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Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation

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This report is intended as a reference and not as a substitute for clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied

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 (CERs) 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 CERs 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 from 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.

This report is based on research conducted by the Tufts Medical Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation

Executive Summary

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

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

The Agency for Healthcare Research and Quality (AHRQ) 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 remains the most common sustained arrhythmia in clinical practice. Its prevalence increases with age, from 0.1 % in people younger than 55 years, to more than 9 % 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% 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 versus 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 versus rate control was performed, a strategy of rhythm control with anti-arrhythmic drugs (AADs) was associated with a worse prognosis 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 should not be a cause to abandon novel strategies aimed at maintaining sinus rhythm. Moreover, restoring sinus rhythm may provide benefit 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: "If an effective method for maintaining SR with fewer adverse effects were available, it might be beneficial." 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 all of 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 which 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 RF energy rendered 62% 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 developed 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 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.

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 may include a roof line, a posterior line, a mitral line, a septal line, or a linear lesion at the inferior aspect of the left atrium which runs parallel to the coronary sinus. 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 AF, 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 the technical expert panel, and in accordance with the HRS Consensus Statement, we only reviewed studies which included the targeting of the PVs or PV antrum, with or without the addition of other strategies. Based on these clinical trials, current guidelines for

the management of AF consider catheter ablation a reasonable alternative in patients with symptomatic AF who have failed AAD therapy.

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

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, readmissions and reinterventions for persistent, paroxysmal and long-standing persistent (chronic) atrial fibrillation?

Our literature search identified five RCTs and two retrospective cohort studies of patients with AF that compared RFA with medical treatment. Studies mainly included patients with PAF who had failed AADs. The patients underwent various ablation approaches and medical treatments across studies, and clinical outcomes were assessed in non-uniform ways. The methodological quality of the studies varied from good to poor. A number of 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., 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 (rate ratio: 3.46 (95% CI, 1.97-6.09)) at 12 months postprocedure. The summary estimate was derived from meta-analysis of three RCTs.

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).

Rates of congestive heart failure

There is insufficient evidence compare the rate of congestive heart failure between RFA and medical treatment. Only one observational study reported 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 insufficient evidence to compare left atrial and ventricular size changes between RFA and medical treatment as no study addressed this question.

Rates of stroke

There is a moderate level of evidence to show that there was 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: 0.7 % (95% CI, –1.2 to 2.6 %; favoring AAD)). The summary estimate was derived from meta-analysis of five RCTs.

Quality of life

There is a low level of evidence to suggest that RFA improves quality of life compared to medical treatment. Two RCTs and one observational study reported more improvement in general or physical functioning score of SF-36 in patients who underwent RFA compared to patients who had medical treatment alone (net difference between two treatments: +7 to +25; favoring RFA). However, these studies assessed the results at non-uniform time points and therefore the findings may not be valid.

Avoiding anticoagulation

There is insufficient evidence to compare the rates of avoiding anticoagulation between RFA and medical treatment as no study addressed this question.

Readmissions

There is low level of evidence to suggest that findings on differences in readmission rates between patients treated with RFA and those treated with AADs are inconsistent. 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 (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 that AF type, namely nonparoxysmal AF, is predictive of a higher rate of AF recurrence. Although univariable analyses are relatively homogeneous in showing a strong association (odds ratio (OR) about 2), only a minority of multivariable analyses bear this out. The data from multivariable analyses were inadequately reported to fully assess the association across studies. Twenty studies reported multivariable analyses of the association between patient-level characteristics and AF recurrence. In five of 13 studies, nonparoxysmal AF was significantly associated with higher rates of AF recurrence. Among the studies that reported sufficient data, the hazard ratios for AF recurrence of nonparoxysmal versus paroxysmal AF ranged from 1.1 to 22. Twenty-one studies reported rates of AF recurrence for different subgroups of patients based on their type of AF. Meta-analysis of the 10 studies comparing persistent and paroxysmal AF revealed statistically homogeneous results despite the clinical heterogeneity of the studies; the OR of AF recurrence for persistent versus paroxysmal AF was 2.24 (95% CI 1.71, 2.91, $P<0.001$). Only three studies compared chronic versus paroxysmal AF. Though statistically heterogeneous, the summary OR for AF recurrence was 1.64 (95% CI 1.07, 2.51, $P=0.02$). Ten studies comparing nonparoxysmal and paroxysmal AF had similar findings. Though minimally statistically heterogeneous, the summary OR for AF recurrence was 1.97 (95% CI 1.51, 2.58 $P<0.001$). No study or population factors were found to explain the heterogeneity among the studies.

There is a moderate level of evidence that EF and LAD are not independent predictors of AF recurrence. In multivariable analyses, 3 of 15 studies found an association between lower EF and AF recurrence, and 3 of 16 found an association between larger LAD and AF recurrence.

There is a high level of evidence that age, sex, and the presence of structural heart disease are not associated with AF recurrence. No study found consistent associations between structural

heart disease (17 studies) or duration of AF (13 studies) and AF recurrence. All studies found no association with age and 19 studies found no association with sex.

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

There is insufficient evidence 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

Fifteen RCTs, one non-randomized but controlled trial (nonRCT), two prospective cohort studies, and 15 retrospective cohort studies met eligibility criteria and reported outcomes of AF after RFA using different approaches. Approaches used in these studies included PVI within and around PV ostia, a wide area circumferential approach, 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, roof or posterior LA 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. Only one RCT examined the incremental benefit of adding a CTI ablation line in patients undergoing RFA for AF. This study, which included patients with AF and at least one episode of AFL, 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.

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 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. Data from three 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 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, imaging guidance methods, postprocedure durations of observation in the EP laboratory, or various mapping techniques (e.g., circular mapping alone versus circular mapping enhanced with intracardiac echocardiogram with or without monitoring of microbubbles).

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

There is a moderate level of evidence to show that adverse events associated with RFA are relatively uncommon. Sixty-eight studies 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 in a number of the studies. 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. Fifty-six studies assessed the rates of asymptomatic or symptomatic PV stenosis. The majority of these studies reported asymptomatic PV stenosis rates of 4% or less; 21 studies did not identify a single case of PV stenosis (i.e., reported zero events). Symptomatic PV stenosis requiring interventions occurred in less than 1% of patients in four studies. Cardiac tamponade was reported to occur in less than 1% of patients in the majority of the 45 studies that evaluated this adverse event. Rates of cerebrovascular events were reported at 4% or less in the majority of the 51 studies that evaluated stroke and/or TIA, and 12 additional studies reported no cerebrovascular events. Ten studies assessed for atrioesophageal fistula. Among these, one study reported a rate of 1.2% and another study reported a rate of 0.1%; the remainder did not identify any cases. Among 56 studies, four deaths were reported within 30 days post-procedure; one patient died from a pulmonary infection, one died from anaphylaxis after the procedure, and two died from atrioesophageal fistulas.
Major adverse events associated with RFA are relatively uncommon, overall occurring in less than 5% 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

RFA was superior to medical treatments at maintaining sinus rhythm in patients with PAF over one 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 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. 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.

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 meaningful comparative analyses could be performed.

Further investigations on the efficacy of RFA for AF should also be targeted at patient population under-represented in the current literature but often encountered in clinical practice (e.g., the elderly, patients with multiple comorbidities).

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] – and the rising prevalence of chronic conditions predisposing to AF such as heart disease and hypertension. However, implementation of recent guidelines to more aggressively treat hypertension and dyslipidemia in high risk patients may somewhat alleviate the rising prevalence of AF.

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. In other patients, controlling the ventricular response rate is not 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, 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.[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 recent meta-analysis 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 benefit 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 SR 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 in many patients.[12] Sleeves of atrial muscle fibers extend from the left atrium into all of 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 developed a variation of Haissaguerre's initial technique known as wide area circumferential ablation (or left atrial circumferential ablation) in which radiofrequency (RF) 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 (3-D) 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 paroxysmal AF (PAF). PAF 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 chronic AF

(continuous AF of greater than 1 year duration) has required the development of additional lesions sets in order to improve clinical outcomes.[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 may include a roof line (connecting the superior aspect of the encircling lesions), a posterior line (connecting the posterior aspect of the encircling lesions), a mitral line (from the left inferior PV to the mitral annulus), a septal line (from the right inferior PV to the mitral annulus), or a linear lesion at the inferior aspect of the left atrium that runs parallel to the coronary sinus. 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 AF, 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) assembled for this report, 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 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 will examine 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, readmissions and reinterventions 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 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 (SRC) for the 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 SRC drafted final key questions and submitted them to AHRQ for approval.

This comparative effectiveness review (CER) of RFA for the treatment of AF is based on a systematic review of the literature. The Tufts EPC held teleconferences with a 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 CER 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 explanations for abbreviations of frequently used technical terms have been repeated several times throughout the entire document to help clarify highly technical terminologies. See **Abbreviations** for a list of abbreviations used for the entire document.

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 texts of the major search strategies are given in **Appendix A**.

We searched the Medline database from 2000 to April, 2008 for studies involving adults with 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. Detailed search strategy is described in Appendix A. 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 inputs 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 pre-approval studies will be included.

We assessed titles and/or 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, and 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 one-year duration.[1] For a study to be included, at least 80 percent of the patients had to be treated specifically for AF. Study eligibility was not based on type or duration of AF, previous treatments for AF, or comorbid conditions. We excluded studies that were limited to patients with congenital heart disease, hypertrophic cardiomyopathy, or Wolff-Parkinson-White (WPW) syndrome.

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, as a repeat procedure following a failed RFA, and with or without concurrent antiarrhythmic drugs (AADs).

We included studies of RFA strategies in which the explicit or intended goal was targeting of the 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 (SVT), standalone atrial flutter (AFL) and RFA in conjunction with cardiac surgery.

We did not evaluate cryoablation or microwave ablation. We excluded studies that only examined surgical 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 only included studies utilizing 8 mm tip or irrigated tip catheters. We excluded studies that only included 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 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 months 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.
    - whether a "blanking" period was defined; we did not exclude studies or findings based on this criterion, however
- congestive heart failure (CHF)
- left atrial and ventricular size changes
- stroke
- quality of life measures
- avoiding anticoagulation
- readmissions and reinterventions for AF
- Adverse events due to RFA
    - Symptomatic or severe pulmonary vein stenosis
    - Cardiac tamponade or pericardial effusion requiring intervention
    - Peri-procedural stroke or TIA
    - 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)

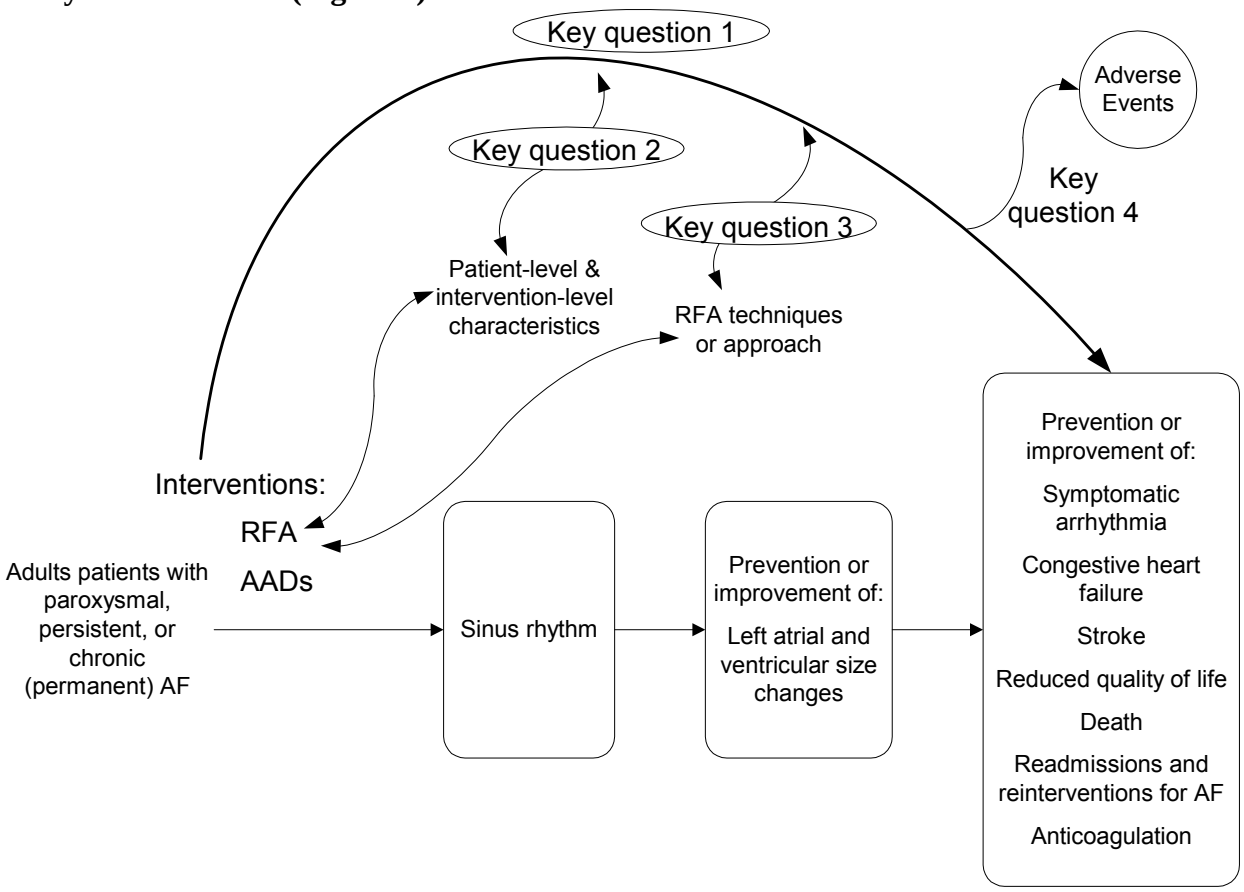
Study designs of interest

We included studies of any design: randomized 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 included RCTs of any sample size. For 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.

Analytic Framework (Figure 1)



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 cardiologist in the Tufts 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, nonRCTs, 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 nonRCTs 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 as 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 percent 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 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 (EF), LA diameter (LAD), sex, age, structural heart disease, and hypertension (HTN). 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 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 was available, the corresponding odds ratio (OR) was calculated. For these comparisons, we performed meta-analysis, as described below.

