Washington State Health Care Authority

Health Technology Assessment

Catheter Ablation Procedures For Supraventricular Tachyarrhythmia

Including Atrial Flutter & Atrial Fibrillation

Final Evidence Report

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Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Appendices are published in a separate document that is publically available on the WA HTA website.

EXECUTIVE SUMMARY

Introduction

Cardiac arrhythmias can be defined as abnormal rhythms or changes in the heart rate, and its incidence increases with age. AF is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations for cardiac dysrhythmias[1]. It affects an estimated 2.7 to 6.1 million people in the US, with an estimated projected prevalence of 5.6 to 12.1 million by 2050[2]. The overall incidence of atrial flutter, or macroreentrant atrial tachycardia, in a population of predominantly white, rural individuals in Wisconsin was 0.088% (based on one epidemiologic study)[3]. AV nodal reentrant tachycardia (AVNRT) is the most common form of paroxysmal SVT[3].

Catheter ablation is a procedure used to treat some types of heart arrhythmias, most commonly, those tachyarrhythmias that originate above the ventricles. These **supraventricular tachyarrhythmias (SVTs)** can be categorized by the origin of the tachyarrhythmia[4]:

- **Atrial tachyarrhythmias** initiate within the atrium and include sinus tachycardia (including inappropriate sinus tachycardia and sinus nodal reentrant tachycardia, atrial tachycardia (including focal and multifocal), macroreentrant atrial tachycardia (i.e., **atrial flutter (AFl)**), and **atrial fibrillation (AF).**
- Atrioventricular tachyarrhythmias originate within the atrioventricular (AV) node or the surrounding area and include **AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT, which includes Wolf-Parkinson-White (WPW) Syndrome)**, focal junctional ectopic tachycardia, and nonparoxysmal junctional tachycardia.

Catheter ablation is typically performed in a catheter lab and involves guided insertion of catheters from the arm, groin, or neck through the blood vessel and into the heart. In radiofrequency catheter ablation, radiofrequency energy is sent through the catheters to a focal point in the heart that is believed to be the source of the arrhythmia; this energy ablates or destroys very small areas of the heart to disrupt abnormal electrical activity. Cryoablation uses a pressurized refrigerant in the catheter tip to ablate the source of the arrhythmia. Other types of catheter ablation are becoming available, such as cryoballoon ablation, which involves cooling and freezing of the targeted tissue using coolant inside a balloon to alter abnormal electrical activity.

Eighteen radiofrequency ablation (RF) and three cryoablation catheter devices examined for this study have been approved for use by the FDA from 1994 to 2012. These devices are used to treat

heart arrhythmias including atrial flutter/fibrillation and atrioventricular nodal re-entrant tachycardia.

This technical review systematically assesses the evidence on this topic based on the context and key questions provided by the Washington State Health Technology Assessment Program. The following is taken from their published key questions document:

> The HCA has selected ablation therapies for supraventricular tachyarrhythmia including atrial flutter and atrial fibrillation for review. The topic was nominated on high levels of concern around efficacy and cost, and on medium levels of concern around safety.

Key Questions

The primary aim of this assessment is to systematically review, critically appraise, and analyze research evidence comparing the efficacy, effectiveness, and safety of ablation procedures for supraventricular tachyarrhythmias (including atrial flutter, supraventricular tachycardia, and atrial fibrillation) with other treatment alternatives. The differential effectiveness and safety as well as the cost-effectiveness of catheter ablation will also be evaluated. This health technology assessment set out to answer the following key questions, which were provided by the State:

Key Question 1
Does catheter ablation improve patient outcomes in persons with supraventricular tachyarrhythmias compared with other treatment options: What is the evidence for comparative efficacy and effectiveness over the short term and longer term?

Key Question 1a
If catheter ablation is efficacious compared with other treatment options, is there differential efficacy between the different types of ablation (e.g., radiofrequency ablation versus cryoballoon ablation)?

Key Question 2
What is the evidence regarding the comparative efficacy of various approaches to radiofrequency catheter ablation (e.g., PVI alone versus PVI with additional ablation lines, etc.)?

Key Question 3
What is the evidence of the safety of catheter ablation?

Key Question 4
Does catheter ablation have any differential efficacy or safety compared with other treatment options in subpopulations? Include consideration of age, gender, race, ethnicity, or disability.

Key Question 5
What is the evidence of cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term?

Key Question 1 examines the larger question of the efficacy and effectiveness of catheter ablation compared with other treatments for rhythm control, while Key Question 2 focuses specifically on the comparative efficacy of different approaches to radiofrequency catheter ablation. Key Question 3 assesses the adverse events and safety of catheter ablation. Key question 4 asks whether there are any special population characteristics that differentially affect the efficacy or safety of catheter ablation, and Key Question 5 evaluates whether catheter ablation in this patient population is cost effective.

Methods for evaluating comparative effectiveness

We conducted a formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Pertinent studies were critically appraised using our Level of Evidence (LoE) system which evaluates the methodological quality based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the LoE with consideration of the number of studies and the consistency, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

For Key Questions 1 and 2, the results of the search performed in the AHRQ HTA on catheter ablation for atrial fibrillation[5] was accepted and used; this search identified studies published between 2000 and December 2008, thus our search identified relevant studies published after the AHRQ HTA's search period through September, 2012. For comparative studies for key questions 1 and 2, data abstraction from the recent AHRQ HTA on catheter ablation for atrial fibrillation was accepted and used; thus we did not re-abstract efficacy or effectiveness data from the studies included in that report. We did re-abstract safety data.

Research reports were selected for summarization based on the following Patients-Intervention-Comparators-Outcomes (PICO) summary:

Study Component	Inclusion	Exclusion

Population	Adults with supraventricular tachyarrhythmia, to include:
	• Atrial fibrillation (AF)
	• Atrial flutter (AFl)
	• Supraventricular tachycardia:
	  • Sinus tachycardia (inappropriate sinus tachycardia and sinus nodal reentrant tachycardia)
	  • Atrioventricular reentrant tachycardia (AVRT), (including Wolff-Parkinson-White (WPW) Syndrome)
	  • Atrioventricular nodal reentrant tachycardia (AVNRT)
	  • Atrial tachycardia (including focal and multifocal)
	  • Focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia
		• Patients < 18 years of age
		• Ventricular tachycardia and paroxysmal ventricular tachycardia
		• Any tachyarrhythmia that does not originate from the sinus node, atrial tissue, or junctional sites between the atria and ventricles
		• Bradycardia
		• Patients with prior catheter ablation

Intervention	• Catheter ablation:
	  • For atrial fibrillation, we will only consider studies evaluating targeting of the pulmonary vein or pulmonary vein antrum and use of irrigated or 8 mm catheter tips
	  • Radiofrequency
	  • Cryoablation
	  • Cryoballoon
		• Ablation as an adjunct to surgery, intraoperative ablation
		• Use of non-FDA approved devices or devices not in final stages for FDA approval
		• For atrial fibrillation, studies in which PV electrical isolation was not the goal of ablation (e.g., standalone RFA of complex fractionated atrial electrograms (CFAE) and linear ablations), as well as studies of ablation of the atrioventricular (AV) junction will be excluded
		• Complete AV node ablation requiring pacemaker implantation

Comparator	• Medical therapy • Maze or other surgical procedures • Therapies intended to control rhythm • For Key Question 2, comparison of common different ablation approaches used to treat AF will be considered (e.g., pulmonary vein isolation versus pulmonary vein isolation with additional areas (lines))	• Comparisons of different techniques used in catheter ablation (i.e., imaging, types of catheter tips, etc.) • Cardioversion alone (ie., in the absence of antiarrhythmic medical therapy)
Outcomes	<u>Efficacy/effectiveness:</u> • Freedom from recurrence of supraventricular tachyarrhythmia • Improvement of symptoms (including palpitation, tachypnea, chest stuffiness, syncope, anxiety) • Quality of life and other patient-reported outcomes • Medication use (e.g. need for anticoagulants) • Hospitalization/ readmission	• Non clinical outcomes

Study Component	Inclusion	Exclusion
	• Repeat ablation • Intermediate outcomes (including maintenance of sinus rhythm, chamber size, ejection fraction) • Prevention of mortality, embolic events, and congestive heart failure. <u>Safety: (procedure or treatment related)</u> • Mortality • Embolic complications (including stroke or ischemic attack) • Congestive heart failure • Other reported complications (including pericardial effusion or cardiac tamponade, pulmonary vein stenosis, atrioesophageal fistula, deep vein thrombosis, peripheral vascular complication (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury) • Radiation exposure	
Study Design	• For all key questions, focus will be placed on studies with the least potential for bias. • Key Question 1: Randomized controlled trials (RCTs) to assess efficacy; nonrandomized studies (for atrial fibrillation only, we will require at least 100 patients and a low risk of bias) will be considered to evaluate effectiveness. If no comparative studies are available for a given condition, prospective case series with N ≥ 50 will be considered. • Key Question 2: RCTs comparing PVI with different ablation approaches for atrial fibrillation only • Key Question 3 (safety), RCTs and non-randomized studies from Key Question 1 will be included. Additional comparative studies and prospective case series designed specifically to evaluate adverse events will also be considered. • Key Question 4 (differential efficacy): RCTs or high quality cohort studies with low risk of bias • Formal, full economic studies will be sought for Key Question 5	• Non-clinical studies, studies of technique, imaging. • Studies with < 10 patients per treatment group. • Studies with less than 80% of patients having first time catheter ablation will be excluded • For Key Questions 1, 2, and 4: studies with less than 6 months' follow-up. • For Key Question 3, retrospective case series and prospective case series with N < 1000 (AF), N < 100 (atrial flutter), or N < 500 (SVTs) will be excluded. • For Key Question 3, case series that evaluated only surgical or medical approaches will be excluded.
Publication	• Studies published in English in peer-reviewed journals, published HTAs or publically available FDA reports • Full, formal economic analyses (e.g. cost-utility studies) published in English in HTAs or in a peer-reviewed journals published after those represented in previous HTAs	• For atrial fibrillation and atrial flutter, studies with a publication date prior to 2000 will be excluded on the basis that they used conventional tips that are obsolete for these diagnoses • Studies reporting only on the

Study Component	Inclusion	Exclusion
		technical aspects of ablation (e.g., imaging, type of catheter, etc.) • Abstracts, editorials, letters • Unpublished studies • Duplicate publications of the same study which do not report on unique outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

Overall summary of the highest quality evidence

The following summaries of the overall quality of evidence for primary findings have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report.

Key Question 1: Does catheter ablation improve patient outcomes in persons with supraventricular tachyarrhythmias compared with other treatment options: What is the evidence for comparative efficacy and effectiveness over the short term and longer term?

Atrial fibrillation

Pulmonary vein isolation (PVI) versus Anti-Arrhythmic Drugs (AADs)

Studies. Nine RCTs (10 studies)[6-16] and four cohort studies[17-20] which compared pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) were included. One RCT was included which compared cryoablation with AADs[21]. All RCTs were considered to be at moderately low risk of bias (Class of Evidence II), and all cohort studies were considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

Summary of the highest quality evidence.
Freedom from recurrence: There is moderate quality evidence that radiofrequency PVI results in significantly more freedom from recurrence compared with AADs in both the short- and long-term. In the short-term, this conclusion is supported by data from 7 RCTs and PVI is associated with a 50% (95% CI, 43%, 58%) decrease in risk of recurrence

compared with AADs. In the long-term, the conclusion is supported by data from 1 RCT and PVI is associated with a 61% (95% CI, 48%, 70%) decrease in risk of recurrence compared with AADs. There is low quality evidence that cryo-PVI results in significantly more freedom from recurrence in the short- term as supported by data from 1 RCT. Cryo-PVI is associated with a 63% (95% CI, 52%, 70%) decrease in risk of recurrence compared with AADs.

Mortality, stroke, and congestive heart failure (not procedure-related): There is low quality evidence that suggests that there is no difference between radiofrequency PVI and AADs in the 12 month rates of mortality (1 RCT), stroke (2 RCTs), and congestive heart failure (1 RCT) not attributed to any treatment given. There is similarly low quality evidence that suggests that there is no difference between cryo-PVI and AADs in the 12 month rates of mortality, stroke, and congestive heart failure not attributed to any treatment given based on data from 1 RCT.

Pulmonary vein isolation (PVI) versus Cox-Maze surgery

Studies. One retrospective cohort study[22] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

Summary of the highest quality evidence.

Freedom from recurrence: There is insufficient evidence that radiofrequency PVI results in significantly less freedom from recurrence in the absence of AADs compared with Cox Maze surgery (mean follow-up: 54 months). This conclusion is supported by data from 1 cohort study and PVI is associated with a 26% increase in risk of recurrence compared with Cox Maze surgery. There is insufficient evidence that radiofrequency PVI results in similar rates of freedom from recurrence in the presence of AADs compared with Cox Maze surgery (74% versus 84%, respectively; mean follow-up: 54 months). This conclusion is supported by data from 1 cohort study.

Stroke: There is insufficient evidence that radiofrequency PVI results in similarly low rates of stroke compared with Cox Maze surgery (1.7% versus 2%, respectively; mean follow-up: 54 months). This conclusion is supported by data from 1 cohort study.

Atrial flutter

Catheter Ablation versus Antiarrhythmic Drugs (AADs)

Studies. One RCT[23] met our inclusion criteria. The study was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. No cohort studies were identified that met our inclusion criteria.

Summary of the highest quality evidence.
Freedom from recurrence: There is moderate quality evidence that catheter ablation results in significantly more freedom from recurrence in the short-term. This conclusion is based on data from 1 RCT, in which ablation is associated with a 26% (95% CI, 13%, 43%) decrease in risk of recurrence compared with AADs.

Mortality: There is low evidence that catheter ablation results in similarly low rates of mortality not attributed to treatment given compared with AADs (11% versus 16%, respectively; mean follow-up: 13 months) based on data from 1 RCT.

Supraventricular tachycardias (SVTs)

Atrioventricular nodal reciprocating tachycardia (AVNRT)

Catheter Ablation versus Antiarrhythmic Drugs (AADs)
Studies. One prospective cohort study[24] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation. No RCTs were identified that met our inclusion criteria.

Summary of the highest quality evidence.
Patient-reported freedom from symptoms: There is insufficient evidence that catheter ablation results in significantly more freedom from recurrence compared with AADs. This conclusion is based on data from 1 cohort study with 1 to 8 years follow-up, in which ablation is associated with a 39% decrease in risk of recurrence compared with chronic use of AADs and in a 55% decrease in risk of recurrence compared with short-term or no use of AADs.

Catheter Ablation versus Open Perinodal Dissection Surgery
Studies. Two cohort studies[25, 26] met our inclusion criteria, both of which were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. No RCTs were identified that met our inclusion criteria.

Summary of the highest quality evidence.
Freedom from recurrence: There is insufficient evidence that catheter ablation results in similar rates of freedom from recurrence as open perinodal dissection surgery (85-95% versus 88-94%) based on data from two cohort studies.

Catheter Ablation versus no treatment
Studies. One cohort study[27] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation. No RCTs were identified that met our inclusion criteria.

Summary of the highest quality evidence.
Freedom from recurrence: There is insufficient evidence that catheter ablation results in significantly greater freedom from recurrence compared with no treatment (100% versus 36%) based on data from one small cohort study.

AVRT

Catheter Ablation versus AADs or surgery

Studies. One small retrospective cohort study[28] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation

Summary of the highest quality evidence.
Patient-reported freedom from symptoms: There is insufficient evidence that catheter ablation results in significantly greater freedom from symptoms compared with AADs (90% versus 8%) based on data from one small cohort study. There is insufficient evidence that catheter ablation results similar rates of freedom from symptoms compared with surgery (90% versus 100%) based on data from one small cohort study.

WPW Syndrome

Catheter Ablation versus no treatment

Studies. One RCT[29] was identified that met our inclusion criteria and was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation.

Summary of the highest quality evidence.
Freedom from recurrence: There is moderate quality evidence from 1 RCT that catheter ablation results in significantly greater freedom from recurrence in both the short- and long-term versus no treatment. In the short-term, PVI is associated with a 55% (95% CI, 35%, 70%) decrease in risk of recurrence compared with no treatment. In the long-term, PVI is associated with a 55% (95% CI, 34%, 70%) decrease in risk of recurrence compared with no treatment.

Mortality (not treatment-related): There is low quality evidence from 1 RCT that there is no difference in mortality rates following catheter ablation compared with no treatment. There were no deaths in either group.

Mixed populations

Catheter Ablation versus AADs

Studies. One prospective cohort study[30] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

Summary of the highest quality evidence.
Patient-reported freedom from symptoms: There is low quality evidence from 1 cohort study that catheter ablation results in significantly greater freedom from symptoms compared with AADs (85% versus 55%) based on data from one cohort study.

Key Question 1a: If catheter ablation is efficacious compared with other treatment options, is there differential efficacy between the different types of ablation (e.g., radiofrequency ablation versus cryoballoon ablation)?

Atrial fibrillation

No studies identified.

Atrial flutter

Studies. Four RCTs[31-34] were included that compared radiofrequency ablation with cryoablation in patients with typical atrial flutter. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D2 for definitions). All studies failed to meet more than one criterion for a good quality RCT.

Summary of the highest quality evidence.
Freedom from recurrence: There is low quality evidence from 3 RCTs that there is no difference in the rate of freedom from recurrence between radiofrequency ablation and cryoablation (63% versus 57%, respectively) in patients with atrial flutter as measured at 5 to 15 months follow-up.

Persistent bidirectional conduction block: There is low quality evidence from 1 RCT that atrial flutter patients treated with radiofrequency ablation had significantly higher rates of persistent birdirectional conduction block compared with those treated with cryoablation at 3 months follow-up, with a risk difference of 19% (95% CI, 4%, 33%).

SVTs

AVNRT

Studies. Four RCTs[35-38] were included that compared these procedures in patients with SVT. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D2 for definitions). All studies failed to meet more than one criterion for a good quality RCT.

Summary of the highest quality evidence.
Freedom from recurrence : There is moderate quality evidence from 3 RCTs that patients treated with radiofrequency ablation had significantly higher rates of freedom from

recurrence compared with those treated with cryoablation at 6 to 12 months follow-up, with a risk difference of 5% (95% CI, 1%, 9%).

Key Question 2: What is the evidence regarding the comparative efficacy of various approaches to radiofrequency catheter ablation?

Atrial fibrillation

Studies. Thirty-five RCTs[39-73] met our inclusion criteria and reported outcomes related to freedom from recurrence for AF using different approaches of PVI. We identified studies that compared the following approaches: PVI versus wide-area circumferential ablation (WACA), PVI with or without additional left sided ablation lines, PVI with or without additional right sided ablation lines, PVI with or without complex fractionated electrograms, and a variety of miscellaneous comparisons were also found. One study was considered to have a low risk of bias (Class of Evidence I) and the remaining 34 studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions).

Summary of the highest quality evidence.
Freedom from recurrence : There is low quality evidence from 5 RCTs that patients treated with PVI had significantly lower rates of freedom from recurrence compared with those treated with WACA at 3 to 13 months follow-up, with a risk difference of 10% (95% CI, 1%, 18%). There is moderate quality evidence from 8 RCTs that there is no difference in freedom from recurrence at 7 to 36 months follow-up in patients treated with PVI compared with those who received PVI plus additional left sided ablation lines (65.5% versus 70.3%, respectively). There is moderate quality evidence from 4 RCTs that there is no difference in freedom from recurrence at 8 to 12 months follow-up in patients treated with PVI compared with those who received PVI plus additional right sided ablation lines (68.2% versus 70.8%, respectively). There is moderate quality evidence from 6 RCTs that patients that treated with PVI had significantly lower rates of freedom from recurrence compared with those treated with PVI plus CFE at 12 to 23 months follow-up, with a risk difference of 17% (95% CI, 9%, 25%).

Key Question 3: What is the evidence regarding the safety of catheter ablation?

Atrial fibrillation

Studies. We evaluated safety data from all comparative studies included in Key Question 1. In total, nine RCTs[6-12, 14-16], two prospective cohort studies[17, 18] and two retrospective cohort studies[19, 20] comparing radiofrequency PVI to AADs, one retrospective cohort study[22] comparing radiofrequency PVI to Cox-Maze surgery, and one RCT comparing cryoablation to AADs[21]. In addition, we identified six prospective case series[74-79] that were specifically designed to evaluate adverse events in at least 1000 patients who

underwent PVI for atrial fibrillation. We also identified four prospective case series[80-83] that evaluated the incidence of procedure-related esophageal lesions in at least 100 AF patients. These studies were included as this PVI-related complication was not reported in any of the comparative or larger prospective case series. Case series data are briefly summarized here; more detailed information can be found in Appendix F.

Summary of the highest quality evidence.
Procedure- or treatment-related mortality: There is low quality evidence from 1 RCT that there is no difference in procedure- or treatment-related mortality rates following RF PVI compared with AADs. There were no treatment-related deaths in either group.

Procedure- or treatment-related thromboembolic events: There is low quality evidence from 3 RCTs that there is no difference in procedure- or treatment-related thromboembolic event rates following RF PVI compared with AADs (0.7% versus 0.6%, respectively).

Pericardial effusion or cardiac tamponade: There is low quality evidence from 2 RCTs that there is no difference in pericardial effusion or cardiac tamponade rates following RF PVI compared with AADs (1.3% versus 0.8%, respectively). There is low quality evidence from 1 RCT that there is no difference in pericardial effusion or cardiac tamponade rates following cryo-PVI compared with AADs (0.6% versus 1%, respectively).

Pulmonary vein stenosis: There is low quality evidence from 3 RCTs that there is no difference in pulmonary vein stenosis rates following RF PVI compared with AADs, with no reported cases in either group. There were no treatment-related deaths in either group. There is low quality evidence from 1 RCT that there is no difference in pulmonary vein stenosis rates following cryo-PVI compared with AADs (1.2% versus 2%, respectively).

Atrial flutter

Studies. We evaluated safety data from all comparative studies included in Key Question 1: data from one RCT[23] that compared radiofrequency ablation was included. In addition, we identified six prospective case series[84-89] that were specifically designed to evaluate adverse events in at least 100 patients who underwent catheter ablation for atrial flutter. Case series data are briefly summarized here; more detailed information can be found in Appendix table F11.

Summary of the highest quality evidence.
Procedure- or treatment-related mortality: There is low quality evidence from 1 RCT that there is no difference in procedure- or treatment-related mortality rates following RF PVI compared with AADs in patients with atrial flutter. There were no treatment-related deaths in either group.

Supraventricular tachyarrhythmias

Studies. Safety data from all comparative studies included in Key Question 1 were evaluated. For AVNRT, data from three prospective[24, 25, 27] and one retrospective[26] cohort study were included. For AVRT, data from one RCT[29] and one retrospective cohort study[28] were included. For mixed populations of patients with SVT, data from one prospective cohort study[30] were included. In addition, six case series[87-92] that were specifically designed to evaluate adverse events following catheter ablation in at least 500 patients with SVT were also identified for inclusion. Case series data are briefly summarized in the last section on mixed populations; more detailed information can be found in Appendix table F18.

Summary of the highest quality evidence.

Persistent AV block. There is insufficient evidence from one cohort study that ablation results in higher rates of persistent AV block compared with open perinodal dissection ("skeletonization") surgery in patients with AVNRT (22.7% versus 4%, respectively).

Pacemaker implantation. There is insufficient evidence from one cohort study that there is no difference in the rate of pacemaker implantation in AVNRT patients who were treated with catheter ablation compared with open perinodal dissection surgery (3.1% versus 3%, respectively).

No other comparative safety data were available.

Key Question 4: Does catheter ablation have any differential efficacy or safety compared with other treatment options in subpopulations?

Summary

We found no strong evidence of the differential effectiveness of catheter ablation versus any alternative treatment option in any subpopulation for any diagnoses of interest. Although a total of seven studies examined outcomes in various subpopulations, none of these studies pre-specified the subgroup analyses, none of the studies performed a test of interaction as the method of subgroup analysis, and some of the studies were inadequately powered to detect differences in treatment effect.

Key Question 5: What is the evidence of cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term?

