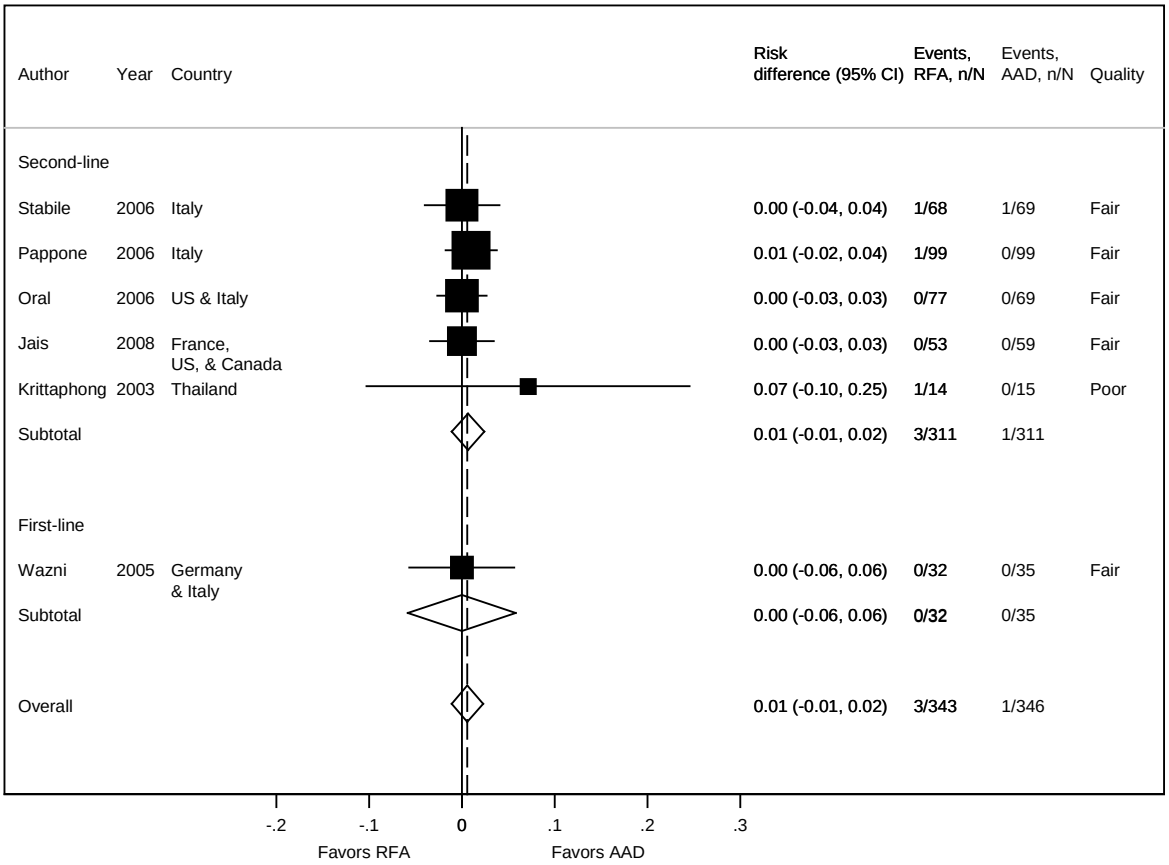
RFA, radiofrequency ablation.
*There are overlaps of studies between key questions
**See Appendix B for detailed rejection reasons

Figure 3. Metaanalysis of RR of rhythm control, RFA vs. medical treatment



Legends: Random effects model meta-analyses of relative risk in maintaining sinus rhythm comparing patients who received RFA with patients treated with medical treatment. Diamonds display summary results centered on combined estimates and extending to 95% confidence interval (CI). Squares and lines indicate estimates of means and 95% CI for individual studies. The size of the closed squares is proportional to the weight of each study in the overall Metaanalysis. Studies are ordered by presence of previous therapeutic interventions (i.e., first-line therapy or second-line therapy), then sample size.
AAD, antiarrhythmic drug; RFA, radiofrequency ablation