KQ 4: For adverse event data collection, 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 (TIA), 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.

Meta analysis

Where the data were amenable to meta-analysis – 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 risk ratio (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 ORs, which effectively excludes studies with zero events in both arms from the analysis.[22] As described above, we performed random effects model meta-analyses of OR for AF type as a predictor of AF recurrence.

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 [to be determined]. The reviewers included experts in [to be determined]. These experts were either directly invited by the EPC 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 search yielded 1,746 citations. We identified 344 of these as potentially relevant and retrieved the full-text articles for further evaluation. Of these 245 did not meet eligibility criteria. A total of 99 studies were included in our analyses. **(Figure 2)**

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, readmissions and reinterventions for persistent, paroxysmal and long-standing persistent (chronic) atrial fibrillation?

RFA versus open surgical procedures

No study compared RFA with an open surgical procedure.

RFA versus medical therapy (Table 1)

Five RCTs enrolling a total of 581 patients with AF compared RFA with medical therapy.[23-27] Sample size ranged from 30 to 198. One trial compared RFA as first line therapy to 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[1]. 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 PVs. AADs used also varied both within and between studies. Utilization of AADs also varied in the RFA arms; in three studies, AADs drugs were discontinued a few months post RFA;[23,26,27] whereas in one RCT, AAD was continued throughout the study period .[25] Methodological quality of one study was good, three studies were fair, and one study was poor.

Two retrospective cohorts[28,29] 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 three months after the procedure. Methodological quality of two studies were poor.[28,29]

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.

Five RCTs consistently reported statistically significant improved rhythm control at 12 months with RFA compared to medical therapy regardless. We performed meta-analysis 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 only reported the participants' rhythm status at 12 months postprocedure irrespective of recurrence during the entire followup period. Overall, patients who underwent RFA (either as first- or second-line therapy) had about a threefold higher

[1] 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.

chance of maintaining sinus rhythm for 12 months compared to those treated with medical therapy (rate ratio (RR): 3.09 (95% CI, 2.02-4.73), Q = 7.60 (P = 0.06), I^2 = 61%). In a subgroup analysis including three studies that used RFA as second-line therapy, it was similarly superior to medical treatment (RR: 3.46 (95% CI, 1.97-6.09), Q = 5.40 (P = 0.07), I^2 = 63%). There was no evidence of statistical heterogeneity in treatment effect between first-line and second-line therapy (Z = 1.04, P = 0.30).

Rhythm control was also reported in two retrospective studies.[28,29] 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).[28] The other 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).[29]

Rates of congestive heart failure **(Table 3)**

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

One retrospective study evaluated CHF 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 CHF developed in 5% of patients who had RFA compared to 10% of patients who had medical treatment although no formal statistical test was performed.[28]

Left atrial and ventricular size changes **(Table 4)**

No RCT directly compared left atrial diameter (LAD) or left ventricular ejection fraction (EF) in patients with AF treated with RFA versus medical therapy. However, one RCT reported that among patients without recurrent AF in the group that underwent RFA, the diameter of the LAD was smaller at 12 months compared to baseline (4.0 cm vs. 4.5 cm, P<0.001) [26]. Similarly, in the same study, among patients who remained in sinus rhythm, the EF was higher at 12 months compared to baseline vein ablation than before the procedure (62% vs, 55%, P<0.001). [26] Both LAD and EF were unchanged in patients with recurrent AF in followup.

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)) as well as in patients who had received medical treatment (no recurrence: -0.3 cm (P<0.01); recurrence: -0.2 cm (P value not reported));[28] however, direct statistical comparison between RFA and medical treatment was not performed.

Rates of stroke **(Table 5)**

All five RCTs evaluated stroke as an adverse event. We performed a meta-analysis on the five RCTs (Figure 4).[23-27] 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. Two studies observed zero events in both arms.[24,26] The summary risk difference of stroke was 0.7 % (95% CI, –1.2 to 2.6 %; favoring AAD); the RCTs had statistically homogeneous results (Q = 1.05 (P = 0.90), I^2 = 0%). The summary risk difference was similar in subgroup analyses of four studies that used RFA as a second-line therapy: 0.8 % (95% CI, –1.2 to 2.8 %; favoring AAD; Q = 1.07 (P = 0.78); I^2 = 0%). There was no statistical heterogeneity in risk difference of stroke between first- and second-line therapy (Z = 0.37, P = 0.71). The results were similar when two RCTs with no events in both arms were excluded in sensitivity analysis (Peto OR = 2.80 (95% CI, 0.39-19.9), favoring AAD; Q = 1.0 (P = 0.60); I^2 = 0%).

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).[28] 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.[29] Both studies did not explore the impact of anticoagulation therapy on the stroke events.

Quality-of-life **(Table 6)**

Two RCTs measured quality-of-life (QoL) using the 36-Item Short-Form General Health Survey (SF-36). 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 non-significant improved 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 (P=0.62).[24]

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.[28]

Avoiding anticoagulation

No studies directly compared freedom from anticoagulation in patients treated with RFA versus medical therapy.

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 non-statistically significant 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));[28] 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 and 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 studies reported multivariable analyses of the association between patient-level characteristics and AF recurrence.[25,27,28,30-46] 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; the studies are ordered by sample size.

Atrial fibrillation type. Thirteen studies tested AF type (paroxysmal versus nonparoxysmal, persistent, or chronic). Five studies found that nonparoxysmal (i.e., chronic or persistent) AF statistically significantly predicted higher rates of recurrent AF,[32,33,36,39,43] with HR ranging from 1.8 to 22 (among the four studies that reported data). Three of the eight studies that reported (or implied) no statistically significant association between AF type and AF recurrence reported the HRs for chronic, persistent, or nonparoxysmal AF (as opposed to the remaining studies, which reported only that there was no significant association).[28,31,38] The nonsignificant HRs ranged from 1.1 to 1.6 for AF recurrence. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Ejection fraction. Among 15 studies that evaluated EF in multivariable analysis for AF recurrence, three[31,35,41] reported statistically significant associations between lower EF and AF recurrence. 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. Al Chekakie et al. found that an EF less than 50% predicted AF recurrence (HR = 2.7, 95% CI 1.1, 6.5);[31] Calò et al. found that EF less than 45% predicted AF recurrence (HR = 5.2, 95% CI 2.0, 13);[31,35] Chen et al. reported only that EF was predictive of AF recurrence.[41] The four studies with nonsignificant associations of EF and AF recurrence that reported data used an EF threshold of 45%, analyzed EF on a continuous scale, or did not report how EF was parameterized; the range of HRs was 0.97 to 1.3. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Left atrial diameter. Sixteen studies analyzed LAD as a predictor of AF recurrence in multivariable models. Three found statistically significant associations between larger LAD and AF recurrence.[28,30,46] Similar to reporting of EF, the majority of studies failed to report how LAD was parameterized. Pappone et al. found that an LAD greater than 4.5 cm was predictive of AF recurrence (HR = 2.1, 95% CI 1.8, 2.7);[28] Berruezo et al. reported that larger LAD was predictive of AF recurrence (HR = 1.1, 95% CI 1.06, 1.2, per mm increase);[30] Oral et al. found a significant

association but failed to report the data.[46] Among the studies that reported no significant associations between LAD and AF recurrence, the HRs ranged from 0.96 to 1.11 when LAD was analyzed on a continuous scale (3 studies), 0.9 for LAD greater than 4.2 cm (1 study), and 1.2 in one study that did not define how the variable was analyzed. The remaining eight studies did not report data beyond stating lack of significance. There were no obvious features that differentiated the studies that found significant or nonsignificant associations.

Structural heart disease. Among seventeen studies that evaluated the presence of structural (or valvular) heart disease as a predictor of AF recurrence in multivariable models, one reported a statistically significant association at 12 months (HR 2.05, 95% CI 1.18, 3.6),[34] 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),[36] and one reported a trend (HR = 2.4, 95% CI 0.9, 6.3, P=.08).[45] Among the remaining studies that found no association, five reported HRs ranging from 0.6 to 2.4. 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. All studies evaluated age, one study did not evaluate sex. Among the studies that described the variables, age was analyzed either on a continuous scale or at thresholds of 65 years in two studies and 50 years in one. All studies found no association between either age or sex and rates of AF recurrence.

Other potential predictors. Among 13 studies, one reported a trend between the association of duration of AF and risk of recurrence of AF.[40] Only eight studies evaluated hypertension as a risk factor; of these only one found a significant association with AF recurrence.[30]. In two studies, frequency of AF episodes pre-procedure was not associated with rate of recurrence.[40,46] 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 two studies.[30,45] History of coronary artery or cardiac disease were not associated with recurrence in two studies.[25,28] Use of a variety of pre-procedure medications, including AAD did not predict recurrence in three studies.[25,31,41] One study each reported no association between AF recurrence and left ventricular mass, stroke or TIA history, body mass index, typical AFL, or other comorbidities. One study reported a statistically significant association between AF recurrence and pre-procedure vagal-mediated AF.[40]

Atrial fibrillation type: Unadjusted, univariable analyses

Twenty-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).[32-34,36-38,43,45,47-59] 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 odds ratio, OR) to explore the associations between AF types and AF recurrence. Separate meta-analyses were performed for the three comparisons reported in the studies: paroxysmal versus persistent AF; paroxysmal versus chronic AF; and paroxysmal versus nonparoxysmal (combined persistent and chronic). We calculated ORs for all studies based on the data provided and estimated P values of these ORs, regardless of how the data were analyzed in the original studies.

Paroxysmal versus persistent atrial fibrillation. Ten studies with 1,550 patients reported AF recurrence rates for both patients with paroxysmal and persistent AF.[32,34,37,47-53] The ten studies included 14 cohorts of patients (based on specific RFA intervention), as shown in **Figure 5**. Most studies reported PAF recurrence rates between 13% and 39%; Zhou et al. reported an atypically low recurrence rate of 5%[49] and Nilsson et al. reported a particularly high recurrence rate of about 73%.[34] The range of ORs for AF recurrence (paroxysmal versus persistent AF) was 1.43 to 11, with a median value of 2.1. Four of the 10 associations were statistically significant. Only two of these studies also included AF type in a multivariable analysis. Richter et al. found that PAF was associated with a lower risk of recurrence in both univariable and multivariable analyses.[32] In contrast, Nilsson et al. found that AF type was associated with recurrence in a univariable analysis, but not in a multivariable analysis.[34] Despite the clinical heterogeneity, including a wide range of rates of AF recurrence, the studies provided statistically homogeneous results (by meta-analysis). The summary OR was 2.24 (95% CI 1.71, 2.91, P<.001).

Paroxysmal versus chronic atrial fibrillation. Three studies with 1,294 patients reported AF recurrence rates for both patients with paroxysmal and chronic AF **(Figure 6)**.[47,54,55] PAF recurrence rates were broadly similar in the three studies, ranging from 13% to 23%. The ORs for AF recurrence (paroxysmal versus chronic AF) varied from 1.05 to 2.64; two of the studies found a statistically significant difference. None of the studies also evaluated AF type in a multivariable analysis. By meta-analysis, the three studies had borderline statistically heterogeneous results. The summary OR was 1.64 (95% CI 1.07, 2.51, P=.02).

Paroxysmal versus nonparoxysmal atrial fibrillation. Ten studies with 2,418 patients reported AF recurrence rates for both patients with paroxysmal and nonparoxysmal (both persistent and chronic) AF.[33,36,38,43,45,47,56-59] The ten studies included 13 cohorts of patients (based on specific RFA intervention), as shown in **Figure 7**. Most studies reported PAF recurrence rates between 13% and 34%; Cheema et al. reported an atypically high recurrence rate of 63%.[33] The range of ORs for AF recurrence (paroxysmal versus nonparoxysmal AF) varied from 0.88 to 4.3, with a median value of 2.0. Five of the 10 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;[33,36,43] one found that the association was highly statistically significant by univariable analysis, but not in a multivariable model;[38] and one study found that there was no significant association between AF type and recurrence in both univariable and multivariable models.[45] By meta-analysis, the studies had borderline statistically heterogeneous results. The summary OR was 1.97 (95% CI 1.51, 2.58 P<.001).

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. In contrast with studies published in previous years, the studies published in 2007 all found no statistically significant association between AF type (paroxysmal versus nonparoxysmal, persistent, or chronic) and AF recurrence. However, the range of ORs for AF recurrence in the 2007 studies (1.6 to 2.4) was consistent with the ORs found in earlier studies.

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 PV myocardium.[12] This involved the identification and ablation of triggering potentials in the PV myocardium. Studies that employed this technique have used the term segmental, focal, or ostial pulmonary vein isolation (PVI). For simplicity, all those 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 annulus (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 (AFL), a cavotricuspid isthmus ablation line (CTI) is also recommended.[1]

Fifteen RCTs,[34,39,45,46,48,50,60-68] one nonrandomized but controlled trial,[69] two prospective cohort,[70,71] and fifteen retrospective cohort studies[32,33,42,44,58,72-82] reported outcomes of RFA for AF using different techniques. Sample size in these studies ranged from 60 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. The one nonrandomized controlled trial compared PVI using antral ablation with versus without additional ablation dependent on residual potentials. Two RCTs excluded patients with PAF.[65,68] Five RCTs included only patients with PAF.[45,46,61,64,66] 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. Rest of the studies was 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.[34,46,50,62,63] 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 higher rate of success (freedom from AF recurrence) than patients who had ostial PVI (67% vs. 49%, $P \leq 0.05$;[50] 88% vs. 67%, $P=0.02$;[46]). Two[34,63] of three

studies[34,62,63] 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).[39,48,60,61,66,68] One study only included patients with persistent AF.[68] 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 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;[48] roof line: 87% vs. 69%, P=0.04;[61] MIL: 74% vs. 83%, no P value;[60] Two studies did not find a significant difference in AF recurrence with the addition of left-sided ablation lines.[39,66]

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.[67] This study of 108 patients with AF (59% PAF) and at least one episode of AFL 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 AFL, while 5% of the patients in the group without CTI had recurrent sustained AFL.