Atrial fibrillation

Studies. Five cost utility analyses which compared pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) were included[93-97]. All studies were reasonably well-conducted, with QHES scores ranging from 84 to 100 (mean score of 91) after

methodological evaluation. Two studies[94, 96] were conducted within the US, while the other three[93, 95, 97] were done from an international perspective (Canada, Sweden, and UK). All studies were published in or after the year 2006.Three of the studies did not include a statement disclosing the source of funding, but authors in four of the studies had consulting relationships with catheter device manufacturers. All of the studies relied on a deterministic Markov decision-analytic model to simulate the evolution of health states over time and estimate associated costs.

Summary

Five-year time horizon: When considering a five-year time horizon, there is moderate evidence that PVI is more cost-effective than AADs depending on how much society is willing to pay per QALY. Three studies evaluated the cost effectiveness of PVI compared with AADs based on a five-year time horizon. The population of interest was hypothetical cohorts of patients with paroxysmal AF and who were refractory to AADs, The patients ranged from 52 to 65 years of age. Only one of the studies was conducted with a US perspective. In two of the studies (including the US study), the incremental cost effectiveness ratio (ICER) ranged from approximately $51,400 to $59,200 per quality-adjusted life year (QALY). In one of the studies, the ICER ranged from $33,201 to $44,221 to QALY, decreasing with increasing stroke risk. All studies concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal AF depending on how much society is willing to pay per QALY.

Lifetime horizon. When considering a lifetime horizon, there is moderate evidence that PVI is more cost-effective than AADs depending on how much society is willing to pay per QALY. Three studies evaluated the cost effectiveness of PVI compared with AADs based on a lifetime horizon. The population of interest was hypothetical cohorts of patients with paroxysmal or persistent AF with low to moderate stroke risks. Two of the studies specified that patients were considered to be refractory to AADs and that patients ranged from 52 to 65 years of age. Only one of the studies was conducted with a US perspective. One study reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation was more cost-effective than AADs. The two other studies reported ICERs ranging from approximately $12,400 to $29,100 per QALY, and concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal or persistent AF depending on how much society is willing to pay per QALY. In general, ablation is more cost-effective in the lifetime horizon compared with the five-year horizon models due to long-term costs associated with AAD therapy.

Atrial flutter

No studies were idenfitied that met our inclusion criteria.

Supraventricular Tachycardias (SVTs)

Studies. Two cost utility analyses which radiofrequency ablation with anti-arrhythmic drugs (AADs) were included[98, 99]. Both studies were reasonably well-conducted, with QHES scores of 88 and 73 after methodological evaluation. Both studies were conducted within the US and were published the years 1993 and 2000, making them older studies. Neither study was funded from nor did authors disclose relationships with device manufacturers. Both studies relied on a deterministic Markov decision-analytic model to simulate the evolution of health states over time and estimate associated costs.

Summary

Lifetime horizon. Considering a lifetime horizon, there is low quality evidence from two cost utility studies that radiofrequency ablation is more cost effective than AADs to treat patients with SVT. Both studies evaluated the cost effectiveness of ablation compared with AADs based on a lifetime horizon. The population of interest was a hypothethical cohort of patients 40 years of age with either highly symptomatic SVT (60% considered to have AVNRT)[99] or with WPW Syndrome[98]. Both studies reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation treatment was more cost-effective than AADs alone.

Quality of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes compared with other treatment options?

KQ1: Atrial fibrillation				Effect		Treatment groups	
Outcome	**Interventions**	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Freedom from Recurrence	**RF PVI vs. AADs**	714 (7 RCTs) 6-12 mos.	Moderate	50% (95% CI, 43%, 58%; *P* < .00001) NNT: 2 (95% CI, 2, 2)	PVI	74.6% (303/406) (56 – 89%)	23.6% (87/369) (9 – 43%)
		198 (1 RCT) 48 mos.	Moderate	61% (95%, CI, 48%, 70%) NNT: 2 (95% CI, 1, 2)	PVI	73% (72/99)	12% (12/99)
	Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Low	63% (95% CI, 52%, 70%) NNT: 2 (95% CI, 1, 2)	PVI	69.9% (114/163)	7% (6/82)
Mortality (not procedure-related)	**RF PVI vs. AADs**	137 (1 RCT**) 12 mos.	Low	NS	NS	1% (1/68) **	3% (2/69) **
	Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Low	NS	NS	0.6% (1/163)	0% (0/82)
Stroke (not procedure-related)	**RF PVI vs. AADs**	140 (2 RCTs††) 12 mos.	Low	NS	NS	0% (both studies) (0/68)††	0% (both studies) (0/72)††
	Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Low	NS	NS	0.6% (1/163)	0% (0/82)
Congestive heart failure	**RF PVI vs. AADs**	198 (1 RCT) 48 mos.	Low	NS	NS	0% (0/99)	0% (0/99)
	Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Low	NS	NS	0.6% (1/163)	0% (0/82)
Freedom from Recurrence	**RF PVI vs Cox Maze**	289 (1 cohort study) 54 mos.	Insufficient	NS	NS	74% (144/194)	84% (81/97)
Freedom from Recurrence (in absence of AADs)	**RF PVI vs Cox Maze**	289 (1 cohort study) 54 mos.	Insufficient	26%	Surgery	56% (109/194)	82% (80/97)
Stroke (not procedure-related)	**RF PVI vs Cox Maze**	289 (1 cohort study) 54 mos.	Insufficient	NS	NS	1.7% (3/194)	2% (2/97)

** Only 1 RCT reported data for both treatment groups. Mortality rates were similar as reported for the PVI group only by 2 additional RCTs and for the AAD group only by 1 additional RCT.

†† 2 RCTs reported data for both treatment groups. Stroke rates were similar as reported for the AAD group only by 1 additional RCT.

The following footnotes apply to all of the strength of evidence tables:

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

KQ1: Atrial flutter				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Freedom from Recurrence	**RF ablation vs. AADs**	104 (1 RCT) 13 ± 6 mos.	Moderate	26% (95% CI, 13%, 41%) NNT: 4 (95% CI, 2, 8)	Ablation	96% (50/52)	70% (36/52)
Mortality (not procedure-related)	**RF ablation vs. AADs**	104 (1 RCT) 13 ± 6 mos.	Low	NS	NS	11% (6/52)	16% (8/52)

KQ1: AVNRT				Effect		Treatment groups		
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**	
Patient-reported freedom from symptoms	**RF ablation vs. AADs**	93 (1 cohort study) 1-8 years	Insufficient	39% (versus chronic AADs) 55% (versus short- term AADs)	Ablation	100% (18/18)	Chronic AADs 61% (15/24)	Short-Term AADs 45% (17/38)
Freedom from Recurrence	**RF ablation vs. Surgery**	242 (2 cohort studies) 14 yrs. (1 study, NR in other)	Insufficient	NS	NS	87.8% (143/163) (85 – 95%)	93% (63/69) (88 – 94%)	
Freedom from Recurrence	**RF ablation vs. no treatment**	27 (1 cohort study) 13 – 23 mos.	Insufficient	64%	Ablation	100% pts (16/16)	36% pts (4/11)	

KQ1: AVRT				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Patient-reported freedom from symptoms	**RF ablation vs. AADs**	32 (1 cohort study) 8 – 58 mos.	Insufficient	82%	Ablation	90% (18/20)	8% (1/12)
	RF ablation vs. surgery	40 (1 cohort study) 8 – 58 mos.	Insufficient	NS	NS	90% (18/20)	100% (20/20)

KQ1: WPW Syndrome				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Freedom from Recurrence	**RF ablation vs. no treatment**	24 mos. 76 (1 RCT) 24 mos. (median)	Moderate	55% (95% CI, 35%, 70%) NNT: 2 (95% CI, 1, 3)	Ablation	95% (36/38)	40% (15/38)
		48 mos. 72 (1 RCT) 5 years	Moderate	55% (95% CI, 34%, 70%) NNT: 2 (95% CI, 1, 3)	Ablation	93% (35/37)	23% (14/35)
Mortality (not procedure-related)	**RF ablation vs. no treatment**	24 mos. 76 (1 RCT) 24 mos. (median)	Low	NS	NS	0% (0/38)	0% (0/38)

KQ1: Mixed SVT diagnoses				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Patient-reported freedom from symptoms	**RF ablation vs. AADs**	95 (1 cohort study) 12 mos.	Low	30%	Ablation	85% (33/39)	55% (24/44)

Quality of evidence summary for Key Question 1a: If catheter ablation is efficacious compared with other treatment options, is there differential efficacy between radiofrequency ablation versus cryoablation?

KQ1a: Atrial flutter				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**RF Ablation (% pts)**	**Cryoablation (% pts)**
Freedom from Recurrence	**RF ablation vs. Cryoablation**	134 (3 RCTs) 5-15 mos.	Low	NS	NS	63% (43/65) (33 – 93%)	57% (37/65) (31 – 85%)
Persistent bidirectional conduction block	**RF ablation vs. Cryoablation**	191 (1 RCT) 3 mos.	Low	19% (95% CI, 4%, 33%) NNT: 5 (95% CI, 3, 24)	RF Ablation	85% (51/60)	62% (42/64)

KQ1a: AVNRT				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**RF Ablation (% pts)**	**Cryoablation (% pts)**
Freedom from Recurrence	**RF ablation vs. Cryoablation**	739 (3 RCTs) 6 - 12 mos.	Moderate	5% (95% CI, 1%, 9%) NNT: 21 (95% CI, 11, 92)	RF Ablation	95.4% (349/366) (71–99%)	90.5% (325/359) (77–92%)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (RF ablation – cryoablation) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT); RF: radiofrequency

Reasons for downgrading quality of evidence:

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)

§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Quality of evidence summary for Key Question 2: What is the evidence regarding the comparative efficacy of various approaches to radiofrequency catheter ablation for patients with atrial fibrillation?

KQ2: Atrial fibrillation				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Approach 1 (% pts)**	**Approach 2 (% pts)**
Freedom from Recurrence	**PVI vs. WACA**	500 (5 RCTs) 3-15 mos.	Low	10% (95% CI, 1%, 18%) NNT: 10 (95% CI, 5, 73)	WACA	PVI 55.5% (141/254) (56 – 89%)	WACA 65.4% (161/246) (9 – 43%)
	PVI vs. PVI + left lines	1243 (8 RCTs) 7-36 mos.	Moderate	NS	NS	PVI 65.5% (366/559) (12 – 87%)	PVI + left lines 70.3% (444/631) (21 – 88%)
	PVI vs. PVI + right lines	683 (4 RCTs) 8-12 mos.	Moderate	NS	NS	PVI 68.2% (236/346) (32 – 100%)	PVI + right lines 70.8% (218/308) (34 – 100%)
	PVI vs. PVI + CFE	587 (6 RCTs) 12-23 mos.	Moderate	17% (95% CI, 9%, 25%) NNT: 6 (95% CI, 4, 11)	PVI+ CFE	PVI 50.5% (159/315) (11 – 89%)	PVI + CFE 67.6% (184/272) (39 – 91%)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)
** Serious risk of inconsistency: 3/5 studies favored WACA, 1/5 studies favored PVI

Quality of evidence summary for Key Question 3: What is the evidence regarding the safety of catheter ablation?

KQ3: Atrial fibrillation				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**PVI (% pts)**	**Control (% pts)**
Mortality (procedure- or treatment-related)	**RF PVI vs. AADs**	112 (1 RCT**) 12 mos.	Low	NS	NS	0% (0/53)**	0% (0/59)**
Thrombo-embolic events (procedure- or treatment-related)	**RF PVI vs. AADs**	310 (3 RCTs††) 2-15 mos.	Low	NS	NS	0.7% (1/153) (0 – 1%) ††	0.6% (1/157) (0 – 1%) ††
Pericardial effusion or cardiac tamponade	**RF PVI vs. AADs**	279 (2 RCTs‡‡) 1-12 mos.	Low	NS	NS	1.3% (2/159) (1 – 2%) ‡‡	0.8% (1/120) (0 – 2%) ‡‡
	Cryo PVI vs. AADs	245 (1 RCT) 0-1 mos.	Low	NS	NS	0.6% (1/163)	1% (1/82)
Pulmonary vein stenosis	**RF PVI vs. AADs**	223 (3 RCTs§§) 6-12 mos.	Low	NS	NS	2.8% (3/108) (0 – 6%) §§	0 % (0/115) (0%) §§
	Cryo PVI vs. AADs	245 (1 RCT) 0-1 mos.	Low	NS	NS	1.2% (2/163)	2% (2/84)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

** 1 RCT reported data for both treatment groups. Treatment-related mortality rates were similar as reported for the PVI group only by 1 additional RCT.
†† 3 RCTs reported data for both treatment groups. Treatment-related thromboembolic rates were also reported for the PVI group only by 4 additional RCTs, and occurred in 0% to 7% of patients of these studies.
‡‡ 2 RCTs reported data for both treatment groups. Pericardial effusion or cardiac tamponade were also reported for the PVI group only by 3 additional RCTs, and occurred in 1% to 9% of patients of these studies.
§§3 RCTs reported data for both treatment groups. Pulmonary vein stenosis was also reported for the PVI group only by 2 additional RCTs, and occurred in 1.7% to 7% of patients of these studies.

KQ3: Atrial flutter				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Mortality (procedure- or treatment-related)	**RF ablation vs. AADs**	104 (1 RCT) 13 ± 6 mos.	Low	NS	NS	0% (0/52)	0% (0/51)

KQ3: AVNRT				Effect		Treatment groups	
	Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Persistent AV block	**RF ablation vs. open perinodal dissection surgery (AVNRT)**	Ablation: 120 (1 cohort study) 1 mos.	Insufficient	19%	Surgery	22.7% (37/163)	4% (3/79)
Pacemaker implantation	**RF ablation vs. open perinodal dissection surgery (AVNRT)**	Ablation: 120 (1 cohort study) 1 mos.	Insufficient	NS	NS	3.1% (5/163)	3% (2/79)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Quality of evidence summary for Key Question 4: Does catheter ablation have any differential efficacy or safety compared with other treatment options in subpopulations

			Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Catheter ablation versus Other treatment	0 studies reporting	Insufficient	-	-		

Quality of evidence summary for Key Question 5: What is the evidence of the cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term?

Note that GRADE has not been developed to evaluate the quality of cost-effectiveness evidence.

KQ5: Atrial fibrillation					
Interventions	**Studies Time horizon**	**Countries**	**QHES Range**	**Overall quality of evidence**	**Conclusions**
PVI versus AADs	3 cost-utility analyses 5- year time horizon	USA Canada UK	90-100	Moderate	In two of the studies (including the US study), the incremental cost effectiveness ratio (ICER) ranged from approximately $51,400 to $59,200 per quality-adjusted life year (QALY). In one of the studies, the ICER ranged from $33,201 to $44,221 to QALY, decreasing with increasing stroke risk. All studies concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal AF depending on how much society is willing to pay per QALY.
	3 cost-utility analyses Lifetime horizon	USA Sweden UK	84-100	Moderate	One study reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation was more cost-effective than AADs. The two other studies reported ICERs ranging from approximately $12,400 to $29,100 per QALY, and concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal or persistent AF depending on how much society is willing to pay per QALY. In general, ablation is more cost-effective in the lifetime horizon compared with the five-year horizon models due to long-term costs associated with AAD therapy.

KQ5: Atrial flutter					
Interventions	**Studies Time horizon**	**Countries**	**QHES Range**	**Overall quality of evidence**	**Conclusions**
	No studies			No evidence	

KQ5: SVTs					
Interventions	**Studies Time horizon**	**Countries**	**QHES Range**	**Overall quality of evidence**	**Conclusions**
Catheter ablation versus AADs	2 cost-utility analyses Lifetime horizon	USA	73-88	Low	Both studies reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation treatment was more cost-effective than AADs alone.

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1. Appraisal

1.1. Rationale

Catheter ablation is most commonly used to treat tachyarrhythmias that originate above the ventricles, including atrial fibrillation, atrial flutter, and supraventricular tachycardias. The procedure involves guided insertion of catheters from the arm, groin, or neck through the blood vessel and into the heart. In radiofrequency catheter ablation, radiofrequency energy is sent through the catheters to a focal point in the heart that is believed to be the source of the arrhythmia; this energy ablates (destroys) very small areas of the heart to disrupt abnormal electrical activity. Other types of catheter ablation are becoming available, such as cryoballoon ablation, which involves cooling and freezing of the targeted tissue to alter abnormal electrical activity. Ablation may be considered early in the course of treatment for arrhythmias that are difficult to treat medically, and may be considered before medical therapy in patients in whom the arrhythmia is poorly tolerated. Ablation is an option for some arrhythmias after drug treatment failure.

Alternate treatment options depend on which condition is being treated and patient comorbidities. General options include medical (pharmacologic) therapy, surgery (including Maze procedures) and other therapies to control rhythm. Treatment of atrial fibrillation traditionally focuses on rate control, thromboembolism prevention and treating the underlying disease (e.g. congestive heart failure, coronary artery disease, hypertension).

The HCA has selected ablation therapies for supraventricular tachyarrhythmia including atrial flutter and atrial fibrillation for review. The topic was nominated based on high levels of concern around efficacy and cost and on medium levels of concern around safety.

The primary aim of this assessment is to systematically review, critically appraise and analyze research evidence comparing the efficacy, effectiveness, and safety of ablation procedures for supraventricular tachyarrhythmia (including atrial flutter, supraventricular tachycardia, and atrial fibrillation) with other treatment alternatives. The differential effectiveness and safety as well as the cost-effectiveness of catheter ablation will also be evaluated.

1.2. Key Questions

In adults with supraventricular tachyarrhythmia (including the following conditions)

- Supraventricular tachycardia
  - Sinus tachycardia (including sinus tachycardia, inappropriate sinus tachycardia (IST), and sinus nodal reentrant tachycardia (SNRT))
  - Atrioventricular reentrant tachycardia (AVRT), including Wolff-Parkinson-White Syndrome

        - Atrioventricular nodal reentrant tachycardia (AVNRT)
        - Atrial tachycardia (including focal and multifocal)
        - Focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia
    - Atrial flutter
    - Atrial fibrillation

Key Question 1: Does catheter ablation improve patient outcomes in persons with supraventricular tachyarrhythmias compared with other treatment options: What is the evidence for comparative efficacy and effectiveness over the short term and longer term?

a. If catheter ablation is efficacious compared with other treatment options, is there differential efficacy between the different types of ablation (e.g., radiofrequency ablation versus cryoballoon ablation)?

Key Question 2: What is the evidence regarding the comparative efficacy of various approaches to radiofrequency catheter ablation (e.g., PVI alone versus PVI with additional ablation lines, etc.)?

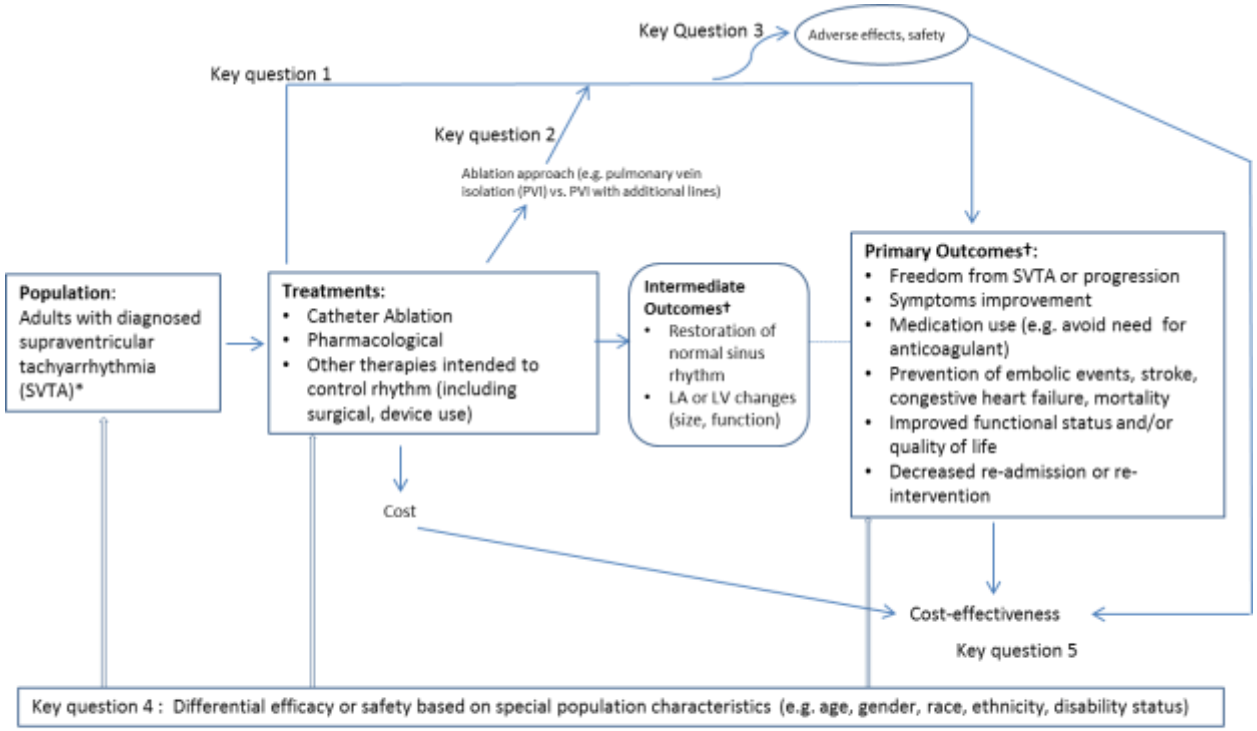
Key Question 3: What is the evidence of the safety of catheter ablation?

Key Question 4: Does catheter ablation have any differential efficacy or safety compared with other treatment options in subpopulations? Include consideration of age, gender, race, ethnicity, or disability.

Key Question 5: What is the evidence of cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term?

Figure 1 provides the analytic framework for this HTA. The population of interest is adult patients with supraventricular tachyarrhythmias undergoing catheter ablation. Key Question 1 examines the larger question of the efficacy and effectiveness of catheter ablation compared with other treatments for rhythm control, while Key Question 2 focuses specifically on the comparative efficacy of different approaches to radiofrequency catheter ablation. Key Question 3 assesses the adverse events and safety of catheter ablation. Key question 4 asks whether there are any special population characteristics that differentially affect the efficacy or safety of catheter ablation,and Key Question 5 evaluates whether catheter ablation in this patient population is cost effective.

Figure 1. Analytic Framework and Key Questions



* SVTA includes supraventricular tachycardias, atrial fibrillation and atrial flutter
† General list of outcomes; not all may be relevant to a specific SVTA or all primary outcomes;
LA = left atrium, LV = left ventricle

1.3 Washington State Utilization and Cost Data

Figure 1 - Catheter Ablation Procedures - Paid Amounts by Agency and Year, 2008-2011

Agency/Year PEB[1]	2008	2009	2010	2011	4 Yr Overall	Average % Change	
Agency Pop. (Fee for Service)	204,804	210,501	213,487	212,596		1.3%	
Patient Count[2]	113	143	147	135	484	5.8%	*
Procedure Count	119	153	154	135	559	4.1%	*
Amount Paid	$2,006,856	$2,722,861	$2,603,480	$2,359,240	$9,692,437	5.8%	*
Per Procedure Average[3]	$16,864	$17,796	$16,906	$17,476	$17,277		
Per Procedure 95% Upper Limit	$48,438	$59,551	$45,243	$54,318	$52,321		
Per Procedure Maximum	$91,721	$108,318	$63,222	$117,729	$117,729		
Medicaid	**2008**	**2009**	**2010**	**2011**	**4 Yr Overall**	**Average % Change**	
Agency Pop. (Fee for Service)	392,808	416,871	424,230	435,187		3.5%	
Patient Count[2]	60	47	63	93	263	16.5%	*
Procedure Count	65	48	65	95	273	15.0%	*
Amount Paid	$589,118	$401,026	$471,307	$587,858	$2,049,309	0.4%	*
Per Procedure Average[3]	$9,063	$8,355	$7,481	$6,998	$7,882		
Per Procedure 95% Upper Limit	$19,321	$15,528	$15,129	$18,811	$17,720		
Per Procedure Maximum	$16,925	$14,744	$12,664	$16,698	$16,925		

Notes:

*Average % Change adjusted for population.

[1]Public Employee Benefits.

[2] Patients who receive treatment in multiple years are counted only once in the "4 Yr Overall" total.

[3] Procedure amounts include related charges on the day of service or the duration of hospitalization.