Figure 4. Metaanalysis of risk difference of stroke events, RFA vs. medical treatment



Legends: Fixed effects model meta-analyses of risk difference in cerebrovascular events comparing patients who received RFA with patients treated with medical treatment. Diamonds display summary results centered on combined estimates and extending to 95% confidence interval (CI). Squares and lines indicate estimates of means and 95% CI for individual studies. The size of the closed squares is proportional to the weight of each study in the overall Metaanalysis. Studies are ordered by presence of previous therapeutic interventions (i.e., first-line therapy or second-line therapy), then sample size.
AAD, antiarrhythmic drug; RFA, radiofrequency ablation

Figure 5. Metaanalysis of RR of recurrence, persistent vs. paroxysmal AF

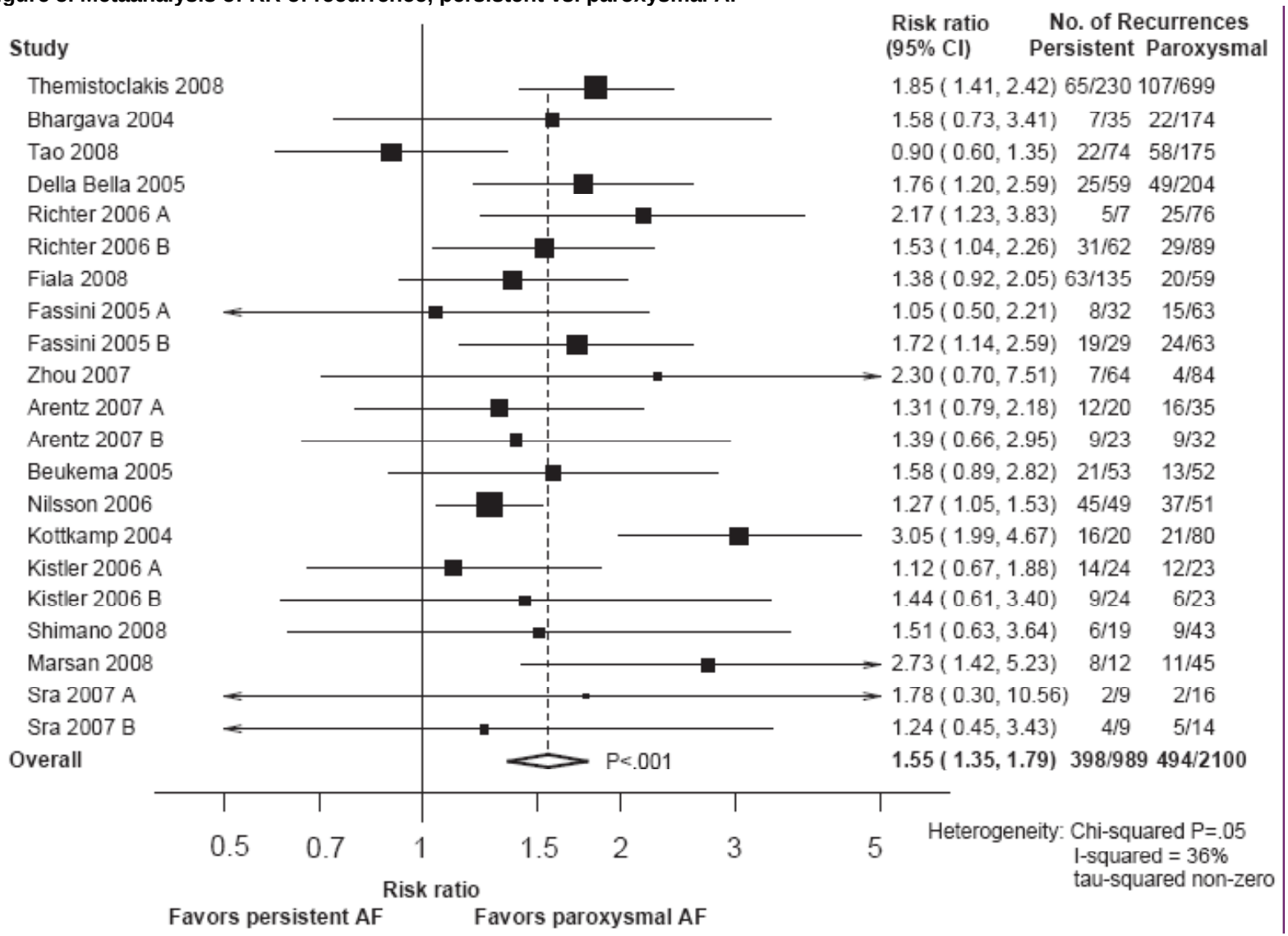


Figure 6. Metaanalysis of RR of recurrence, chronic vs. paroxysmal AF

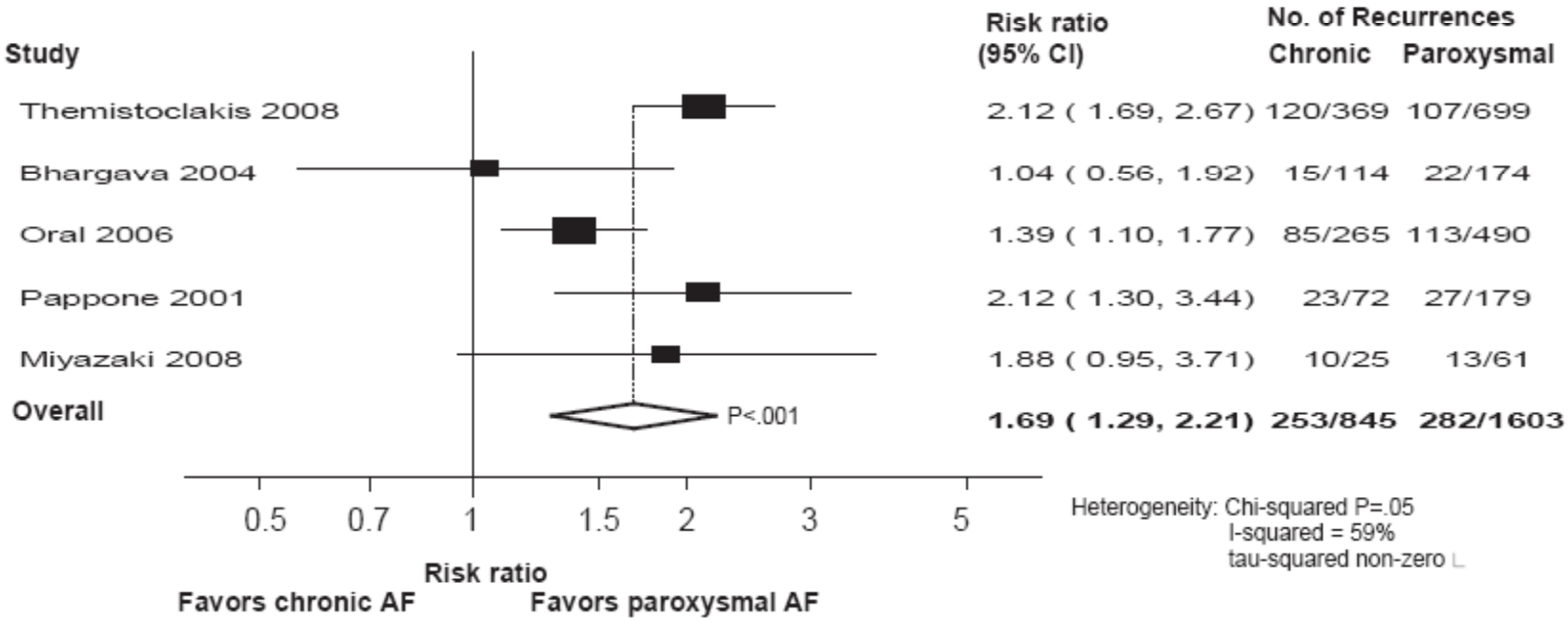


Figure 7. Metaanalysis of RR of recurrence, nonparoxysmal vs. paroxysmal AF