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 close gaps in patients with residual intraoperative PV conduction).[45] 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.[64] 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.[65] At 10 months followup, 48% of patients in the former versus 33% in the latter had no AF or AFL after the initial procedure and did not need AADs (P=0.20).

Nonrandomized controlled 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.[69] At 15 months followup, 13% of patients in the former versus 53% in the latter had stable SR and did not need AADs (P=0.002). This analysis included patients who had repeat procedure (13%).

Prospective cohort

PVI with or without SVC isolation

One study followed 407 patients who had either antral PVI or antral PVI with superior vena cava (SVC) isolation.[70] 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 SVC 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 SVC 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 AFL or AFL during ablation). There was no significant difference in the rate of stable SR at 30 months followup (79% vs. 82%, respectively).[71]

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.[77,78,81] 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;[77] 69% vs. 47%, P<0.05[2];[78]). 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.[81]

Ostial PVI versus WACA

Six studies compared ostial PVI with WACA.[32,33,72,75,78,79,82] Sample size ranged from 73 to 234. Followup ranged from 6 to 26 months. While four[33,72,75,78] of six studies reported that patients who had WACA had less AF recurrence than patients who had ostial PVI, only one of

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

them provided actually statistical comparison (87% vs. 47%, P<0.05[3];[78]). Two studies did not report significant differences in AF recurrence rates between the two groups.[32,79,82]

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.[44] 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.[58,74] Sample size was 84[74] and 200,[58] respectively. Followup were at 9[74] and 12 months,[58] 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%;[74] 85% vs. 80%;[58]). 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.[58]

RFA with or without adenosine infusion

Two studies compared RFA with or without ablation of adenosine-induced potentials.[73,76] Both studies used historical cohorts for comparisons. Sample size was 202;[76] and 252;[73] respectively. Followup were at 20;[76] and 6 months;[73] 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;[76] 73% vs. 60%, P=0.04;[73]).

Miscellaneous comparisons

One study compared 102 patients who had RFA with additional ablation at sites that innervate vagal reflexes[4] to 195 patients who had RFA only.[42] 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 with 20 patients who had ablations of 4 to 5 PVs.[80] At 17 months followup, 90% of patients in the former versus 80% in the latter were free from atrial tachyarrhythmia (no P value reported).

Technical issues related to RFA (Tables 12 and 13)

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

Five RCTs, three nonrandomized controlled trials, and four retrospective cohort studies reported outcomes of PVI for AF comparing catheter tips, energy outputs, imaging guides, or postprocedure duration of observation in the electrophysiology (EP) laboratory. Sample size in these studies ranged from 60 to 335 subjects. Patient characteristics were heterogeneous across

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

[4] 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).

studies, including type of AF (51% to 100%), male gender (52% to 90%), mean LAD (3.5 to 4.8 cm), and mean EF (33% to 66%).

Randomized controlled trials

8 mm versus irrigated (closed or open) tip Catheter

Overall, data from three RCTs [43,83,84] 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 one study was rated good;[43] two were rated fair.[83,84]

Using a two by two 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.[43] The primary outcome, long-term rhythm control of AF, was defined as complete freedom or more than 90 percent 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). One patient who died from an atrioesophageal fistula in the 8 mm tip catheter arm was excluded from the primary endpoint analysis.

Two RCTs compared the outcomes of PVI using an 8 mm versus open irrigated tip catheter for treatment of AF.[83,84] The first RCT randomized 180 patients (mean followup 6 months) into 3 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).[83] 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.[84] 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 3 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).[83] 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 the 3 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.[85] Patients were randomized into

three groups of different observation time after PVI: group A, no additional observation time; group B, 30 minutes of observation; and group C, 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%) in Group A, 3/21 patients (14%) in Group B, and 1/21 patients (5%) in Group C had atrial tachyarrhythmia lasting >30 seconds. The differences between the three groups were significant (P=0.03).

Different Imaging Modalities

One poor quality RCT compared the outcomes of PVI guided by a 3-dimensional (3-D) mapping system versus the same ablation technique using only conventional fluoroscopic guidance in 60 patients with drug refractory AF.[86] An open irrigated tip catheter was used in all patients. Over a mean followup of 7 months, fewer patients in the 3-D 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-D 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 6 patients; the timing of the recurrence was not reported, and in four patients the arrhythmias self-terminated.

Nonrandomized controlled trials

Different Energy Outputs

One poor quality nonRCT 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.[87] After a mean followup of 15 months, there was no significant difference in the proportion of patients with stable SR without symptomatic recurrent AF between groups (76% vs. 74%, respectively; NS).

Different Imaging Modalities

In the first study, the first half of 100 consecutive patients with drug refractory AF underwent PVI guided by conventional 3-D electroanatomic mapping (Carto XP) were compared to the second half of patients who underwent PVI using the same 3-D electroanatomic mapping with the addition of CT image integration technology (Carto MERGE). The addition of CT image integration technology was associated with an improvement in rhythm control with or without AADs as compared to conventional 3-D electroanatomic mapping (Carto XP) used in the historical controls (85% vs. 68% P=0.018).[59]

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-D mapping system. Patients in the two groups had similar rates of rhythm control over a mean followup of 10 months (74% vs. 68%, P=NS).[88]

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 8mm tip catheter compared to those who underwent conventional 4mm tip catheter.{Yamada, 2006 464 /id} 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 or 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 of microbubbles,[89] mapping the earliest PV potential alone versus additional mapping by electrogram polarity reversal approach,[90] and circular mapping versus electroanatomic mapping.[91] A total of 1,149 patient with drug refractory AF and undergone PVI were analyzed.

In one study, rhythm control was significantly bettter in patients who underwent ICE-guided PVI compared to circular mapping guided PVI (87% versus 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).[89] 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.[91] No other significant differences in the patients' outcome were reported in the remaining studies.

Key Question 4. What are 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 PV ostia including WACA) PV ablation.

A total of 79 studies involving 16,616 patients reported adverse events: extraostial RFA with irrigated tip catheters (26 studies, **Table 14**), conventional 8 mm tip catheters (17 studies, **Table 15**), or other catheters (10 studies, **Table 16**), ostial PVI with irrigated tip catheter (17 studies, **Table 17**), conventional 8 mm tip (8 studies, **Table 18**), or other tips (7 studies, **Table 19**), and various ablation approaches (7 studies, **Table 20**).

In general, 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 three 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.

Sixty-eight studies reported at least one adverse event associated with RFA. Adverse events included PV stenosis;[24,33,34,37,41,45,47,50,53,57,59,61-63,67,69,71,76-81,89,91-102] cardiac tamponade;[25,33,36,37,39,41,44,45,47,48,50,53,57,61,66,68,69,71,73,75,76,83,92-94,99-110] stroke and/or TIA;[23,25,27,30,33,34,36,37,41,43,45,47-49,53,54,57,59,62,66,68,75,83,87-89,92,93,95,96,99-102,104,108-111] bleeding/hematoma;[33,35,45,63,78,100,102,108] pseudoaneurysm;[33,78,85,101,102,104,108] femoral vein thrombosis;[37,94,102] or arteriovenous fistula.[37,78,101,102,106,107] **(see Tables 14-20)**

Fifty-six studies assessed the rates of asymptomatic or symptomatic PV stenosis. The majority of these papers reported rates of asymptomatic PV stenosis at 4% or less. Twenty-one studies did not identify a single case of PV stenosis (i.e., reported zero event). Rates of symptomatic PV stenosis requiring interventions were reported at less than 1% in four studies.[37,100-102] Rates of cardiac tamponade were reported at less than 1% in the majority of the 45 studies that evaluated this adverse event. Rates of cerebrovascular events were reported at 4% or less in the majority of 51 studies that evaluated stroke and/or TIA, and twelve additional studies reported no cerebrovascular events. Ten studies assessed for atrioesophageal fistula; of which one study reported a rate of 1.2% (1/82)[43] and another study reported a rate of 0.1% (1/1058).[102] The remainder did not identify any cases. In this review of 56 studies, four deaths were reported within 30 days post-procedures: one died from pulmonary infection,[49] one died from anaphylaxis after the procedure,[102] and two died from atrioesophageal fistula.[43,102]

Patient characteristics associated with adverse events

Nine studies evaluated patient characteristics as predictors of certain procedure-related adverse events. Eight studies used univariate analysis to compare risk of adverse events in patients with or without a single predictor of interest;[41,47,57,86,93,95,96,109] whereas a large patient survey assessed multiple patient-level predictors of various complications.[101] 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

None of the studies examined the relationship between operator-level characteristics and adverse events of RFA.

Only one study reported data on the relationship between a center's learning curve for the procedure and adverse event rates. Using an Italian data registry of 1011 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.[101] In univariate analyses, none of these adverse event rates were statistically different between the first 50 procedures in a center and those performed thereafter.

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, readmissions and reinterventions for persistent, paroxysmal and long-standing persistent (chronic) atrial fibrillation?

Our literature search identified five RCTs and two retrospective cohort studies of patients with AF that compared RFA with medical treatment. Studies mainly included patients with PAF who had failed AADs. The patients underwent various ablation approaches and medical treatments across studies, and clinical outcomes were assessed in non-uniform ways. The methodological quality of the studies varied from good to poor.

Rhythm control

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 (rate ratio: 3.46 (95% CI, 1.97-6.09)) at 12 months postprocedure. The summary estimate was derived from meta-analysis of three RCTs.

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).

Rates of congestive heart failure

There is insufficient evidence compare the rate of congestive heart failure between RFA and medical treatment. Only one observational study reported 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 insufficient evidence to compare left atrial and ventricular size changes between RFA and medical treatment as no study addressed this question.

Rates of stroke

There is a moderate level of evidence to show that there was 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: 0.7 % (95% CI, –1.2 to 2.6 %; favoring AAD)). The summary estimate was derived from meta-analysis of five RCTs.

Quality of life

There is a low level of evidence to suggest that RFA improves QoL compared to medical treatment. Two RCTs and one observational study reported more improvement in general or physical functioning score of SF-36 in patients who underwent RFA compared to patients who had medical treatment alone (net difference between two treatments: +7 to +25; favoring RFA). However, these studies assessed the results at non-uniform time points and therefore the findings may not be valid.

Avoiding anticoagulation

There is insufficient evidence to compare the rates of avoiding anticoagulation between RFA and medical treatment as no study addressed this question.

Readmissions

There is low level of evidence to suggest that findings on differences in readmission rates between patients treated with RFA and those treated with AADs are inconsistent. 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 that AF type, namely nonparoxysmal AF, is predictive of a higher rate of AF recurrence. Although univariable analyses are relatively homogeneous in showing a strong association (OR about 2), only a minority of multivariable analyses bear this out. The data from multivariable analyses were inadequately reported to fully assess the association across studies. Twenty studies reported multivariable analyses of the association between patient-level characteristics and AF recurrence. In five of 13 studies, nonparoxysmal AF was significantly associated with higher rates of AF recurrence. Among the studies that reported sufficient data, the hazard ratios for AF recurrence of nonparoxysmal versus paroxysmal AF ranged from 1.1 to 22. Twenty-one studies reported rates of AF recurrence for different subgroups of patients based on their type of AF. Meta-analysis of the 10 studies comparing persistent and paroxysmal AF revealed statistically homogeneous results despite the clinical heterogeneity of the studies; the OR of AF recurrence for persistent versus paroxysmal AF was 2.24 (95% CI 1.71, 2.91, $P<0.001$). Only three studies compared chronic versus paroxysmal AF. Though statistically heterogeneous, the summary OR for AF recurrence was 1.64 (95% CI 1.07, 2.51, $P=0.02$). Ten studies comparing nonparoxysmal and paroxysmal AF had similar findings. Though minimally statistically heterogeneous, the summary OR for AF recurrence was 1.97 (95% CI 1.51, 2.58 $P<0.001$). No study or population factors were found to explain the heterogeneity among the studies.

There is a moderate level of evidence that EF and LAD are not independent predictors of AF recurrence. In multivariable analyses, three of 15 studies found an association between lower EF and AF recurrence, and three of 16 found an association between larger LAD and AF recurrence.

There is a high level of evidence that age, sex, and the presence of structural heart disease are not associated with AF recurrence. No study found consistent associations between structural heart disease (17 studies) or duration of AF (13 studies) and AF recurrence. All studies found no association with age and 19 studies found no association with sex.

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

There is insufficient evidence 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

Fifteen RCTs, one non-randomized but controlled trial, two prospective cohort studies, and 15 retrospective cohort studies met eligibility criteria and reported outcomes of AF after RFA using different approaches. Approaches used in these studies included PVI within and around PV ostia, a wide area circumferential approach, 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, roof or posterior LA 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. Only one RCT examined the incremental benefit of adding a CTI ablation line in patients undergoing RFA for AF. This study, which included patients with AF and at least one episode of AFL, 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.

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. Data from three 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 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, imaging modalities, postprocedure durations of observation in the EP laboratory, or various mapping techniques (e.g., circular mapping alone versus circular mapping enhanced with intracardiac echocardiogram with or without monitoring of microbubbles).

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

There is a moderate level of evidence to show that adverse events associated with RFA are relatively uncommon. Sixty-eight studies 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 in a number of the studies. 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. Fifty-six studies assessed the rates of asymptomatic or symptomatic PV stenosis. The majority of these studies reported asymptomatic PV stenosis rates of 4% or less; 21 studies did not identify a single case of PV stenosis (i.e., reported zero events). Symptomatic PV stenosis requiring interventions occurred in less than 1% of patients in four studies. Cardiac tamponade was reported to occur in less than 1% of patients in the majority of the 45 studies that evaluated this adverse event. Rates of cerebrovascular events were reported at 4% or less in the majority of the 51 studies that evaluated stroke and/or TIA, and 12 additional studies reported no cerebrovascular events. Ten studies assessed for atrioesophageal fistula. Among these, one study reported a rate of 1.2% and another study reported a rate of 0.1%; the remainder did not identify any cases. Among 56 studies, four deaths were reported within 30 days post-procedure; one patient died from a pulmonary infection, one died from anaphylaxis after the procedure, and two died from atrioesophageal fistulas. Major adverse events associated with RFA are relatively uncommon. 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.