Note: L&I paid 7 claims that include ablation procedures totaling $267,556 (average $38,222) during the 2008-2011 timeframe.

Figure 2a. PEB Catheter Ablation Patients by Age and Gender, 2008-2011

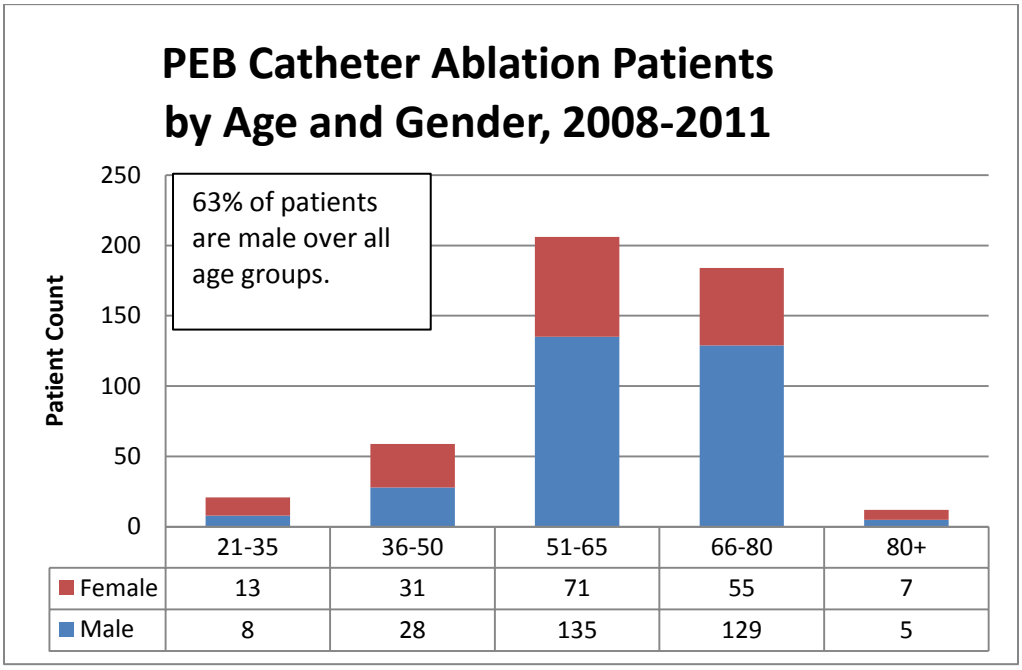


Figure 2b. Medicaid Catheter Ablation Patients by Age and Gender, 2008-2011

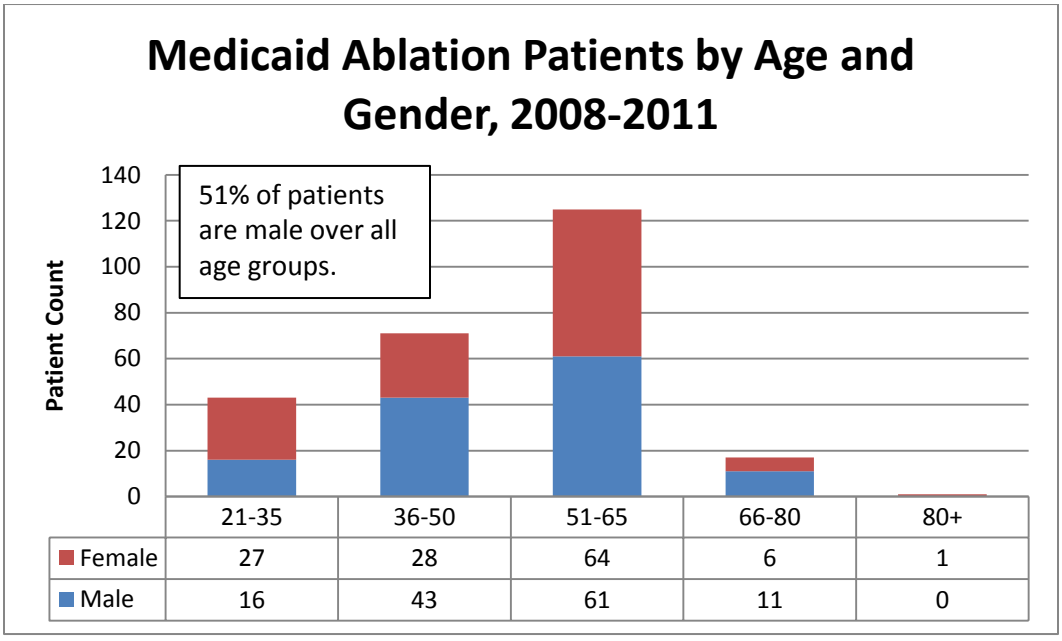


Figure 3. Catheter Ablation Procedure Average Allowed Amounts, 2008-2011

Per Procedure Avg Allowed Charges by Agency, Setting and Payer	PEB Primary Inpatient (n=118)	PEB Primary Out-patient (n=188)	PEB Medicare Inpatient (n=94)	PEB Medicare Out-patient (n=137)	Medicaid Inpatient (n=28)	Medicaid Out-patient (n=207)	Medicaid Medicare Outpatient (n=38)
Breakdown 1							
Professional Services	$3,823	$2,676	$1,758	$1,535	$1,490	$1,299	$76
Facility	$27,444	$22,699	$53,547	$44,322	$13,088	$8,098	$12,447
Breakdown 2							
Equipment/Supplies[1]	$369	$791	$1,231	$2,100	$0	$3	$241
Ablation Procedure	$1,836	$3,048	$1,635	$3,291	$542	$2,454	$397
Heart Function Testing	$8,408	$20,423	$6,107	$15,643	$731	$5,264	$10,466
Other Charges[2]	$1,153	$614	$1,094	$2,121	$228	$317	$1,411
Hospital	$19,501	$498	$45,238	$22,703	$13,077	$59	$0
Avg Allowed	**$31,267**	**$25,375**	**$55,305**	**$45,857**	**$14,579**	**$8,098**	**$12,523**

[1]Catheters, injectable drugs, other consumable supplies

[2]Anesthesia, Lab tests, Imaging and angiography, Pre-procedure preparation

Figure 4a – PEB Comparator Procedure Counts

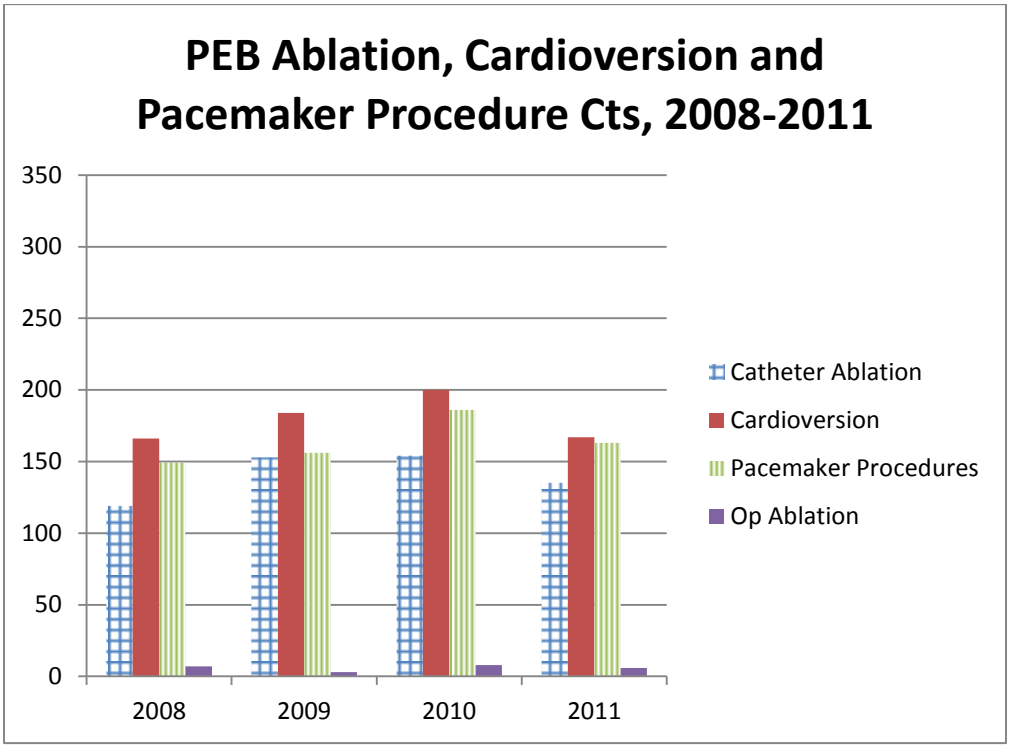
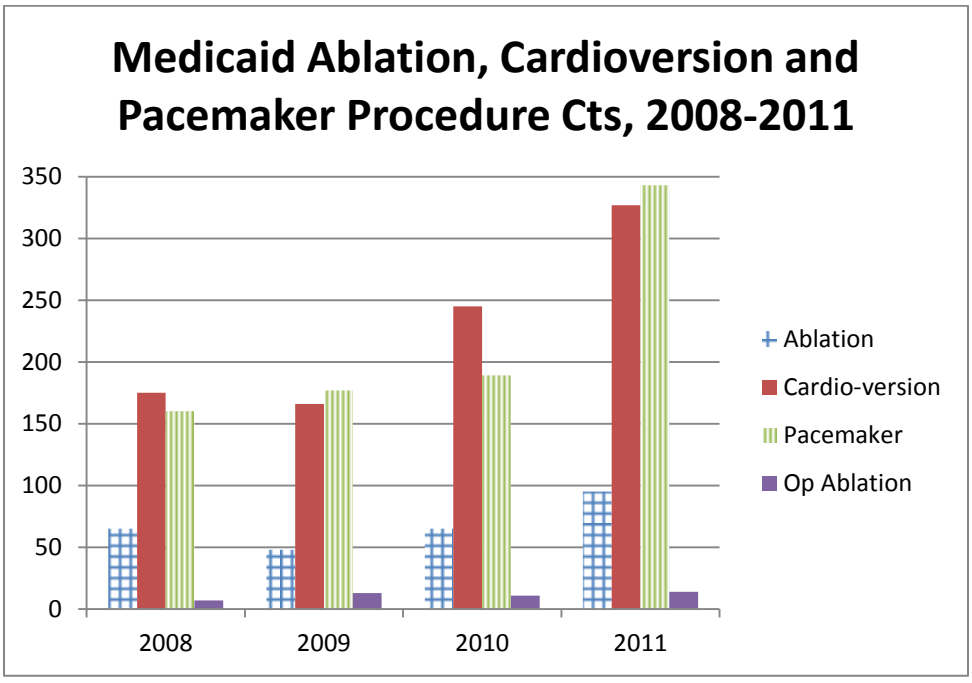


Figure 4b Medicaid Comparator Procedure Counts



Related Medical Codes

CPT	Description	Category	Ablation
93462	Transseptal puncture (alternate (retrograde) approach for 93653/55, included in 93656)	Ablation (addon)	Add-on
93600	Bundle of His recording (Electrophysiologic Study or EPS)	EPS	No
93602	Intra-atrial recording	EPS	No
93603	Right ventricular recording	EPS	No
93609	Intraventricular and/or intra-atrial mapping of tachycardia site(s) with catheter manipulation to record from multiple sites to identify origin of tachycardia (List separately in addition to code for primary procedure)(Use 93609 in conjunction with 93620, 93653) (Do not report 93609 in conjunction with 93613, 93654)	Mapping	Add-on
93610	Intra-atrial pacing	EPS	No
93612	Intraventricular pacing (Do not report 93612 in conjunction with 93620- 93622)	EPS	No
93613	Intracardiac electrophysiologic 3-dimensional mapping (List separately in addition to code for primary procedure) (Use 93613 in conjunction with 93620, 93653) (Do not report 93613 in conjunction with 93609, 93654)	Mapping, optional ab-lation addon	Addon
93615	Esophageal recording of atrial electrogram with or without ventricular electrogram(s);	EPS	No
93616	with pacing	EPS	No
93618	Induction of arrhythmia by electrical pacing (For intracardiac phonocardiogram, use 93799)	EPS	No
93619	Comprehensive electrophysiologic evaluation with right atrial pacing and recording, right ventricular pacing and recording, His bundle recording, including insertion and repositioning of multiple electrode catheters, without induction or attempted induction of arrhythmia (Do not report 93619 in conjunction with 93600, 93602, 93610, 93612, 93618, or 93620- 93622)	EPS	No
93620	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of arrhythmia; with right atrial pacing and recording, right ventricular pacing and recording, His bundle recording (Do not report 93620	EPS	No

CPT	Description	Category	Ablation
	in conjunction with 93600, 93602, 93610, 93612, 93618 or 93619)		
93621	with left atrial pacing and recording from coronary sinus or left atrium (List separately in addition to code for primary procedure) (Use 93621 in conjunction with 93620) (Do not report 93621 in conjunction with 93656)	EPS	No
93622	with left ventricular pacing and recording (List separately in addition to code for primary procedure) (Use 93622 in conjunction with 93620)	EPS (atrial fib)	Addon
93623	Programmed stimulation and pacing after intravenous drug infusion (List separately in addition to code for primary procedure)	EPS (atrial fib)	Addon
93624	Electrophysiologic follow-up study with pacing and recording to test effectiveness of therapy, including induction or attempted induction of arrhythmia	Post ablation test	Addon
93631	Intra-operative epicardial and endocardial pacing and mapping to localize the site of tachycardia or zone of slow conduction for surgical correction (For operative ablation of an arrhythmogenic focus or pathway by a separate individual, see 33250- 33261)	Post ablation test	Addon
93640	Electrophysiologic evaluation of single or dual chamber pacing cardioverter-defibrillator leads including defibrillation threshold evaluation (induction of arrhythmia, evaluation of sensing and pacing for arrhythmia termination) at time of initial implantation or replacement;	EPS	Addon
93641	with testing of single or dual chamber pacing cardioverter-defibrillator pulse generator (For subsequent or periodic electronic analysis and/or reprogramming of single or dual chamber pacing cardioverter-defibrillators, see 93282, 93283, 93289, 93292, 93295, 93642)	EPS	Addon
93642	Electrophysiologic evaluation of single or dual chamber pacing cardioverter-defibrillator (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing and pacing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters)	EPS	Addon
93650	Intracardiac catheter ablation of atrioventricular node function, atrioventricular conduction for creation of	EPS	Addon

CPT	Description	Category	Ablation
	complete heart block, with or without temporary pacemaker placement (93651, 93652 have been deleted. To report, see 93653- 93657)		
93651	Intracardiac catheter ablation of arrhythmogenic focus; for treatment of supraventricular tachycardia by ablation or other atrial foci, singly or in combination (through Dec 2012).	Ablation (Supra-ventricular)	Ablation
93652	Intracardiac catheter ablation of arrhythmogenic focus; for treatment of ventricular tachycardia (through Dec 2012).	(Ventricular)	No
93653	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with right atrial pacing and recording, right ventricular pacing and recording, His recording with intracardiac catheter ablation of arrhythmogenic focus; with treatment of supraventricular tachycardia by ablation of fast or slow atrioventricular pathway, accessory atrioventricular connection, cavo-tricuspid isthmus or other single atrial focus or source of atrial re-entry (Do not report 93653 in conjunction with 93600- 93603, 93610, 93612, 93618-93620, 93642, 93654)	Ablation (Supra-ventricular)	Ablation
93654	with treatment of ventricular tachycardia or focus of ventricular ectopy including intracardiac electrophysiologic 3D mapping, when performed, and left ventricular pacing and recording, when performed (Do not report 93654 in conjunction with 93279- 93284, 93286- 93289, 93600- 93603, 93609, 93610, 93612, 93613, 93618- 93620, 93622, 93642, 93653)	(Ventricular)	No
93655	Intracardiac catheter ablation of a discrete mechanism of arrhythmia which is distinct from the primary ablated mechanism, including repeat diagnostic maneuvers, to treat a spontaneous or induced arrhythmia (List separately in addition to code for primary procedure) (Use 93655 in conjunction with 93653, 93654, 93656)	Ablation (secondary arrhythmia)	Add-on
93656	Comprehensive electrophysiologic evaluation including transseptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with atrial recording and pacing, when possible, right ventricular pacing and	Ablation (atrial fib)	Ablation

CPT	Description	Category	Ablation
	recording, His bundle recording with intracardiac catheter ablation of arrhythmogenic focus, with treatment of atrial fibrillation by ablation by pulmonary vein isolation		
93657	Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation (List separately in addition to code for primary procedure)	Ablation (atrial fib) (secondary ablation)	Addon
93660	Evaluation of cardiovascular function with tilt table evaluation, with continuous ECG monitoring and intermittent blood pressure monitoring, with or without pharmacological intervention (For testing of autonomic nervous system function, see 95921, 95924, 95943)	EPS	Addon
93662	Intracardiac echocardiography during therapeutic/diagnostic intervention, including imaging supervision and interpretation (List separately in addition to code for primary procedure)	EPS	Addon
33202-33249 33262-33264	Pacemaker insertion, repair, repositioning, replacement	Comparator Pacemaker	Pace-maker
33250	Operative ablation of supraventricular arrhythmogenic focus or pathway (eg, Wolff-Parkinson-White, atrioventricular node re-entry), tract(s) and/or focus (foci); without cardiopulmonary bypass (For intraoperative pacing and mapping by a separate provider, use 93631) Codes 33254-33256 are only to be reported when there is no concurrently performed procedure that requires median sternotomy or cardiopulmonary bypass.	Comparator Ablation	Op. Ablation
33251	with cardiopulmonary bypass	Comparator Ablation	Op. Ablation
33254	Operative tissue ablation and reconstruction of atria, limited (eg, modified maze procedure)	Comparator Ablation	Op. Ablation
33255	Operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure); without cardiopulmonary bypass	Comparator Ablation	Op. Ablation
33256	with cardiopulmonary bypass	Comparator Ablation	Op. Ablation

CPT	Description	Category	Ablation
33257	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), limited (eg, modified maze procedure) (List separately in addition to code for primary procedure)	Comparator Ablation	Op. Ablation
33258	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), without cardiopulmonary bypass (List separately in addition to code for primary procedure)	Comparator Ablation	Op. Ablation
33259	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), with cardiopulmonary bypass (List separately in addition to code for primary procedure)	Comparator Ablation	Op. Ablation
33261	Operative ablation of ventricular arrhythmogenic focus with cardiopulmonary bypass	Ventricular	No
92960	Cardioversion, elective, electrical conversion of arrhythmia; external	Comparator Ablation	Cardio-version
92961	Cardioversion, internal	Comparator Ablation	Cardio-version

ICD9	Desc	Category	
427.0	Paroxysmal supraventricular tachycardia Paroxysmal tachycardia: atrial [PAT]atrioventricular [AV]junctionalnodal	Arrhythmia	Supra-ventricular
427.1	Paroxysmal ventricular tachycardia, Ventricular tachycardia (paroxysmal)	Arrhythmia	
427.2	Paroxysmal tachycardia, unspecified, Bouveret-Hoffmann syndrome, Paroxysmal tachycardia: NOS,essential	Arrhythmia	
427.3	Atrial fibrillation and flutter	Arrhythmia	
427.31	Atrial fibrillation	Arrhythmia	
427.32	Atrial flutter	Arrhythmia	
427.4	Ventricular fibrillation and flutter	Arrhythmia	
427.41	Ventricular fibrillation	Arrhythmia	
427.42	Ventricular flutter	Arrhythmia	
427.5	Cardiac arrest, Cardiorespiratory arrest	Arrhythmia	
427.6	Premature beats	Arrhythmia	

ICD9	Desc	Category	
427.60	Premature beats, unspecified, Ectopic beats, Extrasystoles, Extrasystolic arrhythmia, Premature contractions or systoles NOS	Arrhythmia	
427.61	Supraventricular premature beats, Atrial premature beats, contractions, systoles	Arrhythmia	Supra-ventricular
427.69	Other Ventricular premature beats, contractions, or systoles	Arrhythmia	
427.8	Other specified cardiac dysrhythmias	Arrhythmia	
427.81	Sinoatrial node dysfunction,Sinus bradycardia: persistent severe Syndrome: sick sinustachycardia-bradycardia	Arrhythmia	
427.89	Other: Rhythm disorder: coronary sinusectopicnodal Wandering (atrial) pcmaker	Arrhythmia	
427.9	Cardiac dysrhythmia, unspecified Arrhythmia (cardiac) NOS	Arrhythmia	
HCPCS	**Description**	**Category**	**Ablation**
C1732	Catheter, electrophysiology, diagnostic/ablation, 3D mapping	Ablation eqp	Addon
C1733	Catheter, electrophysiology, diagnostic/ablation, other than 3D or vector mapping, other than cool-tip	Ablation eqp	Addon
C1766	Introducer/sheath, guiding, intracardiac electrophysiological, steerable, other than peel-away	Ablation eqp	Addon
C1892	Introducer/sheath, guiding, intracardiac electrophysiological, fixed-curve, peel-away	Ablation eqp	Addon
C1893	Introducer/sheath, guiding, intracardiac electrophysiological, fixed-curve, other than peel-away	Ablation eqp	Addon
C2629	Introducer/sheath, other than guiding, intracardiac EPS, laser	Ablation eqp	Addon
C2630	Catheter, electrophysiology, diagnostic/ablation, other than 3D or vector mapping, cool-tip	Ablation eqp	Addon

2. Background

2.1. Epidemiology and burden of disease

Supraventricular tachyarrhythmias (SVTs) can be categorized by the origin of the tachyarrhythmia[4]:

- Atrial tachyarrhythmias initiate within the atrium and include sinus tachycardia (including inappropriate sinus tachycardia (IST) and sinus nodal reentrant tachycardia (SNRT)), atrial tachycardia (including focal and multifocal), macroreentrant atrial tachycardia (i.e., atrial flutter), and atrial fibrillation,
- Atrioventricular tachyarrhythmias originate within the atrioventricular (AV) node or the surrounding area and include AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT, which includes Wolf-Parkinson-White Syndrome), focal junctional ectopic tachycardia (JET) and nonparoxysmal junctional tachycardia (NPJT).

Atrial fibrillation (AF) is characterized by uncoordinated atrial activation with resulting deterioration of atrial mechanical function[100]. AF can occur in isolation or be associated with other arrhythmias, most commonly atrial flutter or atrial tachycardia. A mechanism consisting of four different positive feedback loops has been proposed to explain the initiation and perpetuation of AF[101]. A variety of factors including aging, neurohumoral activation, inherited diseases, arrhythmias, and chronic atrial stretch resulting from structural heart disease activate numerous signaling pathways leading to atrial remodeling or changes in the electrical, structural, or contractile properties of the atria.

AF is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations for cardiac dysrhythmias[1]. It affects an estimated 2.7 to 6.1 million people in the US, with an estimated projected prevalence of 5.6 to 12.1 million by 2050[2]. A number of factors increase the risk of AF. Age is one factor: the risk of AF increases with age, with an estimated risk of 8%[100] to 10%[2, 101] in persons over 80 years of age. Another risk factor is gender: based on data from the Framingham Heart Study, men had a 1.5-fold greater risk for development of AF compared with women after accounting for age and predisposing conditions[2]. The effect of race on AF is poorly understood. Although African Americans have a higher prevalence of multiple AF risk factors such as obesity, diabetes, hypertension, and heart failure, they have a lower incidence of AF[101]. Based on community-based cohorts, persons who are obese have an increased risk of 1.5 – 2.3 for AF; obesity is also associated with an increased risk for progression from paroxysmal to permanent AF[101]. Other risk factors for AF include smoking, hypertension, diabetes, myocardial infarction, heart failure, valvular heart disease, and cardiac surgery[101].

Atrial flutter, or macroreentrant atrial tachycardia, is characterized by an organized atrial rhythm with a macroreentrant electrical pathway that may or may not involve the cavotricuspid isthmus (CTI)[3, 102, 103]. Typical atrial flutters, those that involve the CTI, most often show an electrical pattern that is counterclockwise around the CTI. Other, less common CTI-dependent atrial flutters can involve a clockwise, double wave, or lower-loop reentry pattern. Atrial flutters that do not involve the CTI are most often related to an atrial scar that creates a conduction block and an obstacle for reentry[3]. Based on the only reported epidemiologic study of patients with atrial flutter, the overall incidence of atrial flutter in a population of predominantly white, rural individuals in Wisconsin was 0.088%[3]. The incidence of atrial flutter increased with age, from 5/100,000 person-years in those 50 years or older to 587/100,000 person-years in persons older than 80 years; atrial flutter was found to be 2.5 times more common in men than women in this study[3].