Discussion

Key Question 1: Medical treatment versus 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 (rate ratio: 3.46 (95% CI, 1.97-6.09)) at 12 months postprocedure. This finding is in general agreement with a previously published meta-analysis.[112] 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 AADs).

Key Question 2: Patient- and intervention-level characteristics associated with rhythm control

There is low level of evidence that AF type, namely nonparoxysmal AF, is predictive of a higher rate of AF recurrence. Although univariable analyses are relatively homogeneous in showing a strong association (OR about 2), only a small minority of multivariable analyses bear this out. The data from multivariable analyses were inadequately reported to fully assess the association across studies.

There is a moderate level of evidence that EF and LAD are not independent predictors of AF recurrence. There is a high level of evidence that age, sex, and the presence of structural heart disease are not associated with AF recurrence. 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 WACA resulted in a higher rate of freedom from AF recurrence compared to ostial PVI (absolute difference: ~20%) in patients with either PAF 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 CTI ablation line to PVI in patients with persistent or permanent AF and a history of AFL 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 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.

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

Key Question 4: Adverse events associated with RFA

There is a moderate level of evidence to show that major adverse events associated with RFA are relatively uncommon. Cerebrovascular events and asymptomatic PV stenosis were reported at rates of 4% or less in the majority of the studies. Symptomatic PV stenosis and cardiac tamponade were generally reported at rates of 1% or less. Two studies reported rates of atrioesophageal fistula at 0.9% and 1.3%. A total of four deaths were reported in all the studies reviewed (one patient died from a pulmonary infection, one died from anaphylaxis after the procedure, and two died from atrioesophageal fistulas). 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, severe and moderate PV stenoses were defined differently across studies. Some clearly reported stroke as peri-procedural, and some reported stroke without stating a time of occurrence.

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 one 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 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. 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 suggests that certain patients with PAF (those in whom symptoms lasted for at least 3 months) may benefit from RFA as a first-line therapy, further characterizations of such patients will be needed.

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 on the efficacy of RFA for AF should also be targeted at patient population under-represented in the current literature but often encountered in clinical practice (e.g., the elderly, patients with multiple comorbidities).

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Abbreviations

3-D	three dimension(al)
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
CHF	congestive heart failure
CS	coronary sinus
CTI	cavotricuspid isthmus line
CVA*	cerebrovascular accident (stroke)
c/w*	consistent with
EF	left ventricular ejection fraction
EP	electrophysiology
EPC	Evidence-based Practice Center
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 (size)
LV*	left ventricle
MI	myocardial infarction
MIL	mitral isthmus line
nd*	no data (not described)
nonParox*	nonparoxysmal (atrial fibrillation)
nonRCT	Nonrandomized, but controlled trial
NS*	(statistically) nonsignificant
OR	odds ratio
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	rate ratio
SF-36	the 36-Item Short-Form General health Survey
SR	sinus rhythm
SVC	superior vena cava
TEE	transesophageal echocardiography
TEP	technical expert panel
TIA	transient ischemic attack
WACA	wide area circumferential ablation
WPW	Wolff-Parkinson-White syndrome

* Used in tables only.

Table 1. Study 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) • Cavotricaspid isthmus line (RA)[f]	8 mm or 3.5 mm cooled[g]	Yes	No		68						

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							
Non-randomized Comparative Studies													
Second-line therapy													
Pappone, 2003[28] Italy 12875749	AAD					582	1998-2001	70	65	58	4.6	54	4.6[o]
	RFA (CPVA)[p]	nd	nd	Yes	No	589							
Rossillo, 2008[29] Italy 18268419	AAD					85	2002-2004	16[q]	62	84	4.3	57	8[r]
	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 dysopyramide 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 mon 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. 5.5 years for RFA group and 3.6 years for AAD group (P<0.001).
p. 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.

q. No patients in AAD group had paroxysmal AF.
r. No data available for AAD group.

Table 2. Rhythm control in patients 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)	Good
					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
Retrospective Comparative										
Second-line therapy										
Pappone, 2003[28] 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[h]		<0.05	
Rossillo, 2008[29] Italy 18268419	RFA (PVI)	AAD	85	85	Stable sinus rhythm[i]	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. 95% CI, 0.24-0.37
i. 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 intervcal; 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 hear failurel in patients received RFA vs. AAD

Study, Year	Description		No. Analyzed		Outcome	Metric/	Results			Quality
UI	Interv	Cont	Interv	Cont		Units	Interv	Cont	P Between	
Retrospective Comparative										
Second-line therapy										
Pappone, 2003[28] 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 size or LV function in patients received RFA vs. AAD

Study, Year UI	Description Interv	 Cont	No. Analyzed Interv	 Cont	Outcome	Metric/ Units	Results Interv	 Cont	 P Between	Quality
Randomized Controlled Trials										
Second-line therapy										
Oral, 2006[26] US & Italy 16510747	RFA (LACA)	Amiodalone	77	69	LAD at 12 mo	cm	4.0	4.5	<0.001[a] (t-test)	Fair
Oral, 2006[26] US & Italy 16510747	RFA (LACA)	Amiodalone	77	69	LVEF at 12 mo	%	62	55	<0.001[b] (t-test)	Fair
Retrospective Comparative										
Second-line therapy										
Pappone, 2003[28] 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; 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 received RFA vs. ADD

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	Good
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
Retrospective Comparative										
Second-line therapy										
Pappone, 2003[28] Italy 12875749	RFA (CPVA)	AAD	589	582	Stroke	Crude %	2	8	nd	Poor
Rossillo, 2008[29] Italy 18268419	RFA (PVI)	AAD	85	85	Stroke	Crude %	1	6	0.09 (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.

Table 6. Quality of life in patients 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	0.69 (ANOVA)	
					SF-36, physical fitness score at 12 mo		+23	-2		
Retrospective Comparative										
Second-line therapy										
Pappone, 2003[28] 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; 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.

Table 7. Re-admission in patients received RFA vs. ADD

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/patien-year	1[c]	2[c]	0.34 (t-test)	Good
Retrospective Comparative										
Second-line therapy										
Pappone, 2003[28] Italy 12875749	RFA (CPVA)	AAD	nd[d]	nd[d]	Change in re-addmission[e]	Time/patient-year	-0.7	+0.5	nd	Poor
			nd[f]	nd[f]			-1.8	-1.2		

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

a. Two patient was 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 recurrence AF.

Table 8A. Predictors of AF recurrence in multivariable analyses

Study	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		
Verma 2005[38]	16	Mixed	700	0	0	0	0		0	0				
Pappone 2003[28]	30	Mixed	589	0	0	0	**++ 2.1**	0	0		0	CAD	0	
												LV mass	0	
												CVA / TIA	0	
Pappone 2004[39]	12	Parox Chronic	560	**++ Chronic 22**				0	0	0				
Chen 2004[41]	14	Mixed	377		0	++ nd	0	0	0			No. of AAD	0	Model included PV ostial size
Pappone 2004[42]	12	Parox	297		0	0	0	0	0	0				
Richter 2006[32]	6	Parox Persist	234	**++ Persist 1.8**		0	0	0	0	0		BMI	0	Model also included AF inducibility
Della Bella 2005[37]	12	Parox Persist	234					0	0	0	0			
Cheema 2006[33]	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[40]	15	Parox	188		**+ nd**	0	0	0	0	0		Vagotonic AF	**++ nd**	
												Frequency of AF episodes	0	
Al Chekakie 2007[31]	14	Mixed	177	0	0	**++ 2.7**	0	0	0	0	0	ACE-I, ARB, or statins (individually / collectively)	0	
Berruezo 2007[30]	13	Mixed	148	0	0	0	**++ 1.1**	0	0	0	**++ 2.8**	Other echo parameters	0	
Essebag 2005[36]	6/12*	Mixed	102	**++ / ++* NonParox 3.2/4.8**				0	0	**++ / 0* 4.0 / NS**	0			Model also included AF inducibility
Nilsson 2006[34]	12	Parox Persist	100	0	0		0	0	0	**++ 2.05**				
Jais 2004[44]	12	Parox	100		0?†	0?†	0?†	0?†	0?†	0				
Liu 2005[45]	13	Mixed	100	0	0	0	0	0	0	+ 2.4		Typical AFlutter	0	
												Other echo parameters	0	
Dixit 2006[43]	6	Mixed	82	**++ NonParox nd**				0			0	Comorbidities	0	
Oral 2003[46]	6	Parox	80		0	0	**++ nd**	0	0	0		Frequency of AF episodes	0	
Calò 2006[35]	14	Persist Perm	80	0?‡		**++ 5.2**	0?‡	0?‡	0?‡	0?‡				Model included continuation of AAD

Study	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		
Stabile 2006[25]	12	Parox Persist	68	0	0	0	0	0	0	0	0	Heart disease	0	
												Various drugs	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.

Table 8B. Details of multivariable models predicting AF recurrence

Study	Predictor Association with Outcome, HR (95% CI)
Pappone 2003[28]	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.
Verma 2005[38]	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 2004[39]	Chronic AF (vs paroxysmal) 22 (6.7, 74); Age, Sex, and Heart disease were nonsignificant.
Chen 2004[41]	AF duration, LA size, Age, Gender, Number of AAD were not predictive. EF was. No further data.
Pappone 2004[42]	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).
Richter 2006[32]	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[37]	Sex, Age >50 years, structural heart disease, mitral valve disease, and HTN not predictive.
Cheema 2006[33]	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[40]	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[31]	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[30]	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.
Essebag 2005[36]	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[34]	Structural heart disease 2.05 (1.18, 3.6). Other predictors nonsignificant. Only LAD variable defined, >4.0 cm.
Jais 2004[44]	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 2005[45]	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[43]	Presence of paroxysmal AF was the only variable that affected (complete freedom from AF at 6 months off AADs])
Oral 2003[46]	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[35]	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.

Table 9. Association between type of atrial fibrillation and recurrence of atrial fibrillation in univariable (unadjusted) analyses

Study	Time, mo	Total N	Paroxysmal, % no/N		Persistent, % no/N		Chronic,* % no/N		Comparison	OR (95% CI)	P value
Bhargava 2004[47]	15	323	13%	22/174	20%	7/35	22%	25/114	Persist vs Parox	1.73 (0.67, 4.43)	NS
									Chronic vs Parox	1.05 (0.52, 2.12)	NS
									Nonparox vs Parox	1.20 (0.63, 2.26)	NS
Della Bella 2005[37]	13	234	24%	49/204	42%	25/59			Persist vs Parox	2.33 (1.27, 4.27)	.007
Richter 2006[32]	6	234	33%	54/165	52%	36/69			Persist vs Parox	2.22 (1.27,4.00)	.006 (c/w multivariable)
Fassini 2005[48]	12	187	~31%	~39/126	~44%	~27/61			Persist vs Parox	1.79 (0.94, 3.33)	.08
Zhou 2007[49]	7	148	5%	4/84	11%	7/64			Persist vs Parox	2.46 (0.69, 8.79)	NS
Arentz 2007[50]	15	110	37%	25/67	49%	21/43			Persist vs Parox	1.61 (0.74, 3.45)	NS
Beukema 2005[51]	15	105	25%	13/52	40%	21/53			Persist vs Parox	1.97 (0.85, 4.54)	NS
Nilsson 2006[34]	12	100	~73%	~37/51	~92%	~45/49			Persist vs Parox	4.26 (1.29, 14.0)	.02 (NS multivariable)
Kottkamp 2004[52]	12	100	26%	~21/80	78%	~16/20			Persist vs Parox	11.2 (3.37, 37.4)	<.001
Kistler 2006[53]	6	94	39%	18/46	48%	23/48			Persist vs Parox	1.43 (0.63, 3.23)	NS
Meta-analysis		**1550**							**Persist vs Parox**	**2.24 (1.71, 2.91) homogeneous**	**<.001**
Oral 2006[54]	24	755	23%	~113/490			32%	~85/265	Chronic vs Parox	1.58 (1.13, 2.20)	.007
Pappone 2001[55]	10	251	15%	27/179			32%	23/72	Chronic vs Parox	2.64 (1.39, 5.02)	.003
Meta-analysis		**1294**							**Chronic vs Parox**	**1.64 (1.07, 2.51) heterogeneous**	**.02**
Verma 2005[38]	16	700	14%	38/274		37%	114/426		Nonparox vs Parox	1.20 (0.63, 2.26)	<.001 (NS multivariable)
Chugh 2005[56]	13	349	13%	30/227		25%	31/122		Nonparox vs Parox	2.24 (1.28, 3.92)	.004
Tang 2006[57]	13	263	23%	45/199		27%	17/64		Nonparox vs Parox	1.24 (0.65, 2.36)	NS
Cheema 2006[33]	26	200	63%	58/92		80%	86/108		Nonparox vs Parox	2.27 (1.22, 4.35)	.01 (c/w multivariable)
Verma 2007[58]	12	200	14%	17/120		23%	18/80		Nonparox vs Parox	1.75 (0.85, 3.70)	NS
Essebag 2005[36]	12	102	26%	~16/60		55%	~23/42		Nonparox vs Parox	3.33 (1.44, 7.67)	.005 (c/w multivariable)
Martinek 2007[59]	6	100	31%	18/59		49%	20/41		Nonparox vs Parox	3.39 (1.07, 10.7)	.07
Liu 2005[45]	13	100	31%	23/75		28%	7/25		Nonparox vs Parox	0.88 (0.32, 2.39)	NS (c/w multivariable)
Dixit 2006[43]		82	34%	20/58		70%	16/23		Nonparox vs Parox	4.34 (1.53, 12.3)	.006 (c/w multivariable)
Meta-analysis		**2418**							**Nonparox vs Parox**	**1.97 (1.51, 2.58) 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
RCTs													
Arentz 2007[50] Germany 17562956	PVI (ostia)	WACA	irrigated	yes	no	110	2004-2006	61	56	75	4.0	nd	5.5
Oral 2003[46] 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[34] 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[62] 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[63]	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[68] 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[39] 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[48] Italy 1630289	PVI	PVI + mitral isthmus line (MIL)	irrigated	yes	no	187	nd	67	55	80	4.26	56	nd
Haissaguerre 2004[60] France 15184286	PVI + (CTI)	PVI + CTI + MIL	4 mm irrigated	yes	yes	70	nd	nd	53	74	4.3	67	5.1