Sinus tachyarrhythmias include inappropriate sinus tachycardia (IST) and sinus nodal re-entrant tachycardia (SNRT). IST is defined as a persistent increase in resting heart rate or sinus rate unrelated to or out of proportion to the level of physical, emotional, or other types of stress[3]. Two mechanisms have been suggested: enhanced automaticity of the sinus node and abnormal autonomic regulation of the sinus node. SNRT arises from reentrant circuits involving the sinus node's production of paroxysmal and often nonsustained bursts of tachycardia. It has been suggested that the sinus node tissue is involved in the reentrant circuit.

Focal atrial tachycardias are characterized by regular atrial activation starting rhythmically from a small focal area and spreading outward[3]. It has been suggested that the focal activity can be caused by abnormal or enhanced automaticity, triggered activity due to delayed afterdepolarization, or microreentry. Multifocal atrial tachycardias are caused by multiple sites of competing atrial activity.

AV nodal reentrant tachycardia (AVNRT) is the most common form of paroxysmal SVT[3]. This arrhythmia typically results from a conduction down a slow AV nodal pathway and up the fast AV nodal pathway, with an almost simultaneous conduction up to the atria and down to the ventricles[103].

AV reentrant tachycardia (AVRT) is characterized by the presence of accessory pathways: extra nodal pathways connecting the atria and ventricles.[3] These accessory pathways can conduct impulses in an anterograde manner, retrograde manner, or both. A type of AVRT, Wolf-Parkinson-White (WPW) Syndrome, is characterized by pre-excitation combined with tachyarrhythmias.

Focal junctional ectopic tachycardia (JET) is an uncommon arrhythmia and originates from the AV node or bundle of His, resulting in abnormally rapid discharges from this area[3]. A related but rare condition is *nonparoxysmal junctional tachycardia* (NPJT), which can be a marker for an underlying condition such as digitalis toxicity, postcardiac surgery, hypokalemia, or myocardial ischemia.

Data from the aforementioned epidemiologic study in Wisconsin suggested that the incidence of documented paroxysmal SVTs was 35/100,000 person-years[104.] Both age greater than 65 years and female sex were found to be significant risk factors.

2.2. Treatment options (surgical and nonsurgical)

Treatment of atrial fibrillation traditionally focuses on rate control, thromboembolism prevention, and treating the underlying disease (e.g. congestive heart failure, coronary artery disease, or hypertension). For rate control, pharmacologic therapy is the primary treatment; for rhythm control, pharmacologic therapy is typically the first choice, with ablation being the second choice[100]. Cardioversion, either with electrical shock or an anti-arrhythmic drug (AAD), can be used to restore sinus rhythm. In special circumstances, surgery can be the preferred option.

Initial treatment options for atrial flutter include DC cardioversion, atrial pacing, pharmacological conversion, and rate control using AV-nodal blockers[3]. If prevention of recurrence is warranted, AADs or catheter ablation can be administered.

Treatment for hemodynamically stable regular SVTs depends on the conditions being treated and patient comorbidities. These treatments include vagal maneuvers (i.e., Valsalva maneuver, carotid massage, and facial immersion in cold water), AADs (including beta, sodium, calcium, and potassium ion blockers), and overdrive pacing/DC cardioversion)[3]. Catheter ablation is recommended as first-line therapy for patients with WPW[3].

2.3. Technology

Catheter ablation is a procedure used to treat some types of heart arrhythmias. The procedure is typically performed in a catheter lab and involves guided insertion of catheters from the arm, groin, or neck through the blood vessel and into the heart. In radiofrequency catheter ablation, radiofrequency energy is sent through the catheters to a focal point in the heart that is believed to be the source of the arrhythmia; this energy ablates or destroys very small areas of the heart to disrupt abnormal electrical activity.

Cryoablation uses a pressurized refrigerant in the catheter tip to ablate the source of the arrhythmia. Other types of catheter ablation are becoming available, such as cryoballoon ablation, which involves cooling and freezing of the targeted tissue using coolant inside a balloon to alter abnormal electrical activity.

Eighteen radiofrequency ablation (RF) and three cryoablation catheter devices have been approved for use by the FDA from 1994 to 2012 (see Appendix G). The RF catheters and/or generators are manufactured by several companies: Boston Scientific (3), Medtronic (1), Cordis (1), St. Jude Medical (2), Biosense Webster (5), C.R. Bard (1), Irvine Biomedical (3), Stereotaxis (1), and Atricure (1). The cryoablation devices are produced by Medtronic Cryocath (2) and Boston Scientific (1). The RF devices utilize catheter tips ranging from 3.5mm to 10mm, while the cryoablation tips range from 4mm to 6.5mm with one device (Arctic Front – Medtronic) employing a balloon 23mm to 28mm in diameter. These devices are used to treat heart arrhythmias including atrial flutter/fibrillation and atrioventricular nodal re-entrant tachycardia.

Various catheter ablation approaches to treat AF include pulmonary vein isolation (PVI), pulmonary vein antrum isolation (PVAI), wide area circumferential ablation (WACA), and complex fractionated atrial electrograms (CFAE)[100]. Additional lines can be ablated, depending on mapping results. A typical target for atrial flutter ablation is between the tricuspid annulus and the inferior vena cava[3]. Ablation treatment for SVTs includes sinus node modification for inappropriate sinus tachycardia (IST), targeting the site of origin of atrial tachycardias, targeting the slow pathway along the posteroseptal region of the tricuspid annulus for AVNRT, ablation of accessory pathways for AVRT, and targeting foci adjacent to the AV node for focal junctional ectopic tachydardia[3].

2.4. Comparators

Pharmacologic therapy is the primary treatment for rate and rhythm control in *AF patients*[100]. Beta-blockers, nondihydropyridine calcium channel antagonists, and digoxin, alone or in combination, can be used to control the ventricular rate in AF patients. Rhythm control therapy consists of administration of AADs (anti-arrhythmic drugs) such as amiodarone, dofetilide, disopyramide, flecainide, propafenone, and sotalol. Direct-current cardioversion, the delivery of an electrical shock either through external chest wall electrodes or through an internal cardiac electrode, can be used in conjunction with AADs to control sinus rhythm[100]. AF patients can be pre-treated with amiodarone, flecainide, ibutilide, propafenone, or sotalol before electrical cardioversion[100]. Because of the risk of thromboembolic complications, long-term anticoagulant therapy, including warfarin and aspirin, is recommended in AF patients, except those with lone AF or contraindications to anticoagulants[100].

Pharmacologic treatment for controlling rate and rhythm in *atrial flutter* patients is similar to that for AF patients. Sodium channel blockers tend to shorten the excitable gap, AADs such as flecainide and propafenone depress conduction can slow flutter, and AADs such as amiodarone and ibutilide can prolong refractoriness and might terminate flutter[3]. It is recommended that long-term anticoagulant therapy be used for atrial flutter patients.

Sinus tachycardias, including inappropriate sinus tachycardia (IST) and sinus nodal reentrant tachycardia (SNRT), can be treated with beta blockers or nondihydropyridine calcium channel blockers (dilitiazem or verapamil) if beta blockers are contraindicated[3].

The efficacy of AADs for *focal atrial tachycardias* is unclear because of a lack of rigorous clinical definition and differentiation from other conditions such as AVRT or AVNRT[3]. However, initial therapy with calcium-channel blockers or beta blockers is recommended, and upon failure of the initial treatment, treatment with AADs such as flecainide or propafenone in combination with AV-node blocking agents or sotalol or amiodarone is considered. Some success has been seen using calcium-channel blockers for treatment of multifocal atrial tachycardias.

If a patient prefers long-term oral treatment rather than catheter ablation for frequent, recurrent sustained *AVNRT*, then nondihydropyridine calcium channel blockers, beta blockers, and digoxin may be used[3]. Long-term treatment for *AVRT*, including *WPW*, may include the use of AADs that modify conduction through the AV node (i.e., digoxin, beta blockers, adenosine, and dilitiazem) and AADs that depress conduction across the accessory pathway (i.e., flecainide, propafenone, amiodarone, and ibutilide), however long-term AAD therapy is increasingly being replaced by catheter ablation[3].

For *focal junctional ectopic tachycardia* (JET), drug therapy is only variably successful, with patients showing some responsiveness to beta blockers and some success with IV flecainide[3]. Managing *nonparoxysmal junctional tachycardia* (NPJT) involves treating the underlying abnormality: if junctional tachycardia is the only clinical manifestation, withholding digitalis is used as the treatment; if ventricular arrhythmias or high-grade heart block are observed, treatment with digitalis-binding agents is indicated.

A surgical approach to treating AF, the Cox-Maze procedure creates transmural lesions that isolate the pulmonary veins and connects these lines to the mitral valve annulus, thus creating electrical barriers in the right atrium that prevent sustained AF or atrial flutter[100, 104]. Although this surgery has a high success rate, it is not commonly performed unless the patient is undergoing simultaneous surgery for coronary or

valvular heart disease[104]. Cox-Maze surgery is very infrequently performed as a standalone procedure in the US.

2.5. Indications and Contraindications

The 2011 American College of Cardiology Foundation/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines recommend the use of catheter ablation in patients with little or no left atrial enlargement to prevent recurrent AF or the use of ablation of AV node or accessory pathway to control heart rate when AAD therapy has failed[105]. Other guidelines recommend catheter ablation as treatment in patients with symptomatic[106-111] AF that is refractory or intolerant to AAD medications[110, 112-114], where medical therapy is contraindicated[112], with lone AF, or with evidence of underlying electrophysiological disorder[107]. In several other guidelines, ablation is conditionally recommended for paroxysmal symptomatic and lone AF[106], and AV junction ablation and implantation of a permanent pacemaker is recommended for patients with symptomatic AF and uncontrolled ventricular rates despite maximally tolerated combination pharmacologic therapy[111].

The 2003 ACC/AHA/ESC guidelines recommend catheter ablation as long-term management in patients with recurrent and well- or poorly-tolerated atrial flutter, after a first episode of well-tolerated atrial flutter, atrial flutter appearing after use of certain AADs for treatment of AF, and for symptomatic non–CTI-dependent flutter after failed AAD therapy[115]. Other guidelines recommend catheter ablation for typical atrial flutter[106], atrial flutter that remain symptomatic despite medical therapy[109, 115], for isthmus dependent atrial flutter[116], or for long-term management of atrial flutter appearing after drug therapy for AF[117]. One guideline also recommends that the final decision for ablation treatment should take into account the stage of disease, presence or severity of underlying cardiovascular disease, treatment alternatives, and patient preference[109].

Regarding SVTs, the 2003 ACC/AHA/ESC guidelines recommend catheter ablation in patients with focal atrial tachycardia (recurrent symptomatic, asymptomatic, nonsustained asymptomatic, or symptomatic incessant), AVNRT (recurrent and poorly tolerated, recurrent with infrequent or single episodes, and infrequent and well-tolerated), well-tolerated WPW, long-term therapy for single or infrequent AVRT, focal junctional tachycardia, inappropriate sinus tachycardia, as long-term management or prophylactic therapy of PSVT (dual AV-nodal pathways) or SVT for CHD, and as prophylactic therapy of SVT during pregnancy[115]. Other guidelines recommend catheter ablation for tachycardia-bradycardia syndrome[117], reciprocating tachycardias[118], and inappropriate sinus tachycardia only when persistent after drug therapy [116]. Ablation of

accessory pathways is recommended in symptomatic AF patients with WPW, especially for syncope due to rapid heart rate or short bypass tract refractory period in one guideline[105]. Another guideline recommends slow-pathway ablation as initial therapy for AVNRT and fast-pathway ablation after failed drug therapy and slow-pathway ablation[116]. Catheter ablation is conditionally recommended in patients with tachycardia[106] in one guideline.

2.6. Potential complications/harms.

Complications from a catheter ablation procedure can occur: at the catheter insertion site, from damage to blood vessels, the heart, or the heart's electrical system during the procedure, from blood clots that can lead to a heart attack or stroke, from pulmonary vein stenosis following the procedure, or from radiation damage. Complications from catheter ablation for AF, atrial flutter, or SVTs include[3, 100, 119, 120]:

- stroke, embolic stroke, transient ischemic attack, or cerebrovascular accident
- cardiac tamponade
- PV stenosis
- catheter insertion site complications, including cardiac or arterial perforation, coronary artery spasm or occlusion, hematoma, pericarditis, valvular damage, microemboli, arteriovenous fistula
- deep vein thrombosis
- femoral pseudoaneurysm
- phrenic nerve injury
- AV block
- necessity for permanent pacing or pacemaker implantation
- sinus node dysfunction
- superior vena cava syndrome
- pneumothorax

Some complications are specific to ablation for AF. One of these is left atrial flutter, possibly resulting from an incomplete line of ablation[100]. Other complications specific to PVI ablation for AF are atrioesophageal fistulas and esophageal lesions. During ablation to the posterior LA wall for AF, thermal damage to the nearby esophagus and esophageal blood supply can occur[121]. These esophageal lesions are thought to be precursors of esophageal fistulas[100]. Although an esophageal fistula is a rare complication, one 2010 survey reported that 71% of the atrioesophageal fistula cases resulted in death[119]. Several methods have been proposed to reduce the formation of esophageal lesions, including preoperative CT/MRI assessment of the esophageal position, real-time visualization of the esophagus and continuous monitoring of the

luminal temperature during the ablation procedure, and reduction of power during radiofrequency energy application when in close proximity to the esophagus[121].

Because the majority of RF ablation procedures use fluoroscopy to guide catheter placement, certain risks are associated with radiation exposure, including skin injury, radiation-induced malignancy, and genetic effects[102]. Techniques to reduce the amount of radiation exposure include shorter fluoroscopy times and the use of non-fluoroscopy catheter location techniques (using magnetic or electric fields)[3]. One study used two dose reduction maneuvers during RF ablation procedures (ultra-low pulsed fluoroscopy rates and removal of the secondary radiation grid) to assess radiation reduction during radiofrequency ablation procedures[102]. The combination of these dose reduction techniques for both simple (including AVNRT, accessory pathways, and atrial flutter) and complex (including AF and atypical atrial flutter/tachycardias) ablation procedures resulted in significant reductions in radiation dose and a corresponding two-thirds reduction in the risk of excess fatal malignancy.

Shapira (2009) has suggested that the overall complication rate for catheter ablation ranges from 0 – 8% for atrial tachycardia patients, 0.5 – 1% for AVNRT patients, 2 – 4% for AVRT patients, 2.5 – 3.5% for atrial flutter patients, and 6 – 10% for AF patients[119]. A 2012 review reported mortality rates after catheter ablation ranging from 0.05% for SVT and atrial flutter patients to 0.1% for AF patients[3].

Side effects from antiarrhythmic drugs (AADs) vary depending upon the particular drug, the dosage, and the mode of delivery (intravenous or oral). Major side effects include pulmonary toxicity, hyper- or hypothyroidism, hypotension, heart block, heart failure, bradycardia, atrial flutter with high ventricular rate, asthma, heart failure, skin discoloration, corneal deposits, optic neuropathy, warfarin or digoxin interaction, gastrointestinal side effects including GI upset and constipation, QT prolongation, and torsades de pointes[3].

2.7. Costs

AF is a very costly public health problem, with the annual cost per patient approximately $3600 and a total societal burden of $15.7 billion in the US; the majority of this cost stems from hospitalization and medication[100].

2.8. Clinical Guidelines

Sources, including the National Guideline Clearinghouse (NGC), major bibliographic databases, professional societies, and Medline were searched for guidelines related to catheter ablation for the treatment of supraventricular tachyarrhythmia. Key word searches were performed: "ablation AND (arrhythmia OR cardiac OR heart OR catheter OR tachycardia OR fibrillation OR flutter)." Twelve documents were recovered that contained specific recommendations regarding this topic.

Guidelines from the following source are summarized:

1. National Guideline Clearinghouse (NCG): sixteen potential current guidelines were retrieved, two of which provided relevant guidance[108, 109].

2. National Institute of Health and Clinical Excellence (NICE): four potential current guideline was retrieved, all guidelines provided relevant guidance[107].

3. Heart Rhythm Society (HRS): five potential current guidelines were retrieved, two of which provided relevant guidance[110, 122].

4. American College of Cardiology (ACC): four potential current guidelines were retrieved, three of which provided relevant guidance[123-125].

5. Institute for Clinical Systems Improvement (ICSI): one potential current guideline was retrieved, this guideline provided relevant guidance[118].

6. Pubmed: eleven potential current guidelines were retrieved, three of which provided relevant guidance[106, 111, 117].

7. American Heart Association (AHA): two potential current guidelines were retrieved, neither of which provided relevant guidance.

Guidelines by Diagnosis (Table 1)

Atrial fibrillation

- ***Heart Rhythm Society/European Heart Rhythm Association/ European Cardiac Arrhythmia Society, 2012:*** *Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design*[110]. The primary indication for catheter AF ablation is the presence of symptomatic AF, refractory or intolerant to at least one class 1 or 3 antiarrhythmic medications. The presence of symptomatic AF prior to initiation of antiarrhythmic drug therapy may also be considered.

- ***National Institute for Health and Clinical Excellence, 2012:*** *Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation*[114]. Recommends ablation procedures for atrial fibrillation when drug therapy is not tolerated or ineffective.
- ***American College of Cardiology/American Heart Association, 2011:*** *Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy*[125]. Recommends radiofrequency ablation for hypertrophic cardiomyopathy patients with AF who are refractory or unable to take antiarrhythmic drugs.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2011/2006:*** *Focused Updates Incorporated Into the 2006 Guidelines for the Management of Patients With Atrial Fibrillation*[124]. Recommends catheter ablation as an alternative to pharmacological therapy to prevent recurrent AF in patients with little/no LA enlargement and in general catheter ablation of AV node in AF patients with failed antiarrhythmic therapy.
- ***Institute for Clinical Systems Improvement, 2011:*** *Heart Failure in Adults*[118]. Recommends radiofrequency catheter ablation in patients with select cases of atrial fibrillation.
- ***National Institute for Health and Clinical Excellence, 2011:*** *Percutaneous Endoscopic Catheter Laser Balloon Pulmonary Vein Isolation for Atrial Fibrillation*[113]*:* Proposes ablation procedures when drug therapy is either not tolerated or ineffective.
- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Ablation is strongly recommended for symptomatic AF after drug therapy and conditionally recommended for paroxysmal symptomatic and lone AF.
- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Rate and Rhythm*
- *Management*[111]. Recommends AV junction ablation and implantation of permanent pacemaker in symptomatic AF patients with uncontrolled ventricular rates despite maximally tolerated combination pharmacologic therapy and radiofrequency ablation of AF in patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm-control strategy remains desired.
- ***European Society of Cardiology, 2010:*** *Guidelines for the Management of Atrial Fibrillation*[109]. In general, catheter ablation should be reserved for patients with AF that remain symptomatic despite medical therapy (including rate and rhythm control). The final decision for ablation treatment should take into account the following: stage of disease, presence/severity of underlying cardiovascular disease, treatment alternatives, and patient preference.
- ***Scottish Intercollegiate Guidelines Network, 2007:*** *Cardiac Arrhythmias in Coronary Heart Disease*[108]. Recommends ablation and pacing for severely symptomatic AF patients.
- ***National Institute for Health and Clinical Excellence, 2006:*** *The Management of Atrial Fibrillation*[107]. Recommends referral for further specialist intervention

(including ablation) for patients with failed pharmacological therapy, those with lone AF, or those with evidence of underlying electrophysiological disorder.

- ***National Institute for Health and Clinical Excellence, 2006:*** *Percutaneous Radiofrequency Ablation for Atrial Fibrillation*[112]*:* Proposes percutaneous radiofrequency ablation as an option for atrial fibrillation refractory to anti-arrhythmic drug therapy or where medical therapy is contraindicated because of co-morbidity or intolerance.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients With Supraventricular Arrhythmias*[123]. The strongest recommendations for catheter ablation pertain to long-term management or prophylactic therapy of PSVT and SVT for CHD especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Heart Rhythm Society, 2003/1992:*** *Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations*[122]. The strongest recommendations for catheter ablation are for AV junction AF.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation after amiodarone treatment for AF, for SVT after failed antiarrhythmic therapy or as prophylactic therapy during pregnancy, and for tachycardia-bradychardia syndrome.

Atrial Flutter

- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Ablation is strongly recommended for typical atrial flutter.
- ***European Society of Cardiology, 2010:*** *Guidelines for the Management of Atrial Fibrillation*[109]. In general, catheter ablation should be reserved for patients with atrial flutter that remain symptomatic despite medical therapy (including rate and rhythm control). The final decision for ablation treatment should take into account the following: stage of disease, presence/severity of underlying cardiovascular disease, treatment alternatives, and patient preference.
- ***Heart Rhythm Society, 2003/1992:*** *Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations*[122]. The strongest recommendations for catheter ablation are for isthmus dependent atrial flutter. The Policy Statement contains other, less strong recommendations.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients With Supraventricular Arrhythmias*[123]. The strongest recommendations for catheter ablation pertain to long-term management or prophylactic therapy of atrial flutter especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation as long-term management of atrial flutter appearing after drug therapy of AF.

Atrial Tachycardia, including focal and multifocal

- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Curative Ablation is conditionally recommended for tachycardia.
- ***Heart Rhythm Society, 2003/1992: Policy Statement on Catheter Ablation:*** *Personnel, Policy, Procedures, and Therapeutic Recommendations*[122]. The strongest recommendations for catheter ablation are for focal atrial tachycardia.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients With Supraventricular Arrhythmias*[123]. The strongest recommendations for catheter ablation pertain to long-term management or prophylactic therapy of PSVT or SVT for CHD and atrial tachycardia, especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation as an alternative to drug therapy in tachycardia-bradycardia syndrome.

Atrioventricular Nodal Reentrant Tachycardia

- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Curative Ablation is conditionally recommended for tachycardia.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients With Supraventricular Arrhythmias*[123]. The strongest recommendations for catheter ablation pertain to long-term management or prophylactic therapy of PSVT or SVT for CHD and AVNRT, especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Heart Rhythm Society, 2003/1992:*** *Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations*[122]. Recommends slow-pathway ablation as initial therapy and fast-pathway ablation after failed drug therapy and slow-pathway ablation.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation as prophylactic therapy for SVT during pregnancy and as treatment of SVT with failed antiarrhythmic drugs and symptomatic repaired ASD.

Atrioventricular Reciprocating Tachycardia, including Wolff-Parkinson-White syndrome

- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2011/2006:*** *Focused Updates Incorporated Into the 2006 Guidelines for the Management of Patients With Atrial Fibrillation*[124]. Recommends catheter ablation of accessory pathway in symptomatic AF patients with WPW, especially for syncope due to rapid heart rate or short bypass tract refractory period.

- ***Institute for Clinical Systems Improvement, 2011:*** *Heart Failure in Adults*[118]. Recommends radiofrequency catheter ablation in patients with reciprocating tachycardias.
- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Curative Ablation is conditionally recommended for tachycardia.
- ***National Institute for Health and Clinical Excellence, 2006:*** *The Management of Atrial Fibrillation*[107]. Recommends referral for further specialist intervention (including ablation) for patients with failed pharmacological therapy or those with evidence of underlying electrophysiological disorder (such as WPW).
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients with Supraventricular Arrhythmias*[123]. The strongest recommendations for catheter ablation pertain to long-term management or prophylactic therapy of PSVT or SVT for CHD and AVRT, WPW syndrome, and atrial tachycardia, especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Heart Rhythm Society, 2003/1992:*** *Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations*[122]. Recommends catheter ablation as treatment for asymptomatic pre-excitation.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation as prophylactic therapy for SVT during pregnancy, as treatment of SVT with failed antiarrhythmic drugs and symptomatic repaired ASD, and as an alternative to drug therapy in tachycardia-bradycardia syndrome.

Focal Junctional Ectopic Tachycardia and Nonparoxysmal Junctional Tachycardia

- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Curative Ablation is conditionally recommended for tachycardia.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients with Supraventricular Arrhythmias*[123]. The strongest recommendations for catheter ablation pertain to long-term management or prophylactic therapy of PSVT or SVT for CHD and focal junctional tachycardia, especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation as prophylactic therapy for SVT during pregnancy, as treatment of SVT with failed antiarrhythmic drugs and symptomatic repaired ASD, and as an alternative to drug therapy in tachycardia-bradycardia syndrome.

Sinus tachycardia

- ***Canadian Cardiovascular Society, 2010:*** *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/Atrial Flutter*[106]. Curative Ablation is conditionally recommended for tachycardia.

- ***Heart Rhythm Society, 2003/1992:*** *Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations*[122]. Recommendations for catheter ablation are for inappropriate sinus tachycardia only when persistent after drug therapy.
- ***American College of Cardiology/American Heart Association/European Society of Cardiology, 2003:*** *Guidelines for the Management of Patients With Supraventricular Arrhythmias*[123]. The recommendations for catheter ablation pertain to long-term management or prophylactic therapy of PSVT or SVT for CHD and inappropriate sinus tachycardia, especially when cases are recurrent or fail in response to antiarrhythmic drugs.
- ***Barcelona Discussion Group, 1999:*** *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation*[117]. Recommends catheter ablation as prophylactic therapy for SVT during pregnancy, as treatment of SVT with failed antiarrhythmic drugs and symptomatic repaired ASD, and as an alternative to drug therapy in tachycardia-bradycardia syndrome.

Table 1. Clinical Guidelines

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
Atrial Fibrillation (AF)					

Heart Rhythm Society /European Heart Rhythm Association/ European Cardiac Arrhythmia Society (2012)[110]
 	
Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design.
	NR	Catheter ablation of AF	NR	Grading system and Class Recommendations adapted from the American College of Cardiology and the American Heart Association*.
				
				<u>Class I Recommendations</u>
				• Symptomatic AF refractory or intolerant to ≥1 Class 1 or 3 antiarrhythmic medication:
				  • Paroxysmal: Catheter ablation is recommended. LOE A
				
				<u>Class IIa Recommendations</u>
				• Symptomatic AF refractory or intolerant to ≥1 Class 1 or 3 antiarrhythmic medication:
				  • Persistent: Catheter ablation is reasonable. LOE B
				• Symptomatic AF prior to initiation of antiarrhythmic drug therapy with Class 1 or 3 antiarrhythmic agent:
				  • Paroxysmal: Catheter ablation is reasonable. LOE B
				
				<u>Class IIb Recommendations</u>
				• Symptomatic AF refractory or intolerant to ≥1 Class 1 or 3 antiarrhythmic medication:
				  • Longstanding Persistent: Catheter ablation may be considered. LOE B
				• Symptomatic AF prior to initiation of antiarrhythmic drug therapy with Class 1 or 3 antiarrhythmic agent:
				  • Persistent: Catheter ablation may be considered. LOE C
				  • Longstanding Persistent: Catheter ablation may be considered. LOE C
					This document is a consensus statement, not a guideline.

National Institute for Health and Clinical Excellence (2012)[114] *Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation*	NR	Percutaneous balloon cryoablation for AF	NR	Class of Recommendation and LOE NR Ablation procedures may be used for atrial fibrillation when drug therapy is either not tolerated or ineffective.	
American College of Cardiology/ American Heart Association (2011)[125] *Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy*	Through January 2011	Various treatments for coexistent hypertrophic cardio-myopathy (HCM) and AF	NR	Class of Recommendation and LOE categorized in ACC/AHA format.* <u>Class IIa recommendations</u> • Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who are unable to take antiarrhythmic drugs. LOE B	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
American College of Cardiology/ American Heart Association/ European Society of Cardiology (2011/2006)[124] *Focused Updates Incorporated Into the 2006 Guidelines for the Management of Patients With Atrial Fibrillation.*	2001 - 2006	Various treatments for AF	NR	Class of Recommendation and LOE categorized in ACC/AHA format.* <u>Class IIa recommendations</u> • It is reasonable to use ablation of the AV node or accessory pathway for AF to control heart rate when pharmacological therapy is insufficient or associated with side effects. LOE B • Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement. LOE C <u>Class IIb recommendations</u> • When the rate cannot be controlled with pharmacological agents, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate. LOE C <u>Class III recommendations</u> • Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in patients with AF. LOE C	
National Institute for Health and Clinical Excellence (2011)[113] *Percutaneous Endoscopic Catheter Laser Balloon Pulmonary Vein Isolation for Atrial Fibrillation*	NR	Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for AF	NR	Class of Recommendation and LOE NR Ablation procedures may be used when drug therapy is either not tolerated or is ineffective.	
Canadian Cardiovascular Society (2010)[106] *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/ Atrial Flutter.*	NR	Catheter ablation for AF	NR	Class of Recommendation and LOE categorized in CCS format.† <u>Strong Recommendations</u> • Catheter ablation of AF recommended in patients who remain symptomatic following adequate trials of anti-arrhythmic drug therapy and in whom a rhythm control strategy remains desired. LOE Moderate Quality <u>Conditional Recommendations</u> • Catheter ablation recommended to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal AF. LOE Low Quality • Catheter ablation recommended in young patients with lone, paroxysmal AF, electrophysiological study to exclude a reentrant tachycardia as a cause of AF; if present, curative ablation of tachycardia recommended. LOE Very Low Quality	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
Canadian Cardiovascular Society (2010)[111] *Atrial Fibrillation Guidelines: Rate and Rhythm Management.*	NR	Catheter ablation for AF and atrial flutter	NR	Class of Recommendation and LOE categorized in CCS format.† Strong Recommendations • AV junction ablation or PV ablation and implantation of permanent pacemaker recommended in symptomatic patients with uncontrolled ventricular rates during AF despite maximally tolerated combination pharmacologic therapy. LOE Moderate Quality • Radiofrequency ablation of AF recommended in patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm-control strategy remains desired. LOE Moderate Quality	-
European Society of Cardiology (2010)[109] *Guidelines for the Management of Atrial Fibrillation.*	NR	Various treatments for AF	NR	Class of Recommendation and LOE categorized in ESC format.‡ Class IIa Recommendations • Catheter left atrial ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed trial of antiarrhythmic medication. LOE A • Left atrial ablation of persistent symptomatic AF refractory to antiarrhythmic therapy should be considered. LOE B • Ablation of AV node to control heart rate should be considered when rate cannot be controlled with pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy or is associated with intolerable side effects, and direct catheter-based or surgical ablation of AF is not indicated, has failed, or is rejected. LOE B • Ablation of the AV node should be considered for patients with permanent AF and indication for CRT (NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy, LVEF ≤35%, QRS width ≥130 ms). LOE B • Ablation of the AV node should be considered for CRT nonresponders in whom AF prevents effective biventricular stimulation and amiodarone is ineffective or contraindicated. LOE C Class IIb Recommendations • Catheter ablation of AF in patients with heart failure may be considered when antiarrhythmic medication, including amiodarone, fails to control symptoms. LOE B • Catheter ablation of AF may be considered prior to antiarrhythmic drug therapy in symptomatic patients despite adequate rate control with paroxysmal symptomatic AF and no significant underlying heart disease. LOE B • Catheter ablation of AF may be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs. LOE B • Ablation of AV node with consecutive implantation of CRT device may be considered in patients with permanent AF, LVEF ≤35%, and NYHA functional class I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side effects. LOE C	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
				Class III Recommendations • Catheter ablation of AV node should not be attempted without prior trial of medication or catheter ablation of AF, to control AF. LOE C	
Scottish Intercollegiate Guidelines Network (2007)[108] *Cardiac Arrhythmias in Coronary Heart Disease.*	1999 - 2005	Various treatments for AF	NR	Class of Recommendation and LOE categorized in SIGN format.§ Class B Recommendations • Ablation and pacing should be considered for patients with AF who remain severely symptomatic in association with poor rate control or intolerance to rate control medication. LOE 2^+, 4, 1^+	
National Institute for Health and Clinical Excellence (2006)[107] *The Management of Atrial Fibrillation*	NR	Various treatments for AF	NR	Class of Recommendation and LOE adapted from Scottish Intercollegiate Guidelines Network (SIGN 50).§ Class B Recommendations: Referral for further specialist intervention (e.g., for, atrioventricular junction catheter ablation) after electrical or pharmacological cardioversion should be considered in the following AF patients: • those in whom pharmacological therapy has failed. • those with lone AF. (not defined)	
National Institute for Health and Clinical Excellence (2006) [112] *Percutaneous Radiofrequency Ablation for Atrial Fibrillation*	NR	Percutaneous radio-frequency ablation for AF	NR	Class of Recommendation and LOE NR Percutaneous radiofrequency ablation is a treatment option for symptomatic patients with atrial fibrillation refractory to anti-arrhythmic drug therapy or where medical therapy is contraindicated because of co-morbidity or intolerance.	
Heart Rhythm Society (2003/1992)[122] *NASPE Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations.*	NR	Ablation for AF	NR	Class of Recommendation and LOE categorized in ACC/AHA format.* Class IIb Recommendations • Atrial fibrillation: accumulated evidence is insufficient to determine complications and long-term outcome. Ablation considered for patients after appropriate trial of antiarrhythmic therapy; patients with permanent atrial fibrillation should be referred to centers with experience in performing more complex procedures. LOE B, C	
Atrial Flutter					
Canadian Cardiovascular Society (2010)[106] *Atrial Fibrillation Guidelines: Catheter Ablation for Atrial Fibrillation/ Atrial Flutter.*	See above	Catheter ablation for atrial flutter	See above	Class of Recommendation and LOE categorized in CCS format.† Strong Recommendations • Curative catheter ablation recommended for symptomatic patients with typical atrial flutter as first line therapy or as a reasonable alternative to pharmacologic rhythm or rate control therapy. LOE Moderate Quality	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
European Society of Cardiology (2010)[109] *Guidelines for the Management of Atrial Fibrillation.*	See above	Various treatments for atrial flutter	See above	Class of Recommendation and LOE categorized in ESC format.‡ Class I Recommendations • Left atrial ablation of common atrial flutter is recommended as part of AF ablation procedure if documented prior to ablation procedure or occurring during AF ablation. LOE B	
Heart Rhythm Society (2003/1992)[122] *NASPE Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations.*	See above	Ablation for atrial flutter	See above	Class of Recommendation and LOE categorized in ACC/AHA format.* Class I Recommendations • Isthmus dependent atrial flutter: ablation can be considered initial therapy. LOE A	
American College of Cardiology/ American Heart Association/ European Society of Cardiology (2003)[123] *Guidelines for the Management of Patients With Supraventricular Arrhythmias.*	NR	Various treatments for supra-ventricular arrhythmias	NR	Class of Recommendation and LOE categorized in ACC/AHA format.* Class I Recommendations • Catheter ablation recommended as long-term management of recurrent and well-tolerated or poorly tolerated atrial flutter. LOE B • Catheter ablation recommended as long-term management of atrial flutter appearing after use of Ic agents or amiodarone for treatment of AF. LOE B • Catheter ablation of flutter isthmus combined with closure of ASD recommended as treatment of SVT for congenital heart disease in unrepaired hemodynamically significant ASD with atrial flutter. LOE C Class IIa Recommendations • Catheter ablation recommended as long-term management of first episode well-tolerated atrial flutter. LOE B • Catheter Ablation recommended as prophylactic therapy for nonsustained and as long-term management of symptomatic non-CTI dependent flutter after failed antiarrhythmic therapy. LOE B	
Barcelona Discussion Group (1999)[117] *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation.*	NR	Catheter Ablation and pace therapy for atrial flutter	NR	Class of Recommendations and LOE: NR • Catheter Ablation recommended as long-term management of First episode and well-tolerated, recurrent and well-tolerated, poorly tolerated Atrial Flutter, Atrial Flutter appearing after use of class Ic agents or amiodarone for treatment of AF, or Symptomatic non-CTI-dependent flutter after failed antiarrhythmic drug therapy.	
Supraventricular tachycardias (SVT)					
Canadian Cardiovascular Society (2010)[106] *Atrial Fibrillation*	See above	Catheter ablation for AVNRT	See above	Class of Recommendation and LOE categorized in CCS format.† Conditional Recommendations • Catheter ablation recommended in young patients with lone,	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
Guidelines: Catheter Ablation for Atrial Fibrillation/ Atrial Flutter.				paroxysmal AF, electrophysiological study to exclude a reentrant tachycardia as a cause of AF; if present, curative ablation of tachycardia recommended. LOE Very Low Quality	
European Society of Cardiology (2010)[109] *Guidelines for the Management of Atrial Fibrillation.*	See above	Various treatments for supra-ventricular tachy-arrhthmias	See above	Class of Recommendation and LOE categorized in ESC format.‡ <u>Class IIb Recommendations</u> • Ablation of AV node to control heart rate may be considered when tachycardia-mediated cardiomyopathy is suspected and rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed, or is rejected. LOE C	

Heart Rhythm Society (2003/1992)[122]
 	
NASPE Policy Statement on Catheter Ablation: Personnel, Policy, Procedures, and Therapeutic Recommendations.
	See above	Catheter ablation for supra-ventricular tachy-arrhthmias	See above	Class of Recommendation and LOE categorized in ACC/AHA format.*
				
				<u>Class I Recommendations</u>
				• AV junction: ablation with subsequent complete heart block recommended for patients with atrial tachycardias, particularly persistent or permanent atrial fibrillation in which ventricular response rate not adequately controlled with AV nodal blocking agents. LOE A
				• Focal atrial tachycardia: patients should receive at least one trial of antiarrhythmic drug therapy prior to ablation; ablation can be offered as initial therapeutic approach when therapy to suppress arrhythmia is required. LOE B
				• AV node reentry
				  ○ Slow pathway ablation: initial therapy option for patients needing AVNRT; recommended for patients who have failed ≥1 antiarrhythmic drug or have significant side effects to drug therapy. LOE B
				  ○ Fast pathway ablation: due to risk of complete heart block, reserve for patients who have failed drug therapy and prior attempts at slow pathway ablation. LOE NR
				• AV reentry: for patients with accessory pathway mediated SVT, same recommendation as for AV node reentry; exception: patients with atrial fibrillation and rapid ventricular response should undergo ablation as initial therapy. Patients with anteroseptal pathways deserve special consideration because increased risk of complete heart block from catheter ablation reduces benefit/risk balance. LOE B
				
				<u>Class IIa Recommendations</u>
				• Nonisthmus-dependent macroreentrant atrial tachycardias: ablation recommended only after trial of drug therapy because of potential complexity of these reentrant circuits. LOE B, C
				
				<u>Class IIb Recommendations</u>
				• Catheter ablation recommended as prophylactic therapy of SVT during pregnancy. LOE C
				• Inappropriate sinus tachycardia: ablation considered only after trials of drug therapy (including β-blockers) because of high recurrence rate and persistence of nonspecific symptomatology postablation. LOE C	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
				Class III Recommendations • Asymptomatic pre-excitation: accessory pathway ablation recommended (except possible extenuating circumstances relating to pediatric population or high-risk occupational situations). LOE NR	
American College of Cardiology/ American Heart Association/ European Society of Cardiology (2003)[123] *Guidelines for the Management of Patients With Supraventricular Arrhythmias.*	See above	Various treatments for supra-ventricular tachy-arrhthmias	See above	Class of Recommendation and LOE categorized in ACC/AHA format.* Class I Recommendations • Catheter ablation recommended for documented PSVT with only dual AV-nodal pathways or single echo beats demonstrated during electrophysiological study and no other identified cause of arrhythmia. LOE B • Catheter Ablation recommended as prophylactic therapy for recurrent symptomatic focal AT, asymptomatic or symptomatic incessant ATs. LOE B • Catheter ablation recommended as treatment of SVT for CHD after failed antiarrhythmic drugs and symptomatic repaired ASD. LOE C • Catheter ablation recommended as treatment of SVT for congenital heart disease after failed antiarrhythmic drugs and symptomatic Mustard or Senning repair of transposition of great vessels. LOE C • Catheter ablation of flutter isthmus combined with closure of ASD recommended as treatment of SVT for congenital heart disease in unrepaired hemodynamically significant ASD with atrial flutter. LOE C • Catheter Ablation recommended as long-term treatment of patients with recurrent AVNRT: with poorly tolerated AVNRT with hemodynamic intolerance or recurrent symptomatic AVNRT. LOE B • Catheter ablation recommended for recurrent AVNRT with infrequent or single episode in patients who desire complete control of arrhythmia. LOE B • Catheter ablation recommended for infrequent, well-tolerated AVNRT. LOE B Class IIa Recommendations • Catheter Ablation recommended as long-term therapy of single or infrequent AVRT episode(s) (no pre-excitation). LOE B • Catheter Ablation recommended as long-term therapy of pre-excitation, asymptomatic accessory pathway–mediated arrhythmias. LOE B • Catheter Ablation recommended as treatment of Focal Junctional Tachycardia. LOE C Class IIb Recommendations • Catheter ablation recommended as prophylactic therapy of SVT during pregnancy. LOE C • Catheter Ablation-sinus node modification/elimination recommended as interventional treatment of Inappropriate Sinus Tachycardia. LOE C Class III Recommendations • Catheter ablation recommended for focal nonsustained	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available	Recommendation	Comments
				asymptomatic AT. LOE C	
Barcelona Discussion Group (1999)[117] *Report of a Study Group on Ablate and Pace Therapy for Paroxysmal Atrial Fibrillation.*	See above	Catheter ablation and pace therapy for supra-ventricular tachy-arrhthmias	See above	Class of Recommendations and LOE: NR • Catheter Ablation recommended as prophylactic therapy for SVT during pregnancy. • Catheter Ablation recommended in experienced center as treatment of SVT in adults with failed antiarrhythmic drugs and symptomatic repaired ASD or Mustard or Senning repair of transposition of the great vessels. • Catheter ablation recommended as alternative to drug therapy for patients with tachycardia–bradycardia syndrome who have bradycardia indication for pacemaker. It is probably most appropriate to undertake trial period of pacing therapy before proceeding to AVJ ablation or these patients may receive AVJ ablation and pacemaker at single session (i.e. one-step procedure). • Catheter Ablation recommended as prophylactic therapy for SVT during pregnancy. • Catheter Ablation recommended in experienced center as treatment of SVT in adults with failed antiarrhythmic drugs and symptomatic repaired ASD or Mustard or Senning repair of transposition of the great vessels. • Catheter ablation recommended as alternative to drug therapy for patients with tachycardia–bradycardia syndrome who have bradycardia indication for pacemaker. It is probably most appropriate to undertake trial period of pacing therapy before proceeding to AVJ ablation or these patients may receive AVJ ablation and pacemaker at single session (i.e. one-step procedure).	
American College of Cardiology/ American Heart Association/ European Society of Cardiology (2011/2006)[124] *Focused Updates Incorporated Into the 2006 Guidelines for the Management of Patients with Atrial Fibrillation.*	See above	Various treatments for AF, including a few supra-ventricular tachy-arrhthmias	See above	Class of Recommendation and LOE categorized in ACC/AHA format.* <u>Class I recommendations</u> • Catheter ablation of accessory pathway recommended in symptomatic patients with AF who have WPW, particularly those with syncope due to rapid heart rate or those with short bypass tract refractory period. LOE B • Catheter Ablation recommended as long-term therapy of WPW syndrome (well tolerated pre-excitation and symptomatic arrhythmias, AF and rapid-conduction, or poorly tolerated AVRT). LOE B • Catheter Ablation recommended as long-term therapy of AVRT, poorly tolerated (no pre-excitation). LOE B	
Institute for Clinical Systems Improvement (2011)[118] *Heart Failure in Adults*	See above	Catheter ablation for AVRT	See above	Class of Recommendation: NR Quality of evidence: GRADE system (all RCTs and cohort studies evaluated using GRADE system, other studies evaluated using transitional system from ICSI and GRADE). Details of grading NR Radiofrequency catheter ablation may be indicated in patients with heart failure and "reciprocating tachycardias" or selected patients with atrial fibrillation.	

ACC: American College of Cardiology; AF: atrial fibrillation; AHA: American Heart Association; ASD: atrial septal defect; AT: atrial tachycardia; AV: atrioventricular; AVJ: atrioventricular junction; AVNRT: atrioventricular nodal reentrant tachycardia; AVRT: atrioventricular reciprocating tachycardia; CCS: Canadian Cardiovascular

Society; CHD: congenital heart disease; CRT: cardiac resynchronization therapy; CTI: cavo-tricuspid isthmus; ECG: electrocardiogram; ESC: European Society of Cardiology; f/u: follow-up; HCM: hypertrophic cardiomyopathy; LA: Left atrial; LOE: level of evidence; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association; PSVR: peak systolic velocity ratio; PSVT: paroxysmal supraventricular tachycardia; PV: pulmonary vein; RCT: randomized controlled trial; SVT: supraventricular tachycardia; WPW: Wolff-Parkinson-White syndrome.

Catheter ablation only is considered, surgical ablation not included in this document.

* ACC/AHA Grading System:

- Class of Recommendation defined as: I (the benefits of the AF ablation procedure markedly exceed the risks and AF ablation should be performed), IIa (the benefits of an AF ablation procedure exceed the risks and it is reasonable to perform AF ablation), IIb (the benefit of AF ablation is greater or equal to the risks and AF ablation may be considered), III (AF ablation is of no proven benefit and is not recommended) (Blomstrom-Lundqvist, Scheinman et al. 2003; Scheinman, Calkins et al. 2003; Fuster, Ryden et al. 2011; Gersh, Maron et al. 2011; Calkins, Kuck et al. 2012).
- Level of Evidence defined as: A (data supporting recommendation is derived from multiple randomized clinical trials that included large numbers of patients), B (data supporting recommendation is derived from a limited number of randomized trials including small numbers of patients or from data analysis of nonrandomized studies or observational data registries), C (recommendation is based on consensus of expert opinion without evidence from clinical trials) [110, 122-125].

†CCS Grading System: details NR [106, 111].

‡ESC Grading System

- Class of Recommendation defined as: I (evidence and/or general agreement that given treatment/procedure is beneficial, useful, effective), II (conflicting evidence and/or divergence of opinion about usefulness/efficacy of given treatment or procedure), IIa (weight of evidence/opinion in favor of usefulness/efficacy), IIb (usefulness/efficacy less well established by evidence/opinion), III (evidence or general agreement that given treatment or procedure is not useful/effective, and in some cases may be harmful) [109].
- Level of Evidence defined as: A (data derived from multiple randomized clinical trials or meta-analyses), B (data derived from single randomized clinical trial or large non-randomized studies), C (consensus of opinion of experts and/or small studies, retrospective studies, registries) [109].

§Scottish Intercollegiate Guidelines Network (SIGN 50)

- Class of Recommendation defined as: A (≥1 meta-analysis, systematic review, or RCT rated as 1^{++} and is directly applicable to the target population; or a systematic review of RCTs or a body of evidence that consists principally of studies rated as 1^{+}, is directly applicable to the target population and demonstrates overall consistency of results; or evidence drawn from a NICE technology appraisal), B (Body of evidence including studies rated as 2^{++}, directly applicable to target population and demonstrates overall consistency of results or extrapolated evidence from studies rated as 1^{++} or 1^{+}), C (Body of evidence including studies rated as 2^{+}, directly applicable to target population and demonstrates overall consistency of results or extrapolated evidence from studies rated as 2^{++}), D (Evidence level 3 or 4 or extrapolated evidence from studies rated as 2^{+} or formal consensus), D(GPP) (Good practice point (GPP) is recommendation for best practice based on experience of Guideline Development Group), IP (Recommendation from NICE Interventional Procedures guidance) (Bakhshi, Camm et al. 2006; Lifson, McNeill et al. 2007).
- Level of Evidence defined as: 1^{++}(high-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias); 1^{+} (well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias); 1+ (Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with low risk of bias); 1^{-} (Meta-analyses, systematic reviews of RCTs, or RCTs with high risk of bias); 2^{++} (High-quality systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with very low risk of confounding, bias or chance and high probability that relationship is causal); 2^{+} (Well-conducted case-control or cohort studies with low risk of confounding, bias or chance and moderate

probability that relationship is causal); 2⁻ (Case-control or cohort studies with high risk of confounding, bias, or chance and significant risk that relationship is not causal); 3 (Non-analytical studies (for example, case reports, case series); 4 (Expert opinion, formal consensus) [107, 108].