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
Sheikh 2006[66] 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[61] France 16344401	PVI (antrum) + Cavotricus pid 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[67] 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
Liu 2006[45] China 17239094	WACA, then closing gaps in pts with residual PV conduction (aggressiv e)	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
Oral 2004[64] 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[65] 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-RCTs													

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
Mantovan 2005[69] 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
Prospective cohorts													
Arruda, 2007[70] 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
Shah 2007[71] 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[77] Japan 17397672	PVI (ostia)	circumferential PV antrum ablation	8 mm	yes	yes	77	nd	100	58	84	3.41	67	5
Schwartzman 2003[78] US 14574043	PVI (ostia)	PVI (antrum); WACA	nd	yes	yes	112	nd	100	55	81	4.0	56	nd
Yamane 2007[81] Japan 17457004	PVI (ostia)	PVI (antrum)	8 mm	yes	yes	187	nd	66	53	77	3.9	nd	nd
Richter 2008[82] 2006[32] 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

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
Cheema 2006[33] USA 17019636	PVI (ostia) + Cavotricus pid 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[72] China 16117858	PVI (ostia)	WACA	irrigated tip in WACA	yes	no	151	nd	86	57	72	3.78	67	6.9
Mansour, 2004[75] USA 15149421	PVI (ostia)	WACA	nd	yes	no	80	2000-2002	81	54	85	4.0	nd	nd
Tamborero 2005[79] 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
Jais 2004[44] 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[58] 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[74] 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[73] Japan 17286569	WACA	WACA + ablation of adenosine induced potentials	8 mm	yes	yes	252	2003-2005	78	55	83	4.14	nd	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
Matsuo 2007[76] 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
Walczak 2006[80] 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[42] Italy 14707026	WACA + posterior LA lines + MIL	WACA + posterior LA lines + MIL + vagal denervatio n	nd	nd	nd	297	1999-2002	100	49	nd	3.9	58	7.0

*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
RCTs										
Arentz 2007[50] Germany 17562956	PVI (ostia)	WACA	55	55	Freedom from AF (no AAD, after 1 ablation)	15 mo	49%	67%	≤0.05	Fair
Oral 2003[46] 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[34] 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[62] 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[63]	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[68] 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
Pappone 2004[39] 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

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
					freedom from recurrent AF (3 pts had reablation for AF)	12 mo	87% (est.)	88% (est.)	0.57	
Fassini 2005[48] 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[60] 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[66] 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[61] 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[67] 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	
Liu 2006[45] 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[64] 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[65] 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
Non-RCTs										
Mantovan	PV antrum	PV antrum	30	30	stable SR	15.4 mo	57%	83%	0.024	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
2005[69] Italy 16403059	ablation (PVI not checked)	ablation + assessment of PVI with further ablation for residual potentials			SR (no AADs; 8 pts had reablation)	15.4 mo	13%	53%	0.002	
Prospective cohort										
Arruda, 2007[70] US 17850288	PVI (antrum) or PVI (antrum) + SVC isolation		407		AF recurrence	14.8 mo	16%			Poor
Shah 2007[71] 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[77] Japan 17397672	PVI (ostia)	circumferential PV antrum ablation	50	27	AF free (no AAD)	6 mo	50%	89%	<0.001	Poor
Schwartzman 2003[78] 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[81] 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	

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
			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	
Richter 2008[82] 2006[32] Austria 18328850 17038349	PVI	WACA ± CTI (?)	83	151	freedom from AF (?AADs)	6 mo (median)	64%	60%	nd	Poor
Cheema 2006[33] 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[72] 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[75] 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[79] Spain 16311935	PVI (ostia)	WACA	32	41	Freedom from AF recurrence	15 mo	72%	76%	NS	Poor
Jais 2004[44] 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
Verma 2007[58] 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[74] US 16843185	WACA+ roof line + MIL	CFAE ablation	42	42	no AF (no AAD, single ablation)	9 mo	67%	71%	0.6	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
Hachiya 2007[73] 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[76] 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[80] 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[42] 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

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
RCTs												
Dixit 2006[43] 16879626	PVI - 8 mm	PVI – Closed irrigated tip	No	yes	82	2003-2005	72	57	73	nd	nd	5.2
Marrouche 2007[84] 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[83] 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[85] 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
Tondo, 2005[86] Italy 15683472	PVI guided by 3D electroanatomic mapping (NavX)	Group 2: PVI guided by conventional fluoroscopy	WACA; CTI	no	60	nd	63	56	52	4.0	57	nd
Non-RCTs												
Nilsson 2006[87] 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[a]	4.6 (45 W) vs. 6.4 (30 W)
Martinek 2007[59] Austria 17897124	PVI - conventional electro-anatomic mapping (Carto XP)	PVI - multislice CT integration with electroanatomic mapping (Carto MERGE)	WACA or RFA of CFAEs	no	100	2005	59	56	85	4.8	55	6.5
Estner 2006[88] Germany 16831837	PVI guided by conventional fluoroscopy	PVI guided by 3D electroanatomic mapping (NavX) (without 3D geometric reconstruction)	No	no	64	nd	94 (PVI) vs. 88 (NavX)	59	75	4.7	33	5.6
Retrospective cohorts												
Yamada, 2006[113] 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[89] 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
Yamane, 2002[90] 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

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
Saad 2003[91] USA 12693885	PVI guided by a circular mapping catheter	PVI guided by a 3D electroanatomic mapping system (?which one)	No	no	335	nd	52	54	78	4.2	53	5.2

a. CHF: 4.4% (45 W) vs. 9% (30 W)
b. 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	
RCTs of 8mm vs. irrigated tip											
Dixit 2006[43] 16879626	PVI - 8 mm	PVI – Closed Irrigated tip	41[a]	40	Complete freedom from AF off AAD	6	rate	61%	50%	NS	Good
Kanj 2007[83] (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[83] (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[84] Germany 17490437	PVI – 8 mm	PVI – Open Irrigated tip	27	26	Recurrence of atrial arrhythmia[d]	14	rate	19%	22%	NS	Fair
RCT of different tip outputs											
Kanj 2007[83] (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
RCT of different imaging Modalities											
Tondo, 2005[86] Italy 15683472	PVI guided by 3D electroanatomic mapping (NavX)	PVI guided by conventional fluoroscopy	30	30	AF recurrence	7	rate	10%	20%	nd	Poor
RCT of different Obs time											

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[85] (comparison 1) China 17522081	PVI - no intraoperative post procedure observation (Obs) time	PVI – 30 min Obs time	18	21	Any AT (symptomatic or asymptoatic) lasting >30 secs (documented)	6	rate	39%	14%	.03[g]	Fair
Wang, 2007[85] (comparison 2) China 17522081	PVI - no intraoperative post procedure observation (Obs) time	PVI – 60 min Obs time	18	21	Any AT (symptomatic or asymptoatic) lasting >30 secs (documented)	6	rate	39%	5%	.03[g]	Fair
Non-RCTs											
Nilsson 2006[87] 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[59] Austria 17897124	PVI - conventional electro-anatomic mapping (Carto XP)	PVI - multislice CT integration with electroanatomic mapping (Carto MERGE)	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[88] Germany 16831837	PVI guided by conventional fluoroscopy	PVI guided by 3D electroanatomic mapping (NavX) (without 3D geometric reconstruction)	32	32	Freedom from recurrence of symptomatic AF	10.0 (fluoroscopy) vs. 9.5 (NavX)	rate	87%	90%	nd	Poor
					Sinus rhythm	10.0 (fluoroscopy) vs. 9.5 (NavX)	rate	68%	74%	NS	
					Asymptomatic AF	10.0 (fluoroscopy) vs. 9.5 (NavX)	rate	19%	16%	NS	
Retrospective Cohorts											

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	
Yamada, 2006[113] 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[89] 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[89] 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[90] 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[91] 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

a. Excluding patient who died from atrio-esophageal fistula.
b. Patients with recurrent AFduring 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-mon 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 (%)	
Khaykin, 2004[92] 15851113	18	3/336 (0.9%)[b]	4/336 (1%)	1/336 (0.3%) [1/336 (0.3%)]					
Tang, 2006[57] 17235682	13	2/263 (0.8%)[c]	4/263 (2%)	3/263 (1%)				Pneumothorax	1/31 (3%)
								Cardiac arrest	1/232 (0.4%)
Forleo, 2007[93] I7636302	23	2/221 (0.9%)[c]	4/221 (2%)	2/221 (0.9%) [2/221 (0.9%)]					
Shah, 2007[71] 17655668	30	3/188 (2%)[d]	3/188 (2%)					Embolic events	1/188 (0.5%)
Rotter, 2005[103] 16403060	nd		2/181 (1%)						
Bertaglia, 2005[104] 15869666	19		2/143 (1%)	[1/143 (0.7%)]		1/143 (0.7%)[e]		Phrenic nerve paralysis	1/143 (0.7%)
								AV block	1/143 (0.7%)
Jais, 2004[44] 15520313	12	0/136[f]	4/100 (4%)					Embolic events	0/136[f]
								Coronary artery events	0/136[f]
Liu, 2005[94] 16336813	6	1/130 (0.8%)[c]	1/130 (0.8%)	1/130 (0.8%)		1/232 (0.4%)[g]			
Kanj, 2007[83] 17433955	6	0/121	2/121 (2%)	0/121	0/121	0/121	0/121	Pulmonary edema	2/121 (2%)
Tondo, 2005[86] 15683472	7	No adverse events (no=120)							
Liu, 2006[63] 17062959	9	2/110 (2%)[d]				1/110 (1%)[h]			
Wazni, 2003[67] 14610012	12	2/108 (2%)[i]		0/108					
Ma, 2006[105] 17199954	12	0/106	2/106 (2%)	0/106	0/106		0/106		
Tondo, 2006[106] 16981920	14		1/105 (1%)	0/105		5/105 (5%)[j]			

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 (%)	
Kistler, 2007[107] 17916142	nd		1/101 (1%)	[1/101 (1%)]					
Liu, 2006[45] 17239094	13	2/100 (2%)[d]	1/100 (1%)	1/100 (1%)		1/100 (1%)[h]			
Kistler, 2006[53] 16989651	6	1/94 (1%)[k]	1/94 (1%)	[1/94 (1%)]					
Hocini, 2005[61] 16344401	15	1/90 (1%)[l]	1/90 (1%)					Phrenic nerve paralysis	1/90 (1%)
Wang, 2007[85] 17522081	7		0/90	0/90		2/90 (2%)[e]			
Estner, 2006[88] 16831837	10	0/64	0/64	1/64 (2%)	0/64	0/64			
Mantovan, 2005[69] 16403059	16		1/60 (2%)						
Arentz, 2007[50] 17562956	15	1/55 (1%)[m]	1/55 (1%)					Pulmonary edema	1/55 (1%)
Nilsson, 2006[34] 16923426	12	1/46 (2%)[no]		1/46 (2%) [1/46 (2%)]					
Oral, 2003[46] 14557355	6	0/40						Atrial Flutter	1/40 (3%)
Oral, 2005[65] 16253904	10	No adverse events (no=40)							
Marrouche, 2007[84] 17490437	3	0/26			0/26				

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

l. Asymptomatic PV stenosis with >70% reduction in diameter.
m. Asymptomatic PV with 40% reduction in diameter.
n. Asymptomatic PV stenosis with >30% reduction in diameter.

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

Table 15. Adverse events (Extraostial PVI, Conventional 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 (%)	
Kilicaslan, 2005[95] 15734612	18	4/1125 (0.4%)[b]		7/1125 (0.6%)					
Pappone, 2004[39] 15520310	12	0/560	4/560 (0.7%)	0/560				AT	8/560 (1%)
Wazni, 2007[108] 17998456	nd		2/355 (0.6%)	3/355 (0.8%)		31/355 (9%)[c] 5/355 (1%)[d]			
Chugh, 2005[56]15840468	13	No adverse events (no=349)							
Hachiya, 2007[73] 17286569	6		1/252 (0.4%)						
Kilicaslan, 2006[111] 16684021	nd			4/202 (2%)					
Verma, 2007[58] 17338763	12	0/200	0/200	0/200					
Yamane, 2007[81] 17457004	22	0/117						Atrial flutter	4/117 (3%)
Essebag, 2005[36] 16183686	14	0/102	3/102 (3%)	[1/102 (1%)]	0/102	4/102 (4%)	0/102		
Kottkamp, 2004[52] 15312874	12	No adverse events (no=100)							
Calò, 2006[35] 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%)
Kanj, 2007[83] 17433955	6	0/59	0/59	[1/59 (2%)]	0/59	0/59	0/59		
Tamborero, 2005[79] 16311935	4	0/41[e]							
Wazni, 2005[24] 15928285	12	1/32 (3%)[f]		0/32				Bleeding[g]	2/32 (6%)
Okada, 2007[77] 17397672	6	1/27 (4%)[h]							

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 (%)	
Krittayaphong, 2003[23] 12866763	12	0/14	0/14	1/14 (7%)	0/14	0/14		Gastrointestinal[i]	2/14 (14%)
								Sinus node dysfunction[i]	1 (7%)
								Dizziness[i]	1 (7%)
								Pre-syncope[i]	1 (7%)

a. Pericadial effusion that required cardiocentesis 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. Asymptomatic PV stenosis with >70% reduction in diameter.
f. Asymptomatic PV stenosis with 50-70% reduction in diameter.
g. No details reported.
h. Asymptomatic PV stenosis with >50% reduction in diameter.
i. Details were not reported. This might have been associated with concurrent AAD.
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