2.9. Previous Systematic Reviews/Technology Assessments

Previous systematic reviews

Twenty-five previous systematic reviews (SRs) were found that addressed radiofrequency catheter (RF) ablation or cryoballoon ablation for atrial fibrillation (AF), atrial flutter, or supraventricular tachyarrhythmia (SVT) patients (Table 2)[126-150]. Most of these SRs found evidence for the superiority of RF catheter ablation compared with anti-arrhythmic drugs (AAD) regarding freedom from recurrence[128, 130, 133, 139, 141] and lower complication rates[128, 130] for AF patients. Specific RF ablation approaches that were found to be superior to AAD were AV node ablation[131], circumferential pulmonary vein ablation[140], and pulmonary vein isolation[143]. Two SRs investigating pulmonary vein antrum isolation (PVAI) found that the following approaches superior to pulmonary vein antrum (PVA) ablation: PVAI ablation alone[129] and PVAI ablation with the addition of complex fractionated atrial electrogram (CFAE)[137]. Another SR found that the addition of ganglionated plexi (GP) ablation to either PVI ablation or the Maze procedure was superior to either PVI ablation or the Maze procedure alone[150]. One SR compared cryoballoon ablation to AAD and found greater improvement in freedom from recurrence in paroxysmal AF patients for cryoballoon ablation compared with AADs[126]. For patients with atrial flutter or SVT, one SR and meta-analysis found high efficacy and low complication rates following RF ablation[144].

Table 2. Summary of previous systematic reviews

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Chatterjee (2012)[131] *Atrioventricular Nodal Ablation in Atrial Fibrillation: A Meta-Analysis and Systematic Review*	1948 – June 2011	Atrioventricular nodal ablation (AVNA) for the treatment of refractory AF as compared to AAD.	Total mean f/u for all studies was 26.5 months. ***Refractory AF*** **Efficacy** AVNA vs. AAD • 5 studies (mean f/u 10 months); N = 314 • 4 RCTs • 1 study type NR • AVNA: N = 161 • AAD: N = 153 **Effectiveness**	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** RCTs were evaluated using the Jadad scale, and observational studies were rated using the Downs and Black checklist. Scores not provided.	**Efficacy** • AVNA was associated with minimal increase in ***ejection fraction***. In patients with reduced systolic function, a modest but significant increase in EF after AVNA was noted. • There was a mean increase of 4.80% in EF after AVNA at mean follow up of 13.3 months. However, there was significant heterogeneity across the studies. • Studies with EF < 45%: significant increase in EF after AVNA.	

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			AVNA vs. AAD • 11 studies (study type NR); N = 810 **Safety** AVNA vs. AAD • 47 studies (study type NR); N = 5632		• Studies with EF > 45%: no significant change in EF. • There was significant relative improvement in ***quality of life*** for AVNA treatment group. • There was significant heterogeneity in quality of life scales used, which limited summative analysis. **Safety** • ***Incidence of complications*** included the need for a left-side approach after a failed right-side ablation in 6.9% of patients. In 2.9% of procedures there was a need for a redo procedure after spontaneous recurrence of AV nodal conduction. Other complications included lead failure (0.23%), non-stroke thrombosis (0.27), stroke (0.19%), and hematoma (0.70%). Infection, pleural effusion, pericarditis, pseudoaneurysm, RV perforation, and pneumothorax totaled 1.1%. • 10 deaths were reported at 9.8 months. Five deaths (cause: 60% SCD) were in the AVNA group and five deaths (cause: 100% SCD) were in the AAD group. All deaths occurred at least 1 month after AVNA or study (in the case of AAD group) onset. • Procedure-related mortality was 0.27% and malignant arrhythmia was 0.57%. • At 26.5 months, the incidence of sudden cardiac death following	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					AVNA was 2.1%. **Economic** NR	
Andrade (2011)[126] *Efficacy and Safety of Cryoballoon Ablation for Atrial Fibrillation: A Systematic Review of Published Studies*	January 2000 – January 2011 (language not restricted to English)	Cryoballoon ablation for treatment of paroxysmal AF and persistent AF with or without focal ablation (cryocatheter or irrigated RF catheter) 28 mm or 23 mm cryoballoon.	Majority of studies were single center case series. ***Paroxysmal AF (93.3%) or persistent AF (6.7%)*** Cryoballoon with or without cryocatheter or RF catheter: **Cryoballoon only** 9 studies (study type NR); N = 376 **Cryoballoon combined with focal ablation using cryocatheter** 13 studies (study type NR); N = 910 **Cryoballoon combined with focal ablation using irrigated RF catheter** 1 study (study type NR); N = 22	***Overall critical appraisal:*** followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. Overall score NR. ***Critical appraisal of individual studies:*** Not performed.	**Efficacy** *Paroxysmal AF (5 studies)*: Cryoballoon ablation resulted in 1-year freedom from recurrent AF without AAD in 73% of patients with a 3-month blanking period and 60% of patients with no blanking period. In one of the studies that compared cryoballoon with AAD, 70% of cryoballoon patients were free of recurrent AF compared with 7.3% of AAD patients at 1 year with a 3-month blanking period. *Persistent AF (3 studies)*: Cryoballoon ablation resulted in 1-year freedom from AF in 45% of patients. In 2 of the studies that compared cryoballoon with RF ablation, no significant difference was found between treatment groups in 1-year freedom from recurrent AF. In cases of persistent AF, more extensive ablation beyond PVI may be required. There was an acute procedural success (complete isolation of all targeted PVs) rate greater than 98% for the use of cryoballoon in treating both paroxysmal and persistent AF. **Safety** Complications and adverse events for persistent and paroxysmal AF not reported separately. *Major complications* occurred in 5 –	Because most of the studies were single center case series, efficacy outcomes and adverse events might not have been rigorously or consistently reported.

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					6% of patients. *Incidence of complications* included PNP (any 6.38%, persisting post-procedure 4.73%), stroke or transient ischemic attack (0.32%), cardiac tamponade (0.57%), any groin complication (1.79%), esophageal ulceration (5.17%), pericardial effusion or tamponade (1.46%), pulmonary artery rupture (0.08%), myocardial infarction (0.24%), and PVS (any 0.90%, requiring intervention 0.17%). The potential for complications tended to decrease with increasing operator experience. **Economic** NR	
Balk (2011)[127] *Predictors of Atrial Fibrillation Recurrence After Radiofrequency Catheter Ablation: A Systematic Review*	2000 – December 2008	Radiofrequency ablation (RFA) for treatment of paroxysmal, persistent, and permanent AF. Studies used 8-mm or cooled/irrigated tip catheters.	***Paroxysmal, persistent, or permanent AF*** <u>Multivariable analyses of pre-RFA predictors of AF recurrence</u> 25 studies of a mixed population of paroxysmal, persistent, and permanent AF (% f/u NR, range f/u 6 – 41 months); N = 6747 <u>Univariable analyses of AF type as a predictor of AF recurrence</u> 31 studies of a mixed population of paroxysmal, persistent, and permanent AF (% f/u NR, range f/u 6 –	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Studies appraised using Agency for Healthcare Research's *Quality Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*.[151]	• No individual or group of baseline patient characteristics predicts recurrence of AF after RFA; however, a meta-analysis of AF type alone suggests this characteristic might be a good proxy to predict AF recurrence for a specific patient population. • High level of evidence that age (range 40 – 70 years), sex, presence of structural heart disease, and duration of symptoms are not associated with AF recurrence • Moderate level of evidence that approximately normal EF or LAD parameters are not independent predictors of AF recurrence. • Conflicting evidence that AF type (namely nonparoxysmal AF) is	This review was performed as part of a Health Technology Assessment on the comparative effectiveness of radiofrequency catheter ablation for atrial fibrillation.[5] The aim of this SR was to summarize the evidence of baseline patient characteristics associated with AF recurrence after RFA. Study populations comprised patients 40 – 70 years of age, without severe heart disease, and with approximately normal EF and LAD.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			41 months); N = 72497249		predictive of higher rate of AF recurrence. High level of evidence of this association was found in univariable analyses, but the association was not commonly found among multivariable analyses. • No statistically significant association between AF duration and recurrence of AF was found in majority of studies examining this potential predictor.	
Kong (2011)[136] *Efficacy of Adjunctive Ablation of Complex Fractionated Atrial Electrograms and Pulmonary Vein Isolation for the Treatment of Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials.*	NR	PVI vs. PVI plus CFAE ablation for the treatment of paroxysmal and long-standing persistent AF and other atrial tachyarrhythmias. 3.5 or 8 mm catheter tip	***Paroxysmal AF (50.3%) persistent AF (49.7%)*** PVI vs. PVI plus CFAE • 6 RCTs (f/u 3-17.7 months) ; N = 538 (PVI: n = 291, PVI plus CFAE: n = 237)	***Overall critical appraisal:*** NR. ***Critical appraisal of individual studies:*** NR	**Efficacy** • PVI + CFAE: improved odds of maintaining ***freedom from AF/AT*** as compared to PVI alone (P = .04). • The rate of ***repeat ablation*** was 21% in the PVI + CFAE group and 25% in the PVI alone treatment group. • In patients with ***paroxysmal AF***, adjunctive CFAE did not significantly affect treatment. • In patients with ***long-standing, persistent AF***, adjunctive CFAE had no treatment effect. • PVI + CFAE organized AF into AT during the ablation in 32% of patients. Of these patients, 40% had a successful conversion of sinus rhythm through additional ablation. • PVI alone organized AF into AT in 27% of patients, and 40% of these had successfully converted sinus rhythm through additional ablation. However, the reporting was incomplete for the PVI alone treatment group.	

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					• The ***risk of recurrence*** was inconsistently reported and ranged from 4% in the PVI only group to 12% in the PVI + CFAE group. Two studies only reported AT recurrence in the PVI + CFAE group, ranging from 7%-27%. **Safety** • ***Major complications*** occurred in 3.3% of patients. One study reported 5 of these complications but did not specify if they were in the PVI or PVI + CFAE groups. • ***Incidence of complications*** included bleeding or vascular complications (n = 6), and pericardial effusion (n = 5). Of these, 1 was due to cardiac perforation with tamponade. At least 3 of these patients had undergone PVI + CFAE. Pulmonary vein stenosis occurred in 3 patients in the PVI group and 1 in the PVI + CFAE treatment group. 1 patient in the PVI + CFAE group suffered a prolonged asystolic arrest occurring 3 hours post-procedure during the venous sheath removal. • There were no reported deaths. **Economic** NR	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Li (2011)[137] *Additional Ablation of Complex Fractionated Atrial Electrograms After Pulmonary Vein Isolation in Patients With Atrial Fibrillation: A Meta-Analysis*	NR	Additional CFAE ablation after a single PVAI procedure compared with PVAI alone procedure for patients with paroxysmal or nonparoxysmal AF.	7 trials with 9 comparisons (N = 662) ***Paroxysmal AF*** • 2 RCTs (% f/u NR, f/u 12 months); N = 112 • 1 placebo- controlled non-randomized trial (% f/u NR, f/u 12 months); N = 120 ***Nonparoxysmal AF*** • 3 RCTs (% f/u NR, range f/u 10 – 16 months); N = 220 • 2 placebo- controlled non-randomized trials (% f/u NR, f/u 12 - 19 months); N = 140 ***Paroxysmal/ nonparoxysmal AF*** • 1 placebo controlled non-randomized trial (% f/u NR, f/u 12 months); N = 70	***Overall critical appraisal:*** NR. ***Critical appraisal of individual studies:*** NR	Note: success was defined as rate of maintenance of sinus rhythm in CFAE + PVAI group compared with PVAI only group. **Efficacy** • ***Overall success:*** RR = 1.17 (95% CI 1.03 – 1.33, *P* = .019). • ***Success for nonparoxysmal AF***: RR = 1.35 (95% CI 1.04 – 1.75, *P* = .022). • ***Success for paroxysmal AF***: RR = 1.04 (95% CI 0.92 – 1.18, *P* = .528). **Safety** NR **Economic** NR	No differences in effect size were found between the 2 different types of trials (randomized and placebo-controlled non-randomized).
Maan (2011)[138] *Complications from Catheter Ablation of Atrial Fibrillation: A Systematic Review*	1989 – 2011	Catheter ablation for the treatment of paroxysmal and persistent atrial fibrillation.	***Paroxysmal or persistent AF*** Unspecified number of studies of unknown type including case reports (%f/u NR, range f/u NR); N = NR	***Overall critical appraisal:*** NR. ***Critical appraisal of individual studies:*** NR	**Efficacy** NR **Safety** • ***Commonly reported complications*** (complication rates NR) include pulmonary vein stenosis, esophageal injury/atrioesophageal fistula, cardiac tamponade, thromboembolism, stroke, phrenic nerve injury, and vascular	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					access complications. • ***Less commonly reported complications*** (complication rates NR) include pyloric spasm and gastroparesis, left atrial edema, protamine reaction, transseptal access complications, left atrial tachycardias, focal atrial tachycardias, and organized atrial tachyarrhythmias • ***Complications specific to irrigated tip catheter*** (complication rates NR) can include pulmonary edema, pleural effusion, pericardial effusion and pulmonary edema, and gastrointestinal adverse events such as dysphagia. • ***Complications specific to cryoballoon catheter*** (complication rates NR) can include phrenic nerve palsy, transient esophageal ulcerations, PV stenosis, and pericardial effusion. **Economic** NR	
Parkash (2011)[141] *Approach to the Catheter Ablation Technique of Paroxysmal and Persistent Atrial Fibrillation: A Meta-Analysis of the Randomized*	January 1998 – July 2010	RFA compared with AAD and comparison of specific RFA techniques for the treatment of paroxysmal or persistent AF.	Total of 35 RCTs (% f/u, range f/u NR); N = 4128 ***Paroxysmal AF (61.8%)*** <u>RFA vs. AAD</u> • 3 RCTs <u>PVI vs. AAD</u> • 6 RCTs	***Overall critical appraisal***: NR ***Critical appraisal of individual studies***: methodological quality categorized using Cochrane guidelines. Risk of bias items (percentages are	**Efficacy** Note: all results describe the relative risk for maintaining freedom from recurrent AF on or off AADs after 1 year. ***Paroxysmal AF (27 studies):*** • RFA was strongly favored over AAD (RR = 2.26, 95% CI 1.74 – 2.94). • Wide-area PVI was favored over the use of segmental PVI (RR = 0.78, 95% CI 0.63 – 0.97).	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Controlled Trials			CPVA vs. AAD • 2 RCTs Segmental PVI vs. wide-area PVI • 6 RCTs PVI vs. PVI with linear lesions • 10 RCTs Linear ablation +CPVA or PVI • 8 RCTs PVI vs. PVI + CFE • 2 RCTs ***Persistent AF (38.2%)*** RFA vs. AAD • 5 RCTs Segmental PVI vs. wide-area PVI • 3RCTs PVI vs. PVI with linear lesions • 6 RCTs Linear ablation +CPVA or PVI • 4 RCTs PVI vs. PVI + CFE • 4 RCTs	estimated from a graph): • Adequate sequence generation: low for 65% of the studies and unknown for the others. • Allocation concealment: low for 25% of the studies, high for 3%, and unknown for the others. • Blinding: Low for 25% of the studies, high for 40% of the studies, and unclear for 35% of the studies • Incomplete outcome data addressed: Low for 100% of the studies • Free of selective reporting: Low for 100% of the studies • Free of other bias: Low for 98% of the studies, unclear for 2% of the studies.	• No difference in relative risk between PVI/CPVA plus linear ablation (RR = 1.02) ***Persistent AF (24 studies):*** • RFA was strongly favored over AAD (risk ratio of 3.20, 95% CI 1.29 – 8.41) • Wide-are PVI was favored over segmental PVI (RR = 0.64, 95% CI 0.43 – 0.94). • No difference in relative risk between PVI/CPVA plus linear ablation (risk ratio of 1.00) **Safety** • Complications and adverse events for persistent and paroxysmal AF not reported separately. • ***Major complications*** occurred in 1.5% of cases. • ***Incidence of complications*** included cardiac tamponade (0.19%), stroke/TIA (0.27%), PV stenosis (0.46%), pulmonary edema (0.15%), atrioesophageal fistula (0.03%), and vascular complications or hemo/pneumothorax (0.34%). • There was a 0.07% risk of death. **Economic** NR	
Stern (2011)[145] *Meta-Analysis to Assess the*	1992 – 2007	Radiofrequency ablation or cyroablation, with uniform or	***AVNRT*** RFA with uniform isoproterenol use • 6 cohort studies (%	***Overall critical appraisal:*** NR. ***Critical appraisal of***	**Efficacy** • When used uniformly following the complete ablation of the slow pathway or residual slow	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Appropriate Endpoint for Slow Pathway Ablation of Atrioventricular Nodal Reentrant Tachycardia		nonuniform use of isoproterenol*, for the treatment of atrioventricular nodal reentrant tachycardia (AVNRT) using the following endpoints: • complete ablation of the slow pathway, • modification of the slow pathway with residual jump only, or • modification of the slow pathway with ≤ 1 echo beat.	f/u NR for 6 studies, mean f/u 19.3 months); N = 846 <u>RFA with nonuniform isoproterenol use</u> • 3 cohort studies (% f/u NR for 3 studies, mean f/u 30 months); N = 203 <u>Cryoablation with uniform isoproterenol use</u> • 1 cohort study (% f/u NR, median f/u 24.3 months); N = 155	***individual studies:*** NR	pathway conduction with a jump and/or a single echo beat isoproterenol, had no effect. • When used non-uniformly, incomplete slow pathway ablation resulted in higher recurrence rates in patients with a residual jump (*P* = .002), a single echo (*P* = .003) or a combined residual jump and/or one echo (*P* = .001) then with complete slow pathway ablation. • Recurrence rate for complete slow pathway ablation was 4.4%, recurrence rate for residual jump was 6.8% and recurrence rate for one echo was 6.5%. **Safety** NR **Economic** NR	
Wang (2011)[148] *Dual Atrioventricular Nodal Nonreentrant Tachycardia: A Systematic Review*	1950 – January 2011	Catheter ablation for the treatment of dual AV nodal nonreentrant tachycardia (DAVNNT)	***Dual AV nodal nonreentrant tachycardia*** This review reported on 49 cases of DAVNNT across 44 studies (study type NR, % f/u NR for 44 studies, range f/u 2 – 180 months). Twenty-two of these patients were treated with catheter ablation.	***Overall critical appraisal:*** NR. ***Critical appraisal of individual studies:*** NR	**Efficacy** • Slow pathway ablation is the preferred treatment, with a > 95% success rate and a <1% risk of permanent AV block. • No recurrences were noted when DAVNNT was treated with catheter ablation. • AV junction ablation is preferred in cases where the risk of complete AV block is unavoidable. **Safety** • No complications were reported for catheter ablation	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					Economic NR	
Zhou (2011)[150] *A Meta-Analysis of the Comparative Efficacy of Ablation for Atrial Fibrillation with and without Ablation of the Ganglionated Plexi*	NR	Ganglionated Plexi ablation for the treatment of paroxysmal or persistent atrial fibrillation as compared to PVI alone, GP in addition to Maze, GP in addition to PVI and Maze alone.	***Paroxysmal AF*** GP Ablation vs PVI GP ablation • 2 studies (study type NR for 2 studies, % f/u NR for 2 studies, range f/u 12 months); N = NR PVI + GP ablation vs PVI without GP ablation • 1 study (study type NR, % f/u NR for 2 studies, range f/u 12 months); N = NR ***Paroxysmal and Persistent AF*** PVI + GP ablation vs. PVI without GP ablation • 1 study (study type NR, % f/u NR, range f/u 1 – 15 months); N = NR Maze + GP ablation vs. Maze without GP ablation • 2 studies (study type NR for 2 studies, % f/u NR for 2 studies, range f/u 12 – 37 months); N = NR	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Studies were assessed for adequate sequence generation, allocation concealment, attrition of less than 15%, blinded assessment, intent-to-treat, complete follow up and adequate AF monitoring. Studies were not given an overall score.	**Efficacy** • Early recurrence was significantly higher after GP ablation alone, as compared with PVI alone (P = .02) • There was no significant difference in early recurrence between additional GP ablation to PVI or Maze procedure as compared with PVI or Maze procedure alone (P = .06). • Freedom from AF post ablation was decreased by GP alone, as compared with PVI alone (P = .006) • Freedom from AF post ablation was significantly improved by GP ablation to PVI and Maze procedure, as compared with PVI and Maze without GP. **Safety** • Complications were assessed in 2 studies. • ***Major complications*** occurred in 2 patients. • ***Incidences to complications*** included 1 cardiac tamponade immediately following GP ablation, and 1 non-significant narrowing of both superior PVs. In PVI group, significant left superior PV stenosis occurred in 1 patient and 1 patient suffered repeated upper respiratory tract bleeding 25 months after procedure. • There were no reported deaths.	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					Economic NR	
Bonanno (2010)[128] *Efficacy and Safety of Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation: A Meta-analysis of Randomized Trials*	NR	Radiofrequency catheter ablation (RFCA) for treatment of symptomatic paroxysmal or persistent atrial fibrillation compared with the use of anti-arrhythmic drugs. Studies comprised a variety of surgical techniques for PV isolation and used either 4-mm, 8-mm, or cooled-tip catheters.	***Paroxysmal AF (66%) or persistent/long-standing AF (34%)*** RFCA vs. AAD • 8 RCTs (98.8% f/u, range f/u 6-12 months); N = 844	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Jadad system and Cohrane approach (to assess allocation concealment) used. Overall Jadad score NR. Review included studies with ≥ 3 Jadad score. Overall, many studies failed to meet many of the basic quality expectations of an RCT.	**Efficacy** • In selected patients RFCA was found to be an effective treatment for AF. • RFCA resulted in a 71% reduction in atrial tachyarrhythmia (8 studies, RR = 0.29, 95% CI 0.20 – 0.41, *P* < .00001) compared with AAD therapy. • 23.2% of patients in the RFCA group had a recurrence of atrial tachyarrhythmia compared with 76.6% of patients in the AAD group within a 6 – 12 month follow-up. **Safety** • There was no significant difference in the risk of adverse events or complications between RFCA and AAD treatments (8 studies, RR = 0.72, 95% CI 0.40 – 1.30, *P* = .28). However, some of the complications and adverse events in the RFCA group were more serious than those in the AAD group. • ***Major Complications*** occurred in 9% of RFCA patients and 13% of AAD patients. • ***Incidence of complications*** in the RFCA group included embolic complications (stroke, transient ischemic attack, and thromboembolic events) (1.7%), PV stenosis (3.1%), and bleeding	The outcome of RFCA compared with AAD was influenced by the use of AAD after the RFCA procedure and during the follow-up period in 6 of the studies. One study did not allow AAD in the RFCA group and another study compared RFCA with AAD to AAD alone. Existing RCTs are not sufficiently powered to assess mortality after RFCA treatment.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					(pericardial effusion, tamponade and peripheral vascular hematoma) (3.8%). • One death (cause: brain hemorrhage) occurred 9 months after RFCA (patient suffered a stroke during the procedure). **Economic** NR	

Brooks (2010)[129]
 	
Outcomes of Long-Standing Persistent Atrial Fibrillation Ablation: A Systematic Review
	January 1990 – June 2009	A comparison between PVI alone, pulmonary vein antrum ablation with isolation (PVAI), pulmonary vein antrum ablation without isolation (PVA), PVA with linear ablation, PVAI with linear ablation, posterior wall box isolation, complex fractionated atrial electrogram ablation (CFAE), PVA, PVAI, or PVAI and linear ablation with CFAE, and stepwise ablation , for the treatment of long-standing, persistent AF.
		
		These procedures were evaluated both as stand-
			Long-standing, persistent AF
			PVI only
			• 4 case series (% f/u NR, range f/u 8 – 41 months); N = 164
			
			PVAI vs. PVA
			PVAI
			• 2 RCTs (% f/u NR for 2 studies, range f/u 7-17 months); N = 98
			• 1 case series (% f/u NR for 1 study, range f/u 9-13 months); N = 41
			PVA:
			• 1 case series (% f/u NR for 1 study, range f/u 5-15 months); N = 72
			
			PVA with linear ablation vs. PVAI with linear ablation
			PVA with linear ablation:
			• 2 RCTS (% f/u NR
				Overall critical appraisal: NR
				
				Critical appraisal of individual studies: method NR
				• 4 RCTs: Level II evidence
				• 27 case series: Level IV evidence
					Efficacy
					• Level II evidence from 4 RCTs shows the following:
					  • PVAI is a superior approach to PVA alone.
					  • CFAE ablation is inferior to PVA with linear ablation at the roof and mitral isthmus
					  • There was no benefit of additional right atrial CFAE ablation when AF persisted after a left atrial CFAE ablation.
					  • There may or may not be incremental benefit to adding CFAE ablation to PVAI
					• All other efficacy information is a combination of Level II and Level IV evidence.
					• Total mean success rate was 47% for ***drug-free, single procedures (not including PVI alone or CFAE alone)***. With the addition of ***multiple procedures*** (mean 1.4 per patient), the success rate was mean 65% and with the ***addition of AAD*** the mean success rate was 79%.
					
					PVI only	

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		alone procedures, repeat procedures, and in combination with drug therapy.	for 2 studies, range f/u 7 – 19 months); N = 87 • 3 case series (100% f/u for 1 study, % f/u NR for 2 studies, range f/u NR for 1 study and % f/u NR for 2 studies, range f/u 9 – 15 months for the third study); N = 123 <u>PVAI with linear ablation:</u> • 4 case series (% f/u NR for 4 studies, range f/u 6 – 38 months); N = 194 <u>PVAI and PVA with linear ablation:</u> • 1 case series (% f/u NR for 1 study, range f/u 2-29 months); N = 42 **Posterior wall box isolation** • 3 case series (% f/u NR for 3 studies, range f/u 5-24 months); N = 61 **CFAE** • 2 RCTs (% f/u NR for 2 studies, range f/u 7-23 months) ; N = 106 • 2 case series (% f/u NR for 2 studies,		• The ***drug-free, single procedure*** success rate was found to be 21%-22% at 2 years. ***Multiple procedures*** (mean 1.6 per patient) increased the drug-free success rate to 37%-43%. With the ***addition of AAD and multiple procedures*** the success rate was approximately 54%. <u>PVA/PVAI</u> • PVAI resulted in a37%-56% success rate at 1 year in ***drug-free, single procedures***. ***Multiple procedures*** (mean 1.3 per patient) increased success rate to 59%. With the ***addition of AAD and multiple procedures*** the success rate was 77%. <u>PVA/PVAI with linear ablation</u> • Both procedures yielded a ***drug-free single procedures*** success rate of 11%-74% at 1.5 year follow up. With ***multiple procedures*** (mean 1.5 per patient) the success rate was between 17%-74%. With the ***addition of AAD and multiple procedures***, the success rate was 28%-87%. <u>Posterior wall box isolation</u> • The ***drug-free, single procedure*** success rate was 42%-50% at almost 2 years. ***Multiple procedures*** (mean 1.4 per patient) increased the success rate to 60%-63%. With the ***addition of AAD and multiple procedures*** the efficacy was 88% but only in one	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			range f/u 10-24 months); N = 164 **PVA, PVAI or PVAI and linear ablation with CFAE** PVI with CFAE: • 2 case series (% f/u NR for 2 studies, range f/u 9-31 months) ; N = 65 PVAI with CFAE: • 2 RCTs (% f/u NR for 2 studies, range f/u 7-17 months); N = 99 PVAI and linear ablation with CFAE: • 1 case series (100% f/u, range f/u > 1 year); N = 25 **Stepwise ablation** • 5 case series (100% f/u for 1 study, % f/u NR for 4 studies, range f/u 5-40 months); N = 384		small sample. CFAE only • The ***drug free single procedure*** success rate was between 24%-63% at approximately 1 year. ***Multiple procedures*** (mean 1.4 per patient) increased success rate to 52% - 77%. The incremental gain with the ***addition of AAD and multiple procedures*** NR. CFAE as adjunct to PVA, PVAI or PVAI and linear ablation • PVI and CFAE ablation has a ***drug-free, single-procedure*** success rate of between 36% and 68% at 1 year. With ***multiple procedures*** (mean per patient NR) the success rate increased to 60%-80%. • PVAI and linear ablation with CFAE has not yet been tested in randomized comparison. Stepwise ablation • Stepwise ablation had a ***drug-free, single procedure*** success rate of 38%-62% at approximately 18-month follow up. ***Multiple procedures*** (mean per patient NR) increased success rate to 70%-80%, and the ***addition of AAD and multiple procedures*** improved success to 84%-90%. **Safety** • The overall rate for ***major complications*** was 4.4% out of	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					1690 patients. • ***Incidence of complications*** included pericardial tamponades/effusions (1.4%), vascular complications (0.80%), symptomatic pulmonary vein stenosis (0.71%), cerebrovascular events (0.65%), delayed left atrial appendage emptying or temporary electrical disconnection of atria (0.41%), phrenic nerve injures (0.3%), atrio-esophageal fistula (0.06%), AV block (0.06%), pulmonary edema (0.06%), ST-segment elevation (0.06%), and severe back pain (0.06%). • There were no reported deaths related to the procedure. **Economic** NR	
Jeevanantham (2010)[135] *Meta-Analysis of the Effect of Radiofrequency Catheter Ablation on Left Atrial Size, Volumes and Function in Patients with Atrial Fibrillation*	Through April 2009	RFCA for the treatment of paroxysmal, persistent or permanent AF.	***Paroxysmal, persistent, or permanent AF*** RFCA • 17 studies (study type NR) (f/u 2-21 months); N = 869	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Studies were assessed using a generic criteria.†	This review examined changes in left atrial size, volume, and function after RFCA. • ***LA diameter and volume***: There was significant decrease in left atrial diameter and volume (max) and volume (min) following RFCA as compared to preablation values. These differences were significant among studies that reported no AF recurrence, but not those with AF recurrence. • ***LA ejection fraction and active emptying fraction:*** There was no significant difference in either LAEF or LAAEF as compared to	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					preablation values. When analyzed on the basis of AF recurrence, there were LAEF and LAAEF were significantly decreased in patients with AF recurrence, and not significantly decreased when there was no AF recurrence.	
Calkins (2009)[130] *Treatment of Atrial Fibrillation with Antiarrhythmic Drugs or Radiofrequency Ablation: Two Systematic Literature Reviews and Meta-Analyses*	January 1990 – May 2009	Radiofrequency ablation for the treatment of persistent AF, longstanding AF and paroxysmal AF as compared to AAD.	For all studies combined, mean f/u was 14 months ***Persistent, longstanding, or paroxysmal AF*** RF ablation • Total N = 8789 • 9 RCTs • 11 prospective comparative studies • 31 prospective single-arm studies • 12 retrospective series AAD • Total N = 6589 • 24 RCTs • 1 nonrandomized comparative study • 9 single arm trials	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Overall body of evidence rated according to the schema of evidence assignment developed by the Centre for Evidence-Based Medicine (CEBM). RCTs were evaluated using Jadad scoring method. RF ablation • 5 studies rated level I • 14 studies rated level II • 44 studies rated level III and IV • 2 RCTs had Jadad quality score of 3 or greater • 7 RCTs had Jadad	**Efficacy** • RFA has a higher success rate the AAD therapy for the treatment of AF and lower rates of complications. However, the study does not suggest that catheter ablation is the preferred treatment for AF, noting differences in trial methodologies, patient characteristics, and severity of complications in the both studies surveyed and others. • Ablation success remained steady over time in spite of increasing age of the patients and increasing incidence of persistent AF. This could be the result of either the ablation technology itself or the skill of the operator. **Safety** • ***Incidence of complications*** included symptomatic or asymptomatic pulmonary vein stenosis, which occurred in 1.6% of cases. There were 0.7% cardiac tamponade, 0.6% pericardial effusion, 0.3% periprocedural stroke and 0.2% periprocedural	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
				score of 1 to 2 <u>AAD</u> • 20 studies rated level I • 5 studies rated level II • 9 studies rated levels II and IV	transient ischemic attack. • There were no reported deaths and overall mortality, including during the follow up period, was 0.7%. **Economic** NR	
Dagres (2009)[132] *Mortality After Catheter Ablation for Atrial Fibrillation Compared with Antiarrhythmic Drug Therapy. A Meta-Analysis of Randomized Trials*	NR	Catheter ablation for the treatment of AF as compared to AAD therapy. 3.5-8 mm tips	***Chronic, paroxysmal, or persistent AF*** <u>Catheter ablation vs. AAD</u> • 8 RCTS (98% f/u, 12 months); N = 930 • CA: n = 486 • AAD: n = 444	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Study quality was assessed using a modified Jadad scale.‡ <u>Catheter ablation vs. AAD</u> • 4 RCTs with a score of 3 • 2 RCTs with a score of 2 • 1 RCT with a score of 1 • 1 RCT with a score of ≥ 2	**Efficacy** NR **Safety** • 7 deaths were reported: 3 in CA group, 4 in AAD group. • 4 strokes were reported: 3 in CA group and 1 in AAD group. **Economic** NR	
Inama (2009)[134] *Five Years of Catheter Ablation Procedures in South-Western Europe: Meta-Analysis of National Registries*	2002 – 2006	RF ablation for AVNRT, atrial flutter, AV accessory pathway, AF, supraventricular arrhythmia, and focal atrial tachycardia.	3 national registries (% f/u n/a, range f/u n/a, N n/a): • Spanish Catheter Ablation Registry: retrospective and prospective data. • Portuguese National Registry on Cardiac Electrophysiology: retrospective data	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** *N*R	**Efficacy** • ***Overall procedural success rate:*** 90 – 93% (Spanish registry). • ***AVNRT:*** success rate 98 – 99% (Spanish registry). • ***Atrial flutter:*** success rate 91 – 94% (cavotricuspid isthmus ablation), 46 – 65% (atypical atrial flutter ablation) (Spanish registry). • ***AV Accessory pathways:*** success	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			• Italian Registry of Electrophysiological Procedures: retrospective data collected annually.		rate 89 – 93% (Spanish registry). • ***AF:*** success rate 71 – 81% (Spanish registry). • ***Supraventricular arrhythmias:*** success rate 96 – 99% (Spanish registry) • ***Focal atrial tachycardia:*** success rate 75 – 82% (Spanish registry). **Safety** • ***Overall complication rate***: 1 – 1.7% (Spanish registry). • ***AVNRT:*** complication rate 0.6 – 1.2% (Spanish registry). • ***Atrial flutter:*** complication rate 0.4 – 1.2% (cavotricuspid isthmus ablation), 3 – 12% (atypical atrial flutter ablation) (Spanish registry). • ***AV Accessory pathways:*** complication rate 0.9 – 2% (Spanish registry). • ***AF:*** periprocedural complication rate 1.4 – 6% (Italian Spanish registries). • ***Supraventricular arrhythmias:*** complication rate 0.4 – 1.6%. • ***Focal atrial tachycardia:*** complication rate 0 – 3% (Spanish registry). **Economic** NR	
Nair (2009)[139] *A Systematic Review of Randomized Trials Comparing*	Through February 2008	Radiofrequency ablation for the treatment of paroxysmal or persistent atrial fibrillation as compared to	***Paroxysmal or persistent AF*** • 3 RCTs (% f/u for 3 studies, range f/u NR for 3 studies); N = 237	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Internal validity and quality of studies	**Efficacy** • The pooled ***risk of recurrent AF*** at 1 year was 24% in the RF ablation group compared with 69% in the AAD group, although there was significant heterogeneity between the trials.	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Radiofrequency Ablation with Antiarrhythmic Medications in Patients with Atrial Fibrillation		AAD. irrigated or non-irrigated 3.5mm to 8mm tips	***Persistent AF*** • 1 RCT (% f/u NR, range f/u NR); N = 146 ***Paroxysmal AF*** • 2 RCTs (% f/u NR for 2 studies, range f/u NR for 2 studies); N = 310	were scored on a modified scale.§ • 4 RCTs: intermediate to high quality (scores of 9 – 10) • 2 RCTs: poor quality (score of 5)	• Ablation confers a ***relative risk reduction in recurrence of AF*** at 1 year of 65% compared to AAD (RR = 0.35, 95% CI 0.21 – 0.57). **Safety** NR **Economic** NR	
Perez (2009)[142] *Long-Term Outcomes After Catheter Ablation of Cavo-Tricuspid Isthmus Dependent Atrial Flutter: A Meta-Analysis*	January 1988 – July 2008	Catheter ablation for the treatment of cavotricuspid isthmus-dependent atrial flutter. 4-6 mm and 8-10 mm tips	***Atrial flutter*** 158 studies total (mean f/u 14.26 months); N = 10719 • ***4 to 6 mm RF***: 55 studies (% f/u NR, range f/u NR); N = 2449 • ***8 to 10 mm/ irrigated RF***: 54 studies (% f/u NR, range f/u NR); N = 3098 • ***Cryoablation***: 11 studies (% f/u NR, range f/u NR); N = 11 • ***Bidirectional block at ablation end point***: 125 studies (% f/u NR, range f/u NR); N = 8661 • ***No bidirectional block***: 24 studies (% f/u NR, range f/u NR); N = 820 • ***8 to 10 mm RF/irrigated and bidirectional block***: 49 studies (% f/u NR, range f/u NR); N =	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Studies were examined for causes of potential biases including sample size, repeated publications, and timing of publication; details per study NR.	**Note:** all rates adjusted for reporting bias using Duval and Tweedie trim and fill method unless otherwise specified. **Efficacy** • ***Overall success rate*** (153 studies) was 91.1% (unadjusted 94.3%). • ***Acute treatment success rate*** higher for 8 to 10 mm tips or irrigated tips (92.7%) compared with 4 to 6 mm tips (87.9%). Success rate for use of bidirectional block (92.0%) was higher compared with not using a block (86.9%). All cyroablation procedures used bidirectional block and had a success rate of 88.6%. • ***Overall recurrence rate*** (155 studies with 9942 patients) was 10.9%. • ***Incidence of recurrence*** significantly lower for 8 to 10 mm tips or irrigated tips (6.7%) compared with 4 to 6 mm tips (13.8%) ($P < .05$). Recurrence was significantly lower with the use of bidirectional block as procedural end point (9.3%) compared with no block (23.6%)	If definite cause of bias in study was not identified, Duval and Tweedie trim and fill method was used to create adjusted estimates for each measure in the meta-analysis to account for potential bias.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			3098 • ***4 to 6 mm RF and no bidirectional block***: 16 studies (% f/u NR, range f/u NR); N = 512		(*P* < .05).Recurrence rate for cryoablation was 11.2%. • ***Occurrence rate of atrial fibrillation*** after atrial flutter ablation was 33.6% overall (99 studies, 7328 patients). Patients with a history of AF prior to ablation had a significantly higher risk of post-ablation AF (52.7%) compared with patients with no history of pre-ablation AF (23.1%) (RR = 2.46, 95% CI 1.97 – 3.07, *P* < .05). • ***Post-ablation medication use***: AAD drugs were used in 31.6% cases almost exclusively for AF. Coumadin was used long-term in 65.9% of cases. Quality of life was assessed in 7 studies (600 patients). All studies reported improvement in QOL following ablation. Only one trial controlled against AAD, and this study found no difference in QOL following ablation. • ***Quality of life*** was assessed in 7 studies (600 patients). All studies reported improvement in QOL following ablation. Only one trial controlled against AAD, and this study found no difference in QOL following ablation. **Safety** • ***Major complications*** occurred in 2.6% of patients (93 studies, N = 6293). • ***Incidence of complications*** included vascular complications (n = 26), complete heart block (n	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					= 12), pericardial effusion (n = 8), cerebral vascular events (n = 3), sustained ventricular arrhythmias (n = 2) and myocardial infarction (n = 1). • ***Mortality rate*** was 3.3% (37 studies, 3433 patients); cardiac mortality rate was 1.8% (30 studies, 2616 patients). **Economic** NR	
Piccini (2009)[143] *Pulmonary Vein Isolation for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation: A Meta-Analysis of Randomized, Controlled Trials*	January 1993 – December 2008	PVI for the treatment of paroxysmal or persistent AF as compared to medical therapy (AAD or cardioversion).	***Paroxysmal or persistent AF*** PVI vs. AAD • 3 RCTs (% f/u NR in 3 studies, mean f/u 12 months); N = 237 ***Persistent AF*** PVI vs. AAD and cardioversion • 1 RCT (% f/u NR, mean f/u 12 months); N = 146 ***Paroxysmal AF*** PVI vs. AAD • 2 RCTs (% f/u NR in 2 studies, mean f/u 12 months); N = 310	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** NR	**Efficacy** • PVI was associated with 77% chance of maintaining sinus rhythm compared with medical therapy (29%) (OR = 9.74, 95% CI 3.98 - 23.87) at 12 months. • When studies of predominately paroxysmal AF were considered, PVI resulted in higher odds of freedom from AF compared with medical therapy (OR = 15.78, 95% CI 10.07 - 24.73). • PVI was associated with decreased hospitalization rate for cardiovascular causes (14 vs. 93 per 100 person-years; RR = 0.15, 95% CI 0.10 - 0.23, *P* < .001). • There was a repeat ablation rate of 17% in 4 studies. **Safety** • ***Major complication*** occurred in 2.6% of ablation patients compared with 8% of AAD patients. • ***Incidence of complications in ablation patients*** included tamponade (n = 2), pericardial	In 4 studies reporting crossover data, over 50% of the patients originally randomized to medical therapy crossed over to ablation treatment. The findings from this review might not apply to older patients, patients with multiple co-morbidities, or patients with CHF or other cardiac-related problems.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					effusion (n = 2), phrenic nerve paralysis (n = 1), pulmonary vein stenosis (n = 3), and thromboembolic events (n = 3). **Economic** NR	
Spector (2009)[144] *Meta-Analysis of Ablation of Atrial Flutter and Supraventricular Tachycardia*	January 1990 – January 2007	Radiofrequency ablation for the treatment of typical atrial flutter and atrioventricular node-dependent supraventricular tachycardia (SVT, includes Wolff-Parkinson-White syndrome, accessory pathways, atrioventricular reentrant tachycardia, and AVNRT).	***Atrial flutter*** • 4 RCTS (% f/u NR for 4 studies, range f/u NR for 4 studies); N = 336 • 2 non-randomized controlled trials (% f/u NR for 2 studies, range f/u NR for 2 studies); N = 223 • 9 uncontrolled case series (% f/u NR for 9 studies, range f/u NR for 9 studies); N = 499 • 3 single arm, retrospective (% f/u NR, range f/u NR); N = 265 ***SVT*** • 1 RCT (% f/u NR, range f/u NR); N = 100 • 3 non-randomized controlled trials (% f/u NR, range f/u NR); N = 368 • 1 comparative, retrospective (% f/u NR, range f/u NR); N = 87 • 18 uncontrolled case	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** Overall body of evidence rated according to the schema of evidence assignment developed by the Centre for Evidence-Based Medicine (CEBM) ***Atrial flutter studies*** • Level I: 4 studies • Level II: 2 studies • Level III: 9 studies • Level IV: 3 studies ***SVT studies*** • Level I: 0 studies • Level II: 3 studies • Level III: 20 studies • Level IV: 16 studies	**Efficacy** ***Atrial flutter*** • Single procedure success rate was 91.7% • Multiple procedure success for was 97% • Repeat ablation occurred in 8% of cases. ***SVT*** • Single procedure success rate was 93.3% • Multiple procedure success rate was 94.6% • Repeat ablation was required in 6.5% of cases • Efficacy was slightly higher for AVNRT than accessory pathway tachycardias (94.3% vs. 90.9% and 96.0% vs. 93.3% for multiple procedures). **Safety** • ***Major complications*** occurred in 2.9% of cases. • ***Incidence of complications*** included atrioventricular block (1.4%), need for pacemaker (0.65%), hematoma (0.3%), and cardiac tamponade (0.2%) • Mortality was 0.13%, and there were 2 procedure related deaths. Cause of death NR.	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			series (% f/u NR, range f/u NR); N = 2877 • 16 single arm, retrospective (% f/u NR, range f/u NR); N = 4261		**Economic** NR	
Terasawa (2009)[146] *Systematic Review: Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation*	2000 – December 2008	Radiofrequency catheter ablation for the treatment of atrial fibrillation 4mm and 8 mm tips	***Paroxysmal, persistent, long-standing persistent, chronic, or permanent AF*** ***RFA vs. AAD*** First-line therapy • 1 RCT (% f/u NR, range f/u NR); N = 70 Second line therapy • 5 RCTs (% f/u NR for five studies, range f/u NR for five studies); N = 623 • 2 non-randomized comparative studies (% f/u NR for 2 studies, range f/u NR for 2 studies); N = 1341 ***Comparison of RFA techniques*** PVI vs. WACA • 5 RCTs (% f/u NR for 5 studies, range f/u NR for 5 studies); N = 500 RFA with or without additional left-sided ablation lines	***Overall critical appraisal:*** Strength of body of evidence was assessed based on a modified scale developed by the AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[151] ***Critical appraisal of individual studies:*** Study quality was assessed based on a modified scale developed by the AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[151] ***RFA vs. AAD*** First-line therapy • 1 RCT of fair quality Second line therapy • 4 RCTs of fair	**Efficacy** • ***Paroxysmal or persistent AF***: moderate evidence that WACA + ablation of residual potentials yielded lower rates of AF recurrence compared with segmental ostial PVI. • ***Paroxysmal AF:*** RFA as second-line therapy is superior to AAD in maintaining sinus rhythm at 12 months. • Insufficient evidence in rates of recurrent AF in RFA first-line treatment compared with AAD. • Low strength of evidence suggesting that RFA improves QOL, avoidance of anticoagulation, or decreased readmission rates compared with AAD. • Insufficient evidence on the effects of adding left- or right-sided ablation lines to RFA. • There is moderate evidence of no difference in long-term rhythm control achieved using an 8-mm tip compared with an irrigated-tip catheter for RFA. **Safety** • Low level of evidence that adverse effects associated with RFA were uncommon.	Most studies comprised relatively young patients with near-intact cardiac function. Accurate summary estimates of adverse events are not possible because of nonuniform definitions and assessments of adverse events across studies.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			• 6 RCTs (% f/u NR for 6 studies, range f/u NR for 6 studies); N = 1069 <u>PVI vs. PVI with right-sided lines</u> • 2 RCTs (% f/u NR for 2 studies, range f/u NR for 2 studies); N = 214 <u>8-mm tip vs. closed irrigated tip catheter</u> • 2 RCTs (% f/u NR for 2 studies, range f/u NR for 2 studies); N = 91 <u>8-mm tip vs. open irrigated tip catheter</u> • 2 RCTs (% f/u NR for 2 studies, range f/u NR for 2 studies); N = 233 • 1 nonrandomized comparative studies (% f/u NR, range f/u NR); N = 221 <u>Different imaging methods</u> • <u>5 RCTs</u> (% f/u NR for 5 studies, range f/u NR for 5 studies); N = 340 • 3 nonrandomized comparative studies (% f/u NR for 3 studies, range f/u NR for 3 studies); N = 330 <u>Miscellaneous comparisons</u>	quality • 1 RCT of poor quality • 2 non-randomized comparative studies of poor quality ***Comparison of RFA techniques*** <u>PVI vs. WACA</u> • 4 RCTs of fair quality • 1 RCT of poor quality <u>RFA with or without additional left-sided ablation lines</u> • 4 RCTs of fair quality • 2 RCTs of poor quality <u>PVI vs. PVI with right-sided lines</u> • 1 RCT of fair quality • 1 RCT of poor quality <u>8-mm tip vs. closed irrigated tip catheter</u> • 2 RCTs of good quality <u>8-mm tip vs. open irrigated tip catheter</u> • 2 RCTs of fair quality • 1 nonrandomized comparative study of poor quality <u>Different imaging</u>	• Insufficient evidence in comparing rate of CHF between RF and AAD treatments. • Low strength of evidence for no difference between RFA and AAD treatments in risk of cerebrovascular events at 12 months. • ***Commonly reported complications*** included asymptomatic (0% - 19%, median 0.3%) or symptomatic (requiring intervention, < 1%) PV stenosis, cardiac tamponade (0%-5%), cerebrovascular events (0%-7%), and atrioesophageal fistula (0.1%-0.9%). • ***Mortality:*** 5 deaths (1 case of pulmonary infection, 1 case of anaphylaxis, and 3 cases of atrioesophageal fistulas). **Economic** NR	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			• 33 RCTs, nonrandomized comparative and cohort studies (individual study type NR) (% f/u NR for 33 studies, range f/u NR for 33 studies); N = 4854 ***Adverse events*** • 100 cohort studies (% f/u NR for 100 studies, range f/u NR for 100 studies); N ≤ 20000	methods • 3 RCTs of fair quality • 2 RCTs of poor quality • 3 nonrandomized comparative studies of poor quality Miscellaneous comparisons • 4 studies of fair quality • 29 studies of poor quality ***Adverse events*** • 100 cohort studies, quality NR		
Gjesdal (2008)[152] *Curative Ablation for Atrial Fibrillation: A Systematic Review*	Through May 2007	Catheter ablation for the treatment of paroxysmal, persistent and permanent atrial fibrillation as compared to other medical interventions (including maze procedures, AAD, or pacemaker insertion)	***Paroxysmal or persistent AF*** RF ablation vs. AAD • 3 RCTs (% f/u NR for 3 studies, range f/u NR for 3 studies); N = 234 ***Persistent AF*** RF ablation vs. AAD • 1 RCT (%f/u NR, range f/u NR); N = 198 ***Permanent AF*** RF ablation vs. no treatment • 1 RCT (% f/u NR, range f/u NR); N = 146	***Overall critical appraisal:*** The level of evidence for each outcome was assessed using the GRADE criteria. ***Overall quality of evidence***: low (details NR)	**Efficacy** • Radiofrequency ablation was more effective then AAD in preventing AF. At 1 year, AF was present in 25% of the catheter ablation group, as compared with 67% in the AAD or no treatment group. • 3 studies assessed hospitalizations. One study found similar median hospitalizations, while another reported 54% hospital readmission in the AAD group as opposed to 9% in the catheter ablation group. Another study found 24 readmissions out of 99 patients in the RF ablation group, and 167 among 99 patients in the AAD group, in addition to 42 cross-over RF ablations.	Patients included in these RCTs were relatively young compared to the demographic most affected by atrial fibrillation.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					Safety • ***Incidence of complications*** include stroke (n = 2), moderate pulmonary vein stenosis (n = 1), transitory paresis of the phrenic nerve (n = 1), transitory ischemic attack (n = 1), 1 groin hematoma (n = 1) and 2 patients needed pericardial drainage. • There were 2 deaths in the RF-ablation group and 1 death in the control group. 1 patient died of a stroke, 1 patient died from pneumonia. **Economic** NR	
Noheria (2008)[140] *Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation: A Systematic Review*	Through June 30, 2007	Circumferential pulmonary vein ablation (CPVA) for treatment of atrial fibrillation as compared to AAD.	***Paroxysmal or persistent AF*** CPVA vs. AAD • 2 RCTs (% f/u NR for 2 studies, range of f/u 12 months); N = 83 ***Paroxysmal AF*** CPVA vs. AAD • 1 RCT (% f/u NR, range of f/u 12 months); N = 99 ***Monthly symptomatic AF*** CPVA vs. AAD • 1 RCT (% f/u NR, f/u range 2-12 months); N = 32	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** NR	**Efficacy** • Risk of ***recurrence*** at 12 month f/u was 3.73 (95% CI, 2.47-5.63) for CPVA as compared with AAD. • 75.7% of the CPVA group had AT recurrence-free survival at 12 month f/u, while 18.8% of AAD group had AT recurrence-free survival at 12 months. **Safety** • ***Major complications*** were significantly more frequent in the AAD group as opposed to the CPVA group (*P* = .02). • There were 2 deaths, one in the treatment arm and one in the control. Cause of death NR. • Adverse effects in the CPVA group were more severe than those in the AAD group.	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					Economic NR	
Thrall (2006)[147] *A Quality of Life in Patients with Atrial Fibrillation: A Systematic Review*	1887 – January 2005	Ablation techniques (including RFA, AV junction ablation, bundle of HIS ablation, radiofrequency PV ablation, PVI and segmental PVI ablation) for the treatment of AF, as compared to medical interventions (including AAD, pacemaker, Maze procedures).	***AF (16.3%), AF with or without impaired systolic function (11.0%), Paroxysmal AF (26.6%), Chronic AF (22.3%), Permanent AF (11.9%), Persistent AF (25.1%), Paroxysmal and persistent AF (3.9%), Paroxysmal and permanent AF (3.4%), Drug Refractory AF (1.6%), Drug Refractory PAF (1.9%)*** <u>RFA vs. AV modification, AADs, various kinds of pacing or the Maze procedure</u> • 6 prospective studies (% f/u NR for 6 studies, range f/u 1 – 25 months); N = 586 • 1 RCT (% f/u NR, range f/u 13 – 42 months); N = 144 <u>AV junction Ablation vs. AV modification, AADs, various kinds of pacing or the Maze procedure</u> • 3 prospective studies (% f/u NR for 2 studies, range f/u 6-12 months); N = 187 • 4 prospective	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** NR	**Efficacy** • SF-36 scores improved with the use of ablation as compared with AAD. • Ablation and pacemaker implantation improved QOL as compared with AAD therapy. **Safety** NR **Economic** NR	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			randomized studies (% f/u NR for 4 studies, range f/u 4.5 – 12 months); N = 315 <u>Bundle of HIS ablation vs. AV modification, AADs, various kinds of pacing or the Maze procedure</u> • 1 prospective, randomized study (% f/u NR, range f/u 12 months); N = 36 <u>RF PV ablation vs. AV modification, AADs, various kinds of pacing or the Maze procedure</u> • 1 prospective study (% f/u NR, range f/u 12 months); N = 211 <u>PVI vs. AV modification, AADs, various kinds of pacing or the Maze procedure</u> • 2 prospective studies (% f/u NR for 2 studies, range f/u 6 months); N = 268 • 1 RCT (% f/u NR, range f/u 6 months); N = 30 <u>Segmental PVI vs. AV modification, AADs, various kinds of pacing</u>			