Table 16. Adverse events (Extraostial PVI, Various Tips or No information on 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 (%)	
Lakkireddy, 2005[96] 16360082	12	(2%)[b]		(1%)				Pulmonary edema	(0.5%)
Berruezo, 2007[30] 17395676	13	0/148		[2/148 (1%)]				Pericarditis	6/148 (4%)
								Dressler's syndrome	2/148 (1%)
Zhou, 2007[49] 17624261	7			1/148 (0.7%) [2/148 (1%)]			1/148 (0.7%)[c]		
Beukema, 2005[51] 16203925	15	0/105							
Martinek, 2007[59] 17897124	6	3/100 (3%)[d]		1/100 (1%) [2/100 (2%)]				Phrenic nerve paralysis	1/100 (1%)
Sheikh, 2006[66] 17318445	9	0/100	1/100 (1%)	[1/100 (1%)]	0/100	0/100	0/100		
Pappone, 2006[27] 17161267	12			[1/99 (1%)]					
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[62] 15927974	6	3/50 (6%)[d]	0/50	1/50 (2%) [2/50 (4%)]					
Mansour, 2004[75] 15149421	11	0/40	1/40 (3%)	1/40 (3%)		2/40 (5%)			

a. Pericadial effusion that required cardiocentesis 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.
AE, adverse events; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

Table 17. Adverse events (Ostial 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 (%)	
Hsu, 2005[97] 15683473	nd		14/746 (2%)						
Chen, 2004[41] 15028358	14	6/377 (2%)[b]	2/377 (1%)	5/377 (1%)				Pulmonary edema	1/377 (0.3%)
Bhargava, 2004[47] 15028066	15	6/323 (2%)[b]	3/323 (1%)	3/323 (1%)					
Marrouche, 2003[89] 12756153	13	5/315 (2%)[b]		2/315 (0.6%) [3/315 (1%)]					
Della Bella, 2005[37] 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[48] 1630289	Intra-procedural		1/187 (0.5%)	[1/187 (0.5%)]					
Macle, 2002[114] 12475093	9	0/136		0/136					
Hsu, 2004[109] 15575053	12		2/116 (2%)	1/116 (0.9%)				Death at 3 mo[f]	1/116 (0.9%)
Berkowitsch, 2005[98] 15683534	12	16/104 (15%)[b]							
Nilsson, 2006[87] 17043070	15	0/90		[2/90 (2%)]					
Arentz, 2007[50] 17562956	15	1/55 (1%)[g]	1/55 (1%)						
Nilsson, 2006[34] 16923426	12			1/54 (2%) [1/54 (2%)]					
Karch, 2005[62] 15927974	6	6/50 (12%)[h]	0/50	0/50 [1/50 (2%)]					
Thomas, 2004[99] 15172657	nd	2/158 (1%)[i]		1/48					

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 (%)	
Dixit, 2006[43] 16879626	6	0/40 Error! Bookmark not defined.	0/40	[1/40 (3%)]	0/40		0/40		
Oral, 2003[46] 14557355	6	0/40							
Willems, 2006[68] 16782716	17[j]		1/32 (3%)	[1/32 (3%)]					

a. Pericadial effusion that required cardiocentesis 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.
AE, adverse events; nd, no data; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

Table 18. Adverse events (Ostial PVI, Conventional Tip)

Author, Year UI	F/up, mo	Cardiac Tamponade[a], no/N (%)	Cardiac Tamponade, no/N (%) [Effusion]	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 (%)	
Matsuo, 2007[76] 17506857	20	2/148 (1%)[b]	1/148 (1%)						
Yamada, 2006[113] 16607049	6	0/108	0/108	0/108					
Yamane, 2007[81] 17457004	34	3/70 (4%)[c]						Atrial flutter	1/70 (1%)
Okada, 2007[77] 17397672	6	2/50 (4%)[d]							
Dixit, 2006[43] 16879626	6	0/42[e]	0/42	0/42	1/42 (2%)		1/42 (2%)[f]		
Oral, 2005[65] 16253904	10	No adverse events (no=40)							
Tamborero, 2005[79] 16311935	4	6/32 (19%)[e]							
Thomas, 2004[99] 15172657	nd	4/81 (5%)[b,g]	1/31						

a. Pericadial effusion that required cardiocentesis 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.
AE, adverse events; nd, no data; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack

Table 19. Adverse events (Ostial PVI, Various Tips or No information on 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 (%)	
Sauer, 2006[115] 16831982	21	"Major complications" (3%, no=629)							
Gerstenfeld, 2006[100] 16443531	16	1/449 (0.2%)[b] 2/449 (0.4%)[c]	6/449 (1%)	4/449 (0.9%)[d]		1/449 (0.2%)[e]			
Saad, 2003[91] 12693885	5	18/335 (5%)[f]							
Walczak, 2006[80] 16444625	17	5/183 (3%)[g]							
Yamane, 2002[90] 11955852	9	0/157							
Schwartzman, 2003[78] 14574043	6	2/42 (5%)[h]							
Mansour, 2004[75] 15149421	21	0/40	2/40 (5%)	1/40 (3%)		0/40			

a. Pericadial effusion that required cardiocentesis was considered cardiac tamponade.
b. Symptomatic PV stenosis requiring interventions (e.g., stent placement).
c. No explicit definition of PV stenosis reported.
d. Including TIA.
e. Catheter insertion site-related bleeding or hematoma requiring interventions (e.g., transfusion).
f. Asymptomatic PV stenosis with 50-70% reduction in diameter.
g. Asymptomatic PV stenosis with >70% reduction in diameter.
h. Asymptomatic PV stenosis with >50% reduction in diameter.

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

Table 20. Adverse events (Miscellaneous)[a]

Author, Year UI	F/up, mo	PV Stenosis, no/N (%)	Cardiac Tamponade[b], 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 (%)	
Irrigated tip									
Nilsson, 2006[34] 16923426	12							Embolic events	4/173 (2%)[c]
Conventional tip									
Cheema, 2006[33] 17019636	26	3/264 (1%)[d]	6/264 (2%)	3/264 (1%)		21/264 (8%)[e,f]		Heart block	1/264 (0.3%)
								Valve injury	1/264 (0.3%)
Oral, 2006[110] 16606789	11		2/180 (1%)[c]	[2/180 (1%)[c]]					
Various tips or No information on Tip									
Bertaglia, 2007[101] 17905330	nd	1/1011 (0.1%)[g] 3/1011 (0.3%)[h]	7/1011 (0.7%)	4/1011 (0.4%) [1/1011 (0.1%)]		10/1011 (10%)[f] 3/1011 (0.3%)[i]	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[102] 17081205	35	(0.1%)[g] (0.6%)[j]	(0.9%)	(0.5%) [(0.2%)]	1/1058 (0.1%)	(0.6%)[f] (0.7%)[i] (0.8%)[e] (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[54] 16908760	25			10/755 (1%)					
Schwartzman, 2003[78] 14574043	6	4/112 (4%)[m]				1/112 (1%)[e] 3/112 (3%)[f] 2/112 (2%)[i]		Non-cardiogenic pulmonary edema	1/112 (0.9%)

a. Various different ablation techniques were employed (e.g., extraostial PVI and ostial PVI).
b. Pericadial effusion that required cardiocentesis 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 >70% reduction in diameter.

e. Catheter insertion site-related bleeding or hematoma requiring interventions (e.g., transfusion).
f. Pseudoaneurysm.
g. Symptomatic PV stenosis requiring interventions (e.g., stent placement).
h. Asymptomatic PV stenosis with >50% reduction in diameter.
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. Asymptomatic PV stenosis with >50% reduction in diameter.

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

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, *no*
Male	NS (H,I)	NS (H,I)	NS (H,I)	NS (I)		NS (H)	2
Age	NS (B,I)	NS (B,I)	P<0.05 (B) NS (I)	NS (I)		NS (B)	2
Duration of AF	NS (I)	NS (I)	NS (I)				1
Left atrial size	NS (I)	NS (I)	NS (I)				1
EF	NS (A,I)	NS (A,I)	NS (A,I)				2
CHF		NS (G)		P<0.01 (G)		P<0.01 (G) NS (C)	2
Paroxysmal AF	NS (I)	NS (I)	NS (I)	NS (I)			1
History of CVD	NS (I)		NS (I)				1
Vulvular HD	NS (I)	P<0.003 (I)	NS (I)	NS (I)			1
CAD	NS (I)	P<0.005[c] (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)			1
Diabetes						P=0.002[d] (F)	1
Pacemaker or ICD	NS (E)		NS (E)		NS (E)		1
History of cardiac surgery	NS (D)		NS (D)				1
Total studies, *no*	6	5	6	2	1	4	9

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. Studies are coded as follows: A, Chen 2004[41] (no=377); B, Bhargava 2004[47] (no=323); C, Hsu 2004[109] (no=116); D, Kilicaslan 2005[95] (no=1125); E, Lakkireddy 2005[96] (no=172); F, Tang 2006[57] (no=263); G, Tondo 2005[86] (no=105); H, Forleo 2007[93] (no=221); I, Bertaglia 2007[101] (no=1015).
b. One study (Bertaglia 2007[101]) assessed both cardiac tamponade and pericardial effusion requiring prolongation of hospital stay.
c. P<0.008 in multivariate analysis.
d. P=0.001 in multivariate analysis.

Figure 1. Analytic Framework

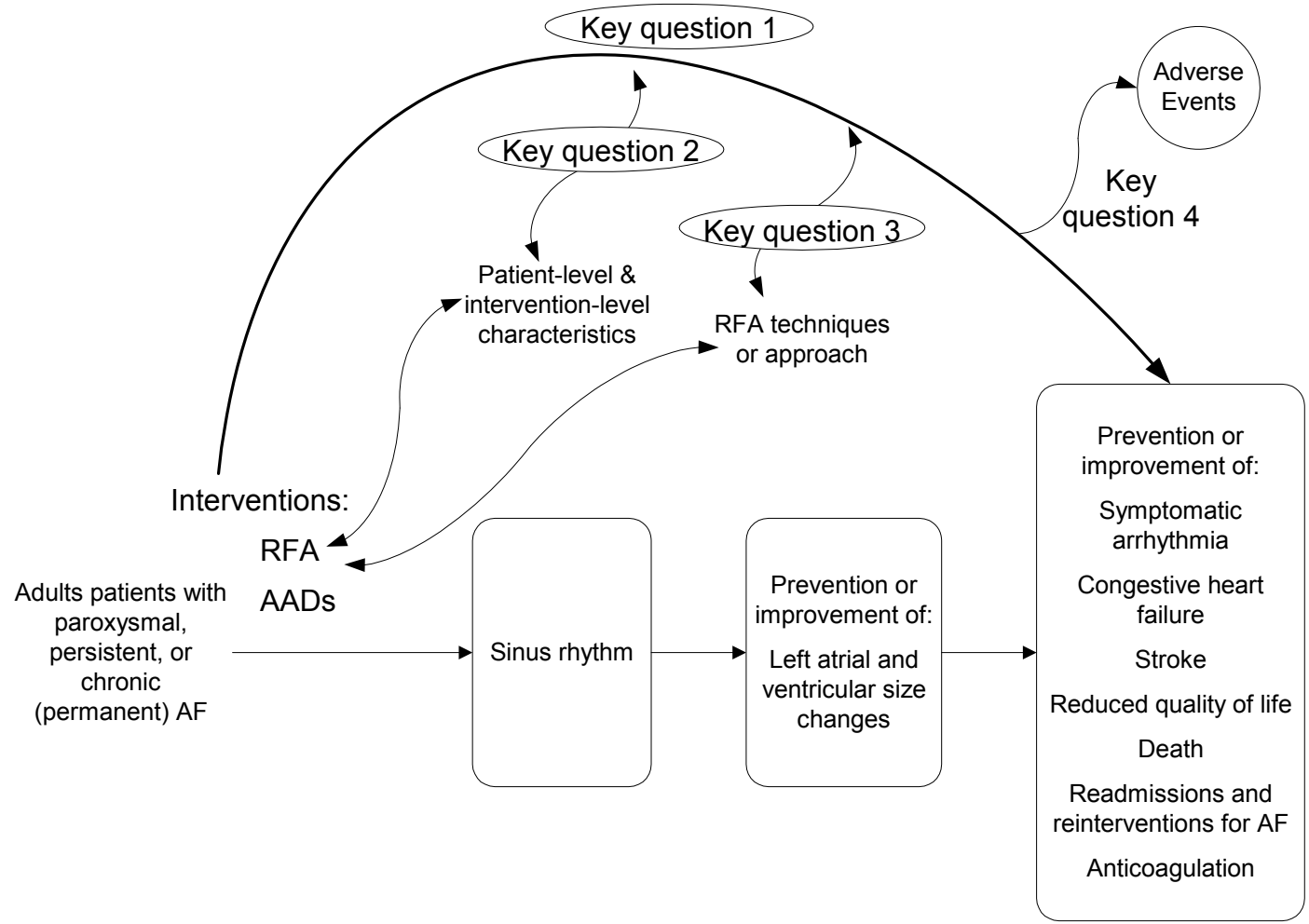
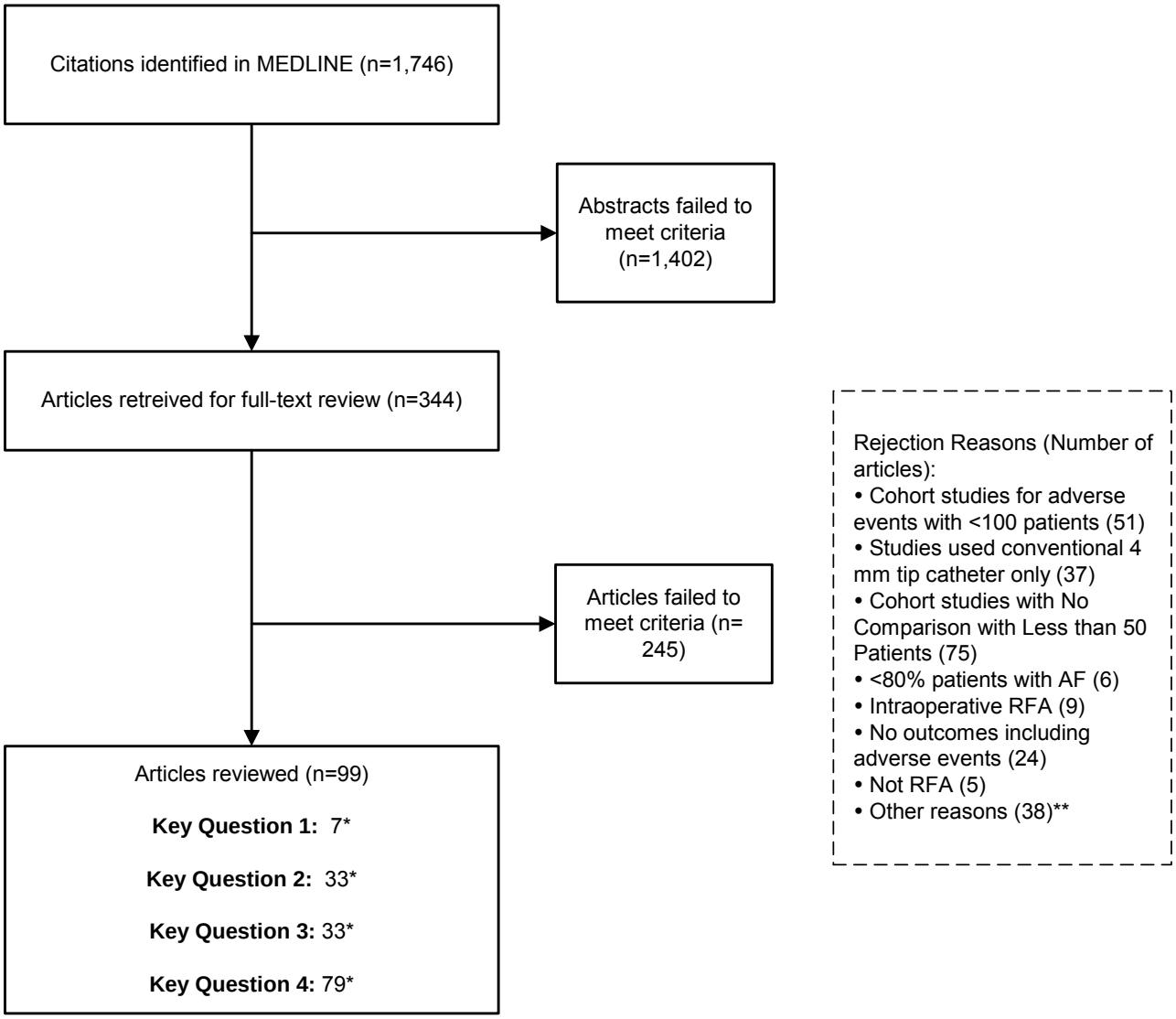
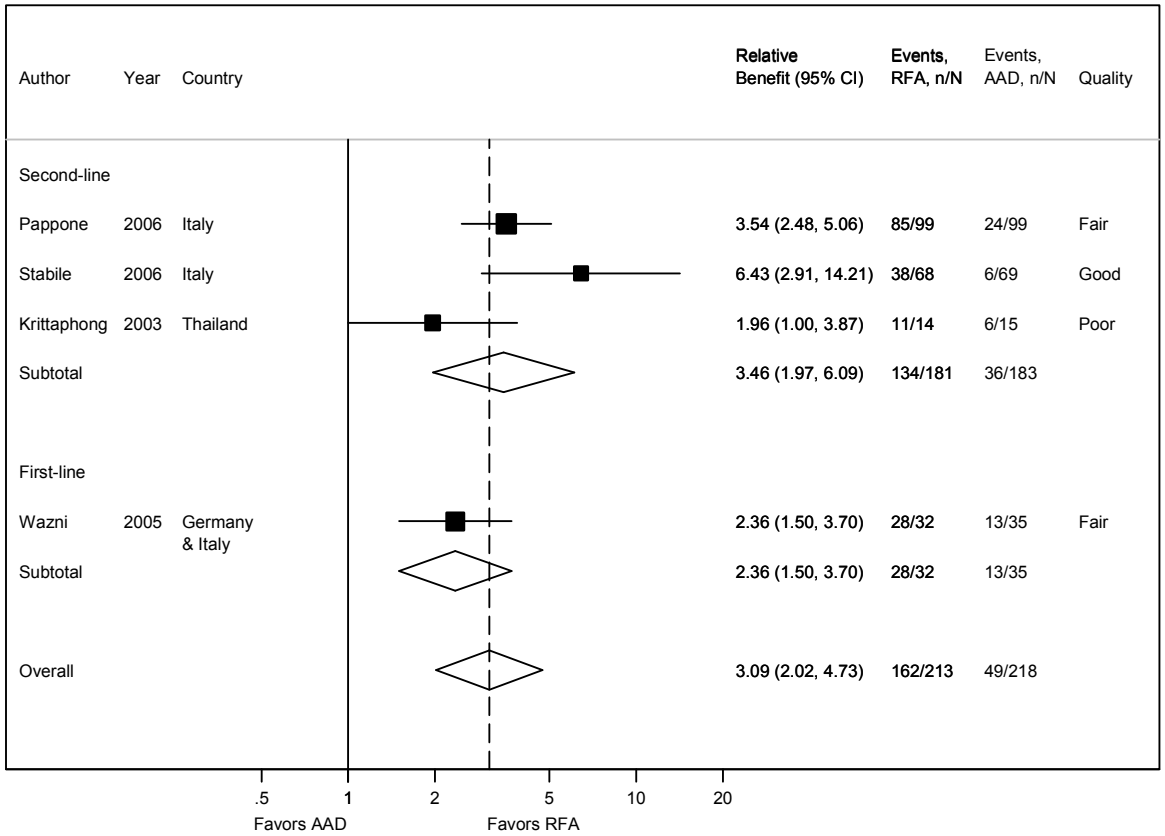


Figure 2. Literature flow diagram



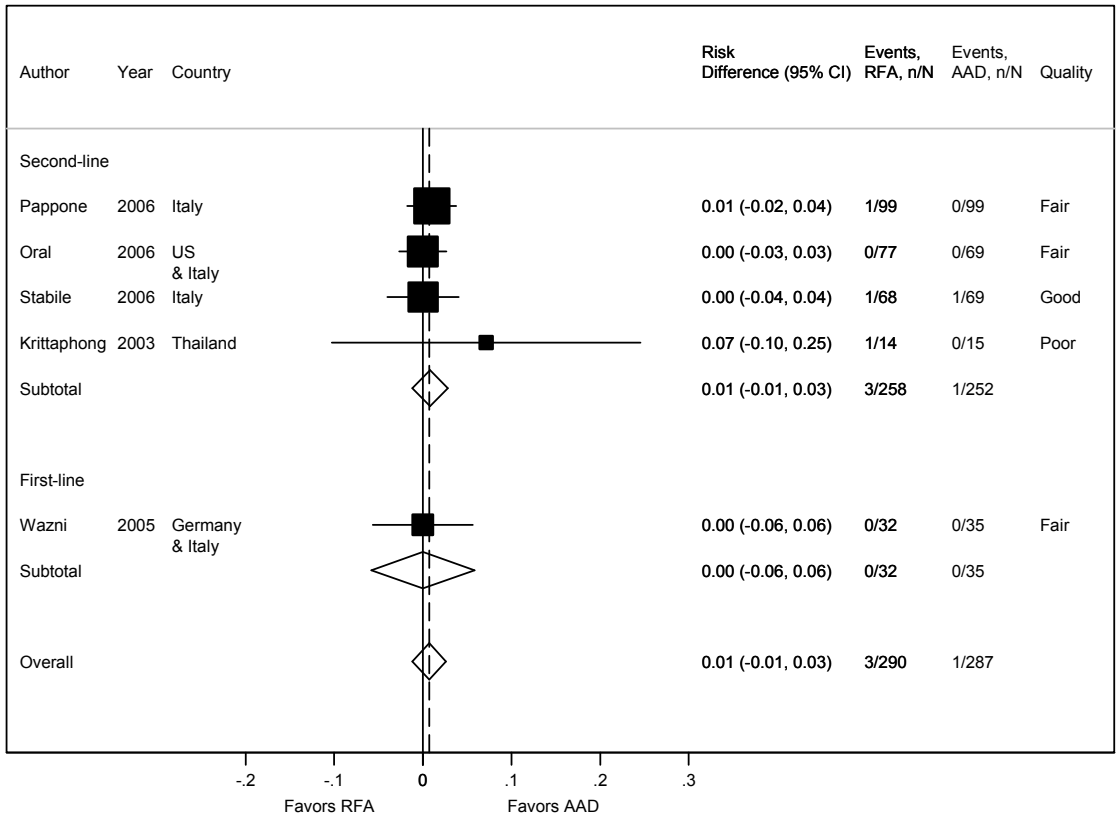
*There are overlaps of studies between key questions
**See Appendix B for detailed rejection reasons

Figure 3. Meta-analysis of rhythm control, RFA vs. medical treatment



Legends: Random effects model meta-analyses of relative benefit (rate ratio) 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 boxes are proportional to the weight of each study in the overall meta-analysis. 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. Meta-analysis 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 boxes are proportional to the weight of each study in the overall meta-analysis. 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. Meta-analysis of recurrence, paroxysmal AF vs. persistent AF

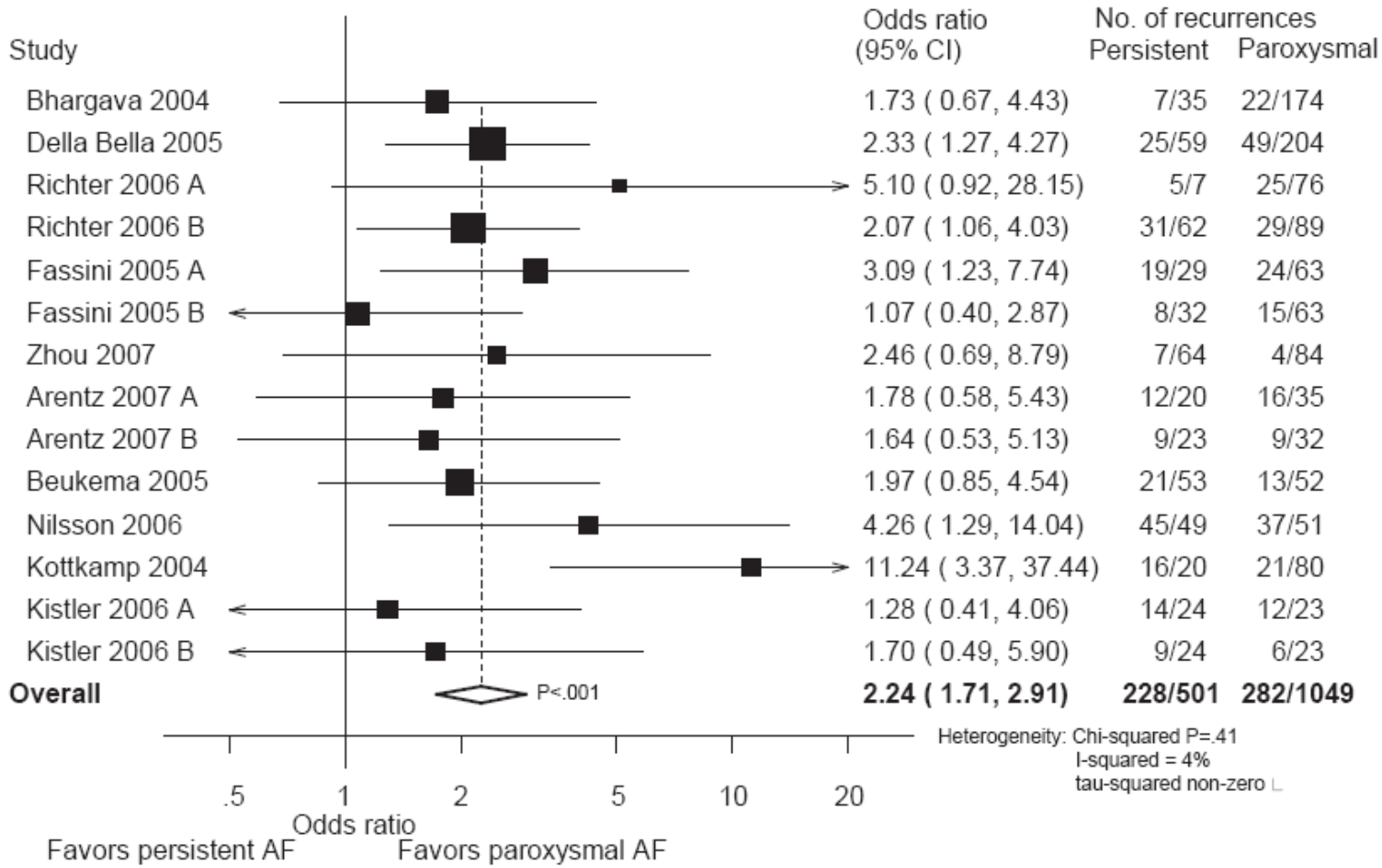


Figure 6. Meta-analysis of recurrence, paroxysmal AF vs. chronic AF

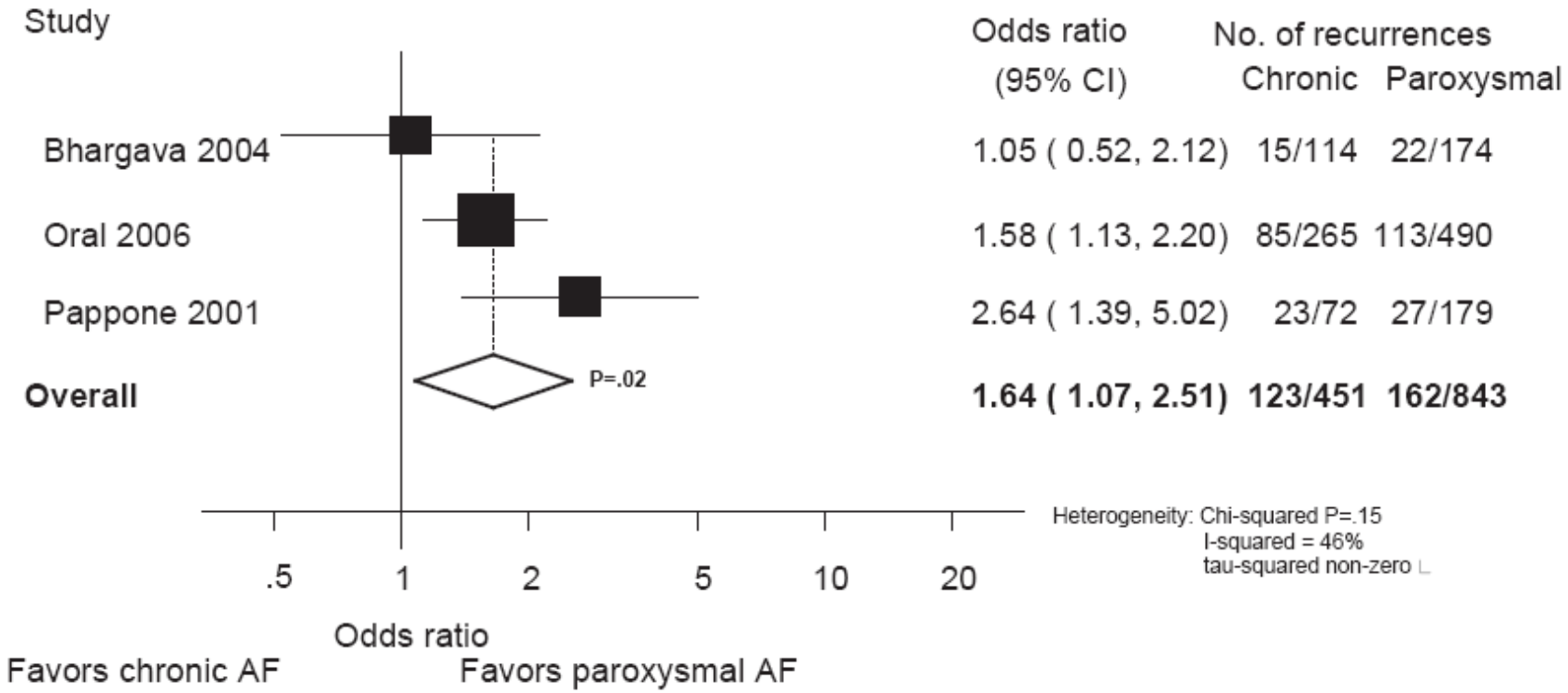
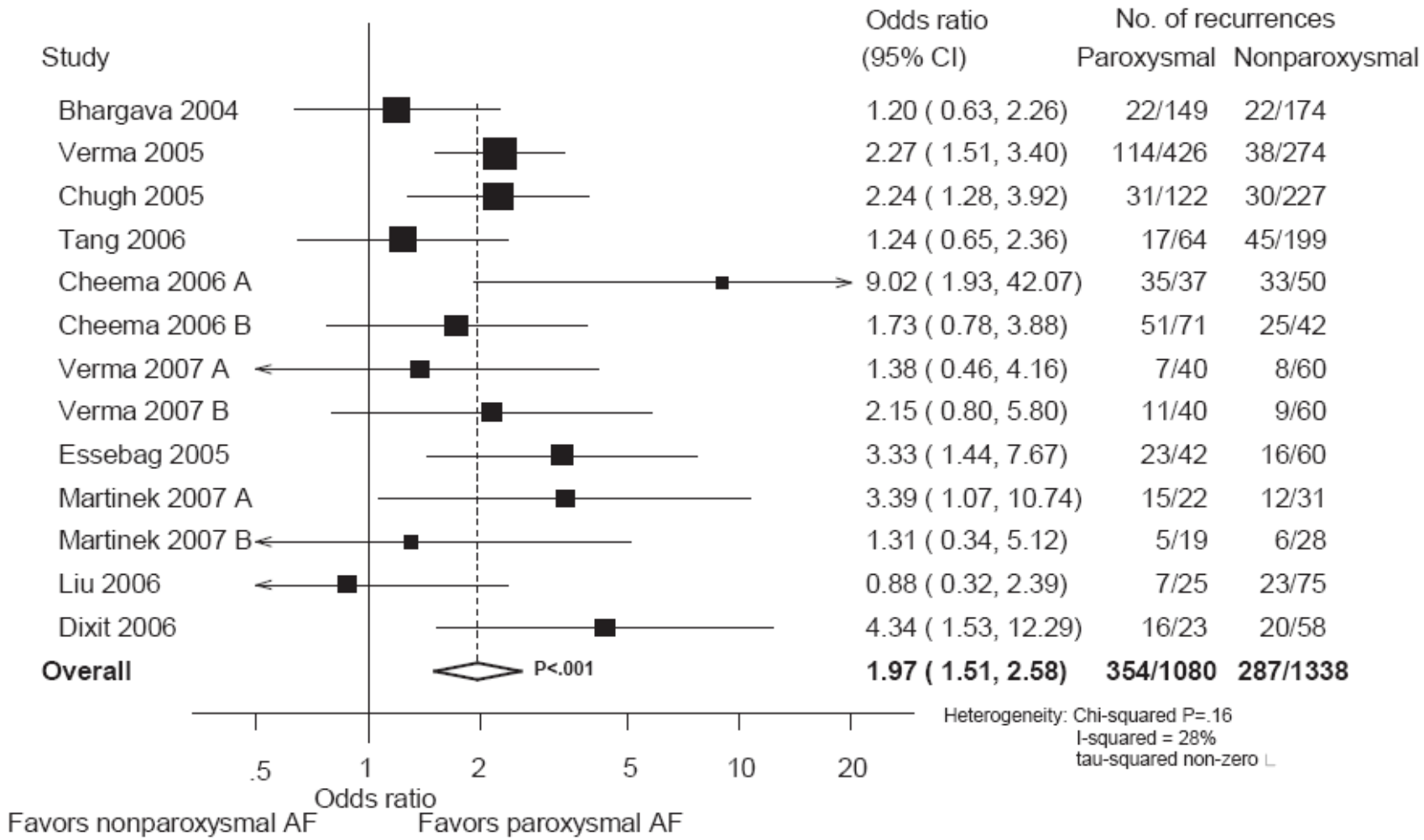


Figure 7. Meta-analysis of recurrence, paroxysmal AF vs. non-paroxysmal AF



Appendix A. Search Strategy

Database: Ovid MEDLINE(R) <1996 to April Week 1 2008>

#	Search History
1	atrial fibrillation.mp. or exp Atrial Fibrillation/ (16780)
2	pulmonary vein$.mp. or exp Pulmonary Veins/ (4107)
3	1 or 2 (19389)
4	exp Catheter Ablation/ or radiofrequency ablation.mp. (10517)
5	radiofrequency catheter ablation.mp. or exp Catheter Ablation/ (10041)
6	ablation.mp. (23497)
7	radiofrequency.mp. (8531)
8	(catheter adj ablation).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (10245)
9	or/4-8 (25805)
10	3 and 9 (3081)
11	limit 10 to (humans and yr="2000 - 2008") (2477)
12	limit 11 to (addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or "review") (731)
13	11 not 12 (1746)

Appendix B. List of Excluded Studies

Reason for Rejection: Cohort Studies for Adverse Events with Less than 100 Patients

Arentz T, von RJ, Blum T et al. Feasibility and safety of pulmonary vein isolation using a new mapping and navigation system in patients with refractory atrial fibrillation. Circulation 2003;108:2484-90.

Arentz T, Ott P, von RJ, Blum T, Kalusche D. Effect of atrial overdrive pacing on pulmonary vein focal discharge in patients with atrial fibrillation. Europace 2003;5:25-31.

Berkowitsch A, Neumann T, Kurzidim K et al. Comparison of generic health survey SF-36 and arrhythmia related symptom severity check list in relation to post-therapy AF recurrence. Europace 2003;5:351-5.

Berkowitsch A, Greiss H, Vukajlovic D et al. Usefulness of atrial fibrillation burden as a predictor for success of pulmonary vein isolation. Pacing & Clinical Electrophysiology 2005;28:1292-301.

Bertaglia E, Stabile G, Senatore G et al. Long-term outcome of right and left atrial radiofrequency ablation in patients with persistent atrial fibrillation. Pacing & Clinical Electrophysiology 2006;29:153-8.

Callans DJ, Gerstenfeld EP, Dixit S et al. Efficacy of repeat pulmonary vein isolation procedures in patients with recurrent atrial fibrillation. Journal of Cardiovascular Electrophysiology 2004;15:1050-5.

Cauchemez B, Extramiana F, Cauchemez S et al. High-flow perfusion of sheaths for prevention of thromboembolic complications during complex catheter ablation in the left atrium. Journal of Cardiovascular Electrophysiology 2004;15:276-83.

Cheema A, Dong J, Dalal D et al. Long-term safety and efficacy of circumferential ablation with pulmonary vein isolation. Journal of Cardiovascular Electrophysiology 2006;17:1080-5.

Chen J, Hoff PI, Erga KS, Rossvoll O, Ohm OJ. A clinical study of patients with and without recurrence of paroxysmal atrial fibrillation after pulmonary vein isolation. Pacing & Clinical Electrophysiology 2005;28:Suppl-9.

Essebag V, Wylie JV, Jr., Reynolds MR et al. Bi-directional electrical pulmonary vein isolation as an endpoint for ablation of paroxysmal atrial fibrillation. Journal of Interventional Cardiac Electrophysiology 2006;17:111-7.

Gerstenfeld EP, Guerra P, Sparks PB, Hattori K, Lesh MD. Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers. Journal of Cardiovascular Electrophysiology 2001;12:900-8.

Giazitzoglou E, Korovesis S, Karvouni E, Paxinos G, Kourlaba G, Katritsis D. Proarrhythmic effects of atrial fibrillation ablation techniques. Hjc Hellenic Journal of Cardiology 2006;47:211-7.

Gillinov AM, Sirak J, Blackstone EH et al. The Cox maze procedure in mitral valve disease: predictors of recurrent atrial fibrillation. Journal of Thoracic & Cardiovascular Surgery 2005;130:1653-60.

Haissaguerre M, Jais P, Shah DC et al. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 2000;101:1409-17.

Haissaguerre M, Sanders P, Hocini M et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. Journal of Cardiovascular Electrophysiology 2005;16:1125-37.

Horlitz M, Schley P, Shin DI et al. Circumferential pulmonary vein ablation for treatment of atrial fibrillation using an irrigated-tip catheter. American Journal of Cardiology 2004;94:945-7.

Hsieh MH, Tai CT, Lee SH et al. Catheter ablation of atrial fibrillation versus atrioventricular junction ablation plus pacing therapy for elderly patients with medically refractory paroxysmal atrial fibrillation. Journal of Cardiovascular Electrophysiology 2005;16:457-61.

Husser D, Bollmann A, Kang S et al. Effectiveness of catheter ablation for coexisting atrial fibrillation and atrial flutter. American Journal of Cardiology 2004;94:666-8.

Jais P, Hocini M, Sanders P et al. Long-term evaluation of atrial fibrillation ablation guided by noninducibility. Heart Rhythm 2006;3:140-5.

Jayam VK, Dong J, Vasamreddy CR et al. Atrial volume reduction following catheter ablation of atrial fibrillation and relation to reduction in pulmonary vein size: an evaluation using magnetic resonance angiography. Journal of Interventional Cardiac Electrophysiology 2005;13:107-14.

Jiang CY, Wang JA, He H, Sun Y, Zhou BQ. Segmental radiofrequency ablation of pulmonary vein ostia for patients with refractory paroxysmal atrial fibrillation using multi-slice spiral computed tomography guidance. Journal of Zhejiang University 2005;Science.:1153-6.

Kanagaratnam L, Tomassoni G, Schweikert R et al. Empirical pulmonary vein isolation in patients with chronic atrial fibrillation using a three-dimensional nonfluoroscopic mapping system: long-term follow-up. Pacing & Clinical Electrophysiology 2001;24:1774-9.

Klemm HU, Ventura R, Rostock T et al. Correlation of symptoms to ECG diagnosis following atrial fibrillation ablation. Journal of Cardiovascular Electrophysiology 2006;17:146-50.

Kumagai K, Muraoka S, Mitsutake C, Takashima H, Nakashima H. A new approach for complete isolation of the posterior left atrium including pulmonary veins for atrial fibrillation. Journal of Cardiovascular Electrophysiology 2007;18:1047-52.

Lang CC, Santinelli V, Augello G et al. Transcatheter radiofrequency ablation of atrial fibrillation in patients with mitral valve prostheses and enlarged atria: safety, feasibility, and efficacy. Journal of the American College of Cardiology 2005;45:868-72.

Lemola K, Hall B, Cheung P et al. Mechanisms of recurrent atrial fibrillation after pulmonary vein isolation by segmental ostial ablation. Heart Rhythm 2004;1:197-202.

Lemola K, Oral H, Chugh A et al. Pulmonary vein isolation as an end point for left atrial circumferential ablation of atrial fibrillation. Journal of the American College of Cardiology 2005;46:1060-6.

Lim TW, Jassal IS, Ross DL, Thomas SP. Medium-term efficacy of segmental ostial pulmonary vein isolation for the treatment of permanent and persistent atrial fibrillation. Pacing & Clinical Electrophysiology 2006;29:374-9.

Nakashima H, Kumagai K, Noguchi H, Tojo H, Yasuda T, Saku K. Evaluation of the recurrence of atrial fibrillation after pulmonary venous ablation. Journal of Cardiology 2002;40:87-94.

Neumann T, Erdogan A, Dill T et al. Asymptomatic recurrences of atrial fibrillation after pulmonary vein isolation. Europace 2006;8:495-8.

Nilsson B, Chen X, Pehrson S, Hilden J, Svendsen JH. Increased resting heart rate following radiofrequency catheter ablation for atrial fibrillation. Europace 2005;7:415-20.

O'Donnell D, Furniss SS, Dunuwille A, Bourke JP. Delayed cure despite early recurrence after pulmonary vein isolation for atrial fibrillation. American Journal of Cardiology 2003;91:83-5.

Pratola C, Baldo E, Notarstefano P, Toselli T, Ferrari R. Radiofrequency atrial fibrillation ablation based on pathophysiology: a diversified protocol with long-term follow-up. Journal of Cardiovascular Medicine 2008;9:68-75.

Purerfellner H, Martinek M, Aichinger J, Nesser HJ, Kempen K, Janssen JP. Quality of life restored to normal in patients with atrial fibrillation after pulmonary vein ostial isolation. American Heart Journal 2004;148:318-25.

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Appendix C. Evidence Tables

Zip file attached