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			or the Maze procedure • 1 prospective study (% f/u NR, range f/u 3-9 months)			
Yee (2003)[149] *Clinical Review of Radiofrequency Catheter Ablation for Cardiac Arrhythmias*	1985 – January 2001	Radiofrequency catheter ablation for the treatment of pre-excitation syndromes accessory pathway ablation (including Wolff-Parkinson-White syndrome), atrioventricular nodal re-entry tachycardia (AVNRT), slow AV node pathway ablation, isthmus dependent atrial flutter ablation, ablation of atrial tachycardias (including sinus tachycardias), ablation of AF (including AV node ablation, AV node modification, linear ablation, and focal and pulmonary vein ablation).	***Accessory pathway*** RFA vs treatment NR • 13 studies, including 11 cohort studies, 1 survey, and 1 multicenter clinical trial (% f/u NR for 13 studies, range f/u 3-24 months); N = 5696 ***AVNRT*** RFA vs treatment NR • 22 studies, including 1 RCT, 3 non-randomized studies, and 18 cohort studies (%f/u NR for 22 studies, range f/u NR for 22 studies); N = NR ***Isthmus-dependent atrial flutter*** RFA vs treatment NR • 16 studies, including 2 RCTs and 14 cohort studies (% f/u NR for 14 studies, range NR for 14 studies); N = NR ***Other tachycardias*** RFA vs treatment NR • 9 cohort studies (% f/u NR for 9 studies, range of f/u NR for	***Overall critical appraisal:*** NR ***Critical appraisal of individual studies:*** NR	**Efficacy** ***RFA for accessory pathway ablation (13 studies)*** • Procedural success rate: 87% - 99% • Success rate was lower and procedures were longer in patients with multiple accessory pathways. • Advanced age had no effect on outcome. • Recurrence rates: 0% - 11% over follow up range. Most recurrences were successfully treated with a second, or in rare cases, a third ablation. • QOL improved with successful ablation, including symptom scores and exercise capacity, as compared to patients in AAD treatment groups. ***RFA for AVNRT nodal pathway ablation (22 studies)*** • It cannot be concluded that RFA is superior to AAD for treatment of AVNRT. ***RFA for treatment of isthmus-dependent atrial flutter (16 studies)*** • Procedural success rate: 83% - 100% • Recurrence was as high as 15.5% in on study, with the majority of these patients successfully treated with second or third ablation. • One study noted that only	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			9 studies); N = NR ***AF*** <u>RFA vs treatment NR</u> • 15 studies (% f/u NR for 15 studies, range of f/u NR for 15 studies); N = NR <u>AV junctional modification vs treatment NR</u> • 5 studies, including 2 RCTs (% f/u NR for 5 studies, range of 3 – 16 months); N = 219 <u>Linear AF ablation vs treatment NR</u> • 3 cohort studies (% f/u NR, range f/u 11-22 months); N = 117 <u>Focal AF and pulmonary vein ablation vs treatment NR</u> • 6 studies (study type NR for 6 studies, % f/u NR for 6 studies, range f/u 4 – 8 months): N = 551		patients with atrial flutter prior to RFA had AF episodes during follow up. • QOL was assessed by three small studies, one of which concluded that there was RFA resulted in improved QOL scores compared with AAD. Emergency visits, hospitalization and AAD prescription were all decreased following RFA. • 5 studies reported that patients undergoing ablation for atrial flutter were more likely to have symptomatic AF episodes if they have structural heart disease, prior AF or inducible AF during ablation procedure. ***RFA for other tachycardias (9 studies)*** • Procedure success rate: 73% - 100% • There is too little data to comment with certainty on the efficacy of this treatment. ***AF (29 studies)*** <u>RFA for treatment of AF</u> • Current data is insufficient to determine efficacy of RFA as compared to AAD. <u>AV junctional modification</u> • AV junctional modification is not yet a treatment for AF; however, studies surveyed suggested that it is inferior to complete AV junctional ablation. <u>Linear AF ablation</u> • Linear AF ablation is still an experimental procedure and requires significantly more	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					testing. <u>Focal AF and pulmonary vein ablation</u> • Focal AF and pulmonary vein ablation are still being researched and require more investigation. **Safety** ***RFA for accessory pathway ablation (13 studies)*** • ***Major complications*** occurred in 0% - 11% of cases. • Myocardial perforation, myocardial infarction and stroke were associated with left-sided pathways. AV node block was associated with septal pathways. ***RFA for AVNRT nodal pathway ablation (22 studies)*** • Safety information NR ***RFA for treatment of isthmus-dependent atrial flutter (16 studies)*** • Safety information NR ***RFA for other tachycardias (9 studies)*** • Safety information NR ***AF (29 studies)*** <u>RFA for treatment of AF</u> • 2 uncontrolled studies suggested that RFA is associated with sudden death. Potential causes include pacemaker failure, VF, perhaps secondary to QT prolongation, or preexisting heart disease. <u>AV junctional modification</u> • Safety information NR. <u>Linear AF ablation</u> • Safety information NR <u>Focal AF and pulmonary vein</u>	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
					ablation • Safety information NR **Economic** NR	

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; AT: atrial tachyarrhythmia; AVNA: atrioventricular nodal ablation; AV: atrioventricular; AVNRT: atrioventricular nodal reentrant tachycardia; CA: catheter ablation; CFAE: complex fractionated atrial electrogram; CHF: congestive heart failure; CPVA: circumferential pulmonary vein ablation; DAVNNT: dual atrioventricular nodal nonreentrant tachycardia; EF: ejection fraction; GP: ganglionated plexi; LAAEF: left atrial active emptying fraction; LAD: left atrial diameter; LAEF: left atrial ejection fraction; LVED: left ventricular end diastolic diameter; NR: not reported; PNP: phrenic nerve palsy; PV: pulmonary vein; PVI: pulmonary vein isolation; PVA: pulmonary vein antrum; PVAI: pulmonary vein antrum ablation with isolation; PVS: pulmonary vein stenosis; QALY: quality adjust life year; QOL: quality of life; RCT: randomized controlled trial; RF: radiofrequency; RFA: radiofrequency ablation; RFCA: radiofrequency catheter ablation; RR: relative risk; SCD: sudden cardiac death; SR: systematic review; SVT: supraventricular tachycardia; WPW: Wolff-Parkinson-White syndrome; WACA: wide area circumferential ablation;

Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

*Uniform isoproterenol use defined as administration after ablation regardless of whether it was needed to induce AVNRT during the diagnostic portion of the electrophysiology study. Nonuniform isoproterenol use defined as delivered only to those patients who required administration to induce the arrhythmia during the diagnostic portion of the study.[145]

†Quality of studies were assessed by exploring the study design, representativeness of the study participants with regard to patients who undergo RFCA for AF, reporting of loss to follow-up, and limitations and biases.[135]

‡Modified Jadad scale with a maximum of 3 points. A maximum of 2 points were awarded for randomization method and a maximum of 1 point for description of withdrawals and drop out; did not assess blinding.[132]

§Studies were assessed on a 13-point scale adapted from Balk et al[153] using the following parameters: randomized trial, clearly stated research questions, multicenter trial, clearly stated inclusion criteria, well described randomization and appropriate methods for randomization, allocation concealment, patient blinding to intervention, blinding of caregivers, blinding of outcome assessors, blinding of data analysis, intention-to-treat analysis, valid statistical methods, of follow up data including reporting of loss to follow-up. Scoring: poor quality study, ≤ 5 points; intermediate quality study, 6-9 points; high quality study, ≥ 10 points.[139]

Previous health technology assessments

Nine previous health technology assessments (HTAs) were found that addressed RF catheter ablation or cryoballoon ablation for AF, atrial flutter, or SVT patients (table 3)[5, 93, 97, 154-159]. A few HTAs found some evidence for the superiority of RF catheter ablation over AAD regarding recurrence of AF for AF patients[154, 156, 158]; however, other HTAs found insufficient evidence to support either treatment[97, 157]. One HTA found RF catheter ablation to be efficacious as a second-line therapy to maintain sinus rhythm compared with AAD, but data was insufficient to evaluate RF catheter ablation as a first-line treatment[5]. Regarding maintenance of sinus rhythm and success rates for AF patients, RF catheter ablation with PVI was found to be superior to AAD[93] and RF catheter ablation with PVAI was found to be superior to cardioversion[93]. And regarding freedom from AF recurrence in AF patients, wide area circumferential ablation (WACA) was found to be superior to ostial PVI[5] and circumferential PV was superior to segmental PV[154]. One HTA could not draw any definitive conclusions regarding the efficacy or safety of cryoballoon ablation compared with RF catheter ablation or AAD due to lack of randomized studies[155]. Some HTAs investigating RF catheter ablation for AF patients found little or no evidence for the superiority of RF catheter ablation regarding safety[5, 157, 158]. Other HTAs found that complication rates were low[156] or rare[97] after RF catheter ablation. For patients with atrial flutter, two HTAs found some evidence for the superiority of RF catheter ablation over AAD, but insufficient evidence regarding safety[97, 158].

Table 3. Summary of previous health technology assessments.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Atrial Fibrillation						
Cochrane Collaboration (2012)[154] *Catheter ablation for paroxysmal and persistent atrial fibrillation*	1950 – August 2009	For paroxysmal and/or persistent AF: • RF catheter ablation compared with medical treatment. • Comparisons of different catheter ablation methods.	***Paroxysmal or persistent AF*** RF catheter ablation versus AAD**:** • 7 RCTs (96 - 98% f/u or NR in 5 studies, range f/u 1 – 12 months); N = 767 Various catheter ablation methods*: • 25 RCTs (96 – 98% or NR in 23 studies, 3 – 19 months or NR); N = 2793 or NR in 1 study	Methodological quality categorized using Cochrane guidelines†; overall critical appraisal NR. Risk of bias items: • Selection bias (random sequence generation, allocation concealment): low for < 35% of the studies and unknown for the	**Efficacy** Limited evidence suggests catheter ablation might be better than medical therapies for management of persistent AF, for prevention of recurrence of AF, and to restore sinus rhythm. Results suggest that catheter ablation could improve aspect of QOL for patients with paroxysmal or persistent AF. Circumferential PV ablation improved symptoms of AF and reduced recurrence of AF more than segmental PV ablation.	Most RCTs were small in size and of poor quality.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
				others. • Blinding: 100% of the studies have high risk of bias. • Incomplete outcome data addressed: 100% of the studies have high risk of bias. • Adequate sequence generation: <35% of the studies have low risk of bias, bias is unknown for the others.	**Safety** No differences were found in mortality and fatal or non-fatal embolic complications, or death from thrombo-embolic events, for catheter ablation compared with medical therapies. **Economics** There is conflicting evidence regarding the cost effectiveness of catheter ablation and few studies addressed this issue.	
California Technology Assessment Forum (2011)[155] *Cryoballoon ablation for atrial fibrillation*	1966 – April 2011	For paroxysmal or persistent AF: cryoballoon ablation or cryoablation compared with Mesh Ablator catheter or AAD, or RFA	***Paroxysmal or persistent AF*** Cryoballoon ablation or cryoablation: • 10 prospective studies (% f/u NR in 10 studies, range f/u 6 – 33 months); N = 693 ***Paroxysmal AF*** Cryoballoon ablation vs Mesh Ablator catheter: • 1 non-RCT (% f/u NR, 6 month f/u); N = 79 ***Paroxysmal or persistent AF*** Cryoballoon ablation	CTAF methodology‡ used to determine if medical technology improves health outcomes and is safe and effective. **Criterion 1** (government regulatory approval): met **Criterion 2** (evidence of effectiveness): met **Criterion 3** (health outcomes improvement): met **Criterion 4** (as beneficial as alternatives): not	**Efficacy:** Although cryoballoon ablation might be beneficial compared to the other treatments evaluated in two non-RCTs, definitive conclusions cannot be drawn from non-randomized studies. **Safety:** Literature did not support conclusions in this area. Overall, complication rates seem relatively similar when comparing cryoablation with RFA. **Economics:** Not addressed in this review.	Although the main goal of catheter ablation is to decrease symptoms associated with AF, no studies have assessed the impact of cryoballoon ablation or cryoablation on the important outcomes of mortality, stroke, heart failure or progression of paroxysmal AF to more persistent forms. To date no RCTs comparing cryoballoon ablation with other AF treatments have been published. However, two RCTs comparing cryoballoon ablation to either RFA or AAD are ongoing at the time of writing.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			vs RFA: • 1 non-RCT (% f/u NR, 13 month f/u); N = 177	met **Criterion 5** (improvement seen outside investigational studies): not met		
California Technology Assessment Forum (2010)[156] *Radiofrequency Ablation for Drug Refractory Symptomatic Paroxysmal Atrial Fibrillation*	1996 to March 2010	For drug refractory symptomatic paroxysmal AF: RFA compared with AAD.	***AF, no prior AAD*** RFA vs AAD • 1 RCT (% f/u NR, range f/u 9 months); N = 167 ***Drug refractory AF*** RFA vs AAD • 1 RCT (% f/u NR, range f/u 12 months); N = 70 ***Drug refractory paroxysmal or persistent AF*** RFA vs AAD • 2 RCTs (% f/u NR in 2 studies, range f/u 12 months); N = 167 ***Drug refractory paroxysmal AF*** RFA vs AAD • 2 RCTs (% f/u NR in 2 studies, range f/u 12 months); N = 310	CTAF methodology‡ used to determine if medical technology improves health outcomes and is safe and effective. **Criterion 1** (government regulatory approval): met **Criterion 2** (evidence of effectiveness): met **Criterion 3** (health outcomes improvement): met **Criterion 4** (as beneficial as alternatives): met **Criterion 5** (improvement seen outside investigational studies): met	**Efficacy** • In the short term, RFA leads to a significant decrease in recurrent AF and symptomatic AF compared with AAD treatment, although the long-term effects and efficacy in older individuals with significant comorbidities are not known. **Safety** • Complication rate of RAF is relatively low at 1 year, although long-term effects are unknown. • One RCT reported adverse events occurring in 4.5% of RAF patients compared with 8.8% of AAD patients. **Economics** NR	Studies included relatively young healthy individuals. Studies did not assess impact of RFA on mortality, stroke, heart failure, or progression of PAF to more persistent forms.
Canadian Agency for Drugs and Technologies in Health (2010)[93]	Up to April 2010	RFA for treatment of AF using PVI or PVI + atrial ablation compared with cardioversion including AAD,	***Paroxysmal or persistent AF*** RFA (PVI) vs AAD: • 6 RCTs in 7 publications (% f/u NR in 6 studies,	Methodological quality of all RCTs categorized using Jadad scale; all non-RCTs were assigned a quality	**Efficacy**: • ***RFA (PVI) vs AAD:*** Catheter ablation appears to be superior to treatment with AADs in patients with AF for maintenance of sinus rhythm	Long term consequences were not able to be discerned from the studies examined by this review. No studies were found comparing RFA with open surgical procedures.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Ablation procedures for rhythm control in patients with atrial fibrillation: clinical and cost-effectiveness analyses		electrical shocks via paddles or patches on chest, or open heart Cox-Maze procedure.	range f/u 12 months); N = 647 • 2 non-RCTs (% f/u NR in 2 studies, range f/u 12 months); N = 1291 RFA (PVAI) vs cardioversion: • 1 non-RCT (% f/u NR, range f/u 9 - 23 months); N = 170 PVI vs PVI + ablation in left atrium: • 8 RCTs (% f/u NR in 8 studies, range f/u 9 – 15 months); N > 1590 PVI vs PVI + ablation in right atrium: • 2 RCTs (% f/u NR in 2 studies, range f/u 12 months); N = 257 PVI vs PVI + ablation of SVC: • 2 RCTs (% f/u NR in 2 studies, range f/u 12 months); N = 426 PVI vs PVI + ablation of CFAEs: • 3 RCTs (% f/u NR in 3 studies, range f/u 16 – 19 months); N = 345 PVI versus stepwise/ tailored approach: • 2 RCTs (% f/u NR in 2 studies, range f/u 9 – 24 months);	score of 1. RFA (PVI) vs AAD: • 6 RCTs: 4 with score = 2, 1 with score = 3, 1 with score = 4 • 2 non-RCTs with score = 1 RFA (PVAI) vs cardioversion: • 1 non-RCT with score = 1 PVI vs PVI + ablation in left atrium: • 8 RCTs: 1 with score = 5, 1 with score = 3, 3 with score = 2, 3 with score = 1 PVI vs PVI + ablation in right atrium: • 2 RCTs with quality score = 2 PVI vs PVI + ablation of SVC: • 2 RCTs: 1 with score = 4, 1 with score = 3 PVI vs PVI + ablation of CFAEs: • 3 RCTs: 2 with score = 3, 1 with score = 2 PVI versus stepwise/tailored approach	up to one year. Ablation led to better results in patients with paroxysmal AF compared with patients with paroxysmal AF who received AAD. • ***RFA (PVAI) vs cardioversion:*** Catheter ablation had a higher success rate compared to electrical cardioversion. • ***PVI vs PVI + adjunctive atrial ablation:*** More patients who had PVI and adjunctive ablation, particularly of the left atrium, maintained sinus rhythm compared with PVI only. **Safety**: Although adverse events were reported by many studies, overall safety was not evaluated due to insufficient sample sizes and limited reporting of details and timing of adverse events. **Economics**: Using a five-year time horizon, incremental cost effectiveness of AF ablation compared to AAD was $59,194 per quality adjusted life year (patients with $CHADS_2$ score of 2 and failed to respond to at least one AAD). Cost-effectiveness of AF ablation was more favorable for longer time periods.	Assessment also included a review and critical appraisal of guidelines for AF.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			N = 170 PVI compared with PVI + other ablations: • 3 non-RCTs (% f/u NR in 3 studies, range f/u 12 – 19 months); N = 408	• 2 RCTS: 1 with score = 3, 1 with score = 2 PVI compared with PVI + other ablations: • 3 non-RCTs with quality score = 1		
Agency for Healthcare Research and Quality (2009)[5] *Comparative effectiveness of radiofrequency catheter ablation for atrial fibrillation*	2000 – December 2008	RF catheter ablation for treatment of AF using cooled, irrigated, conventional, other or undefined tip compared with medical treatments (anti-arrhythmic drugs, AAD), surgery for persistent, paroxysmal, nonparoxysmal, chronic, drug-refractory, or unspecified AF.	***Persistent, paroxysmal, or chronic AF*** RF ablation as 1st-line therapy vs AAD: • 1 RCT (96% f/u, range f/u 12 months); N = 70 RF ablation as 2nd -line therapy vs AAD: • 5 RCTs (97% f/u or NR in 4 studies, range f/u 12 months); N = 623 • 2 non-RCTs (97% f/u or NR in 1 study, range f/u 36 months or NR in 1 study); N = 1351 ***Persistent or paroxysmal AF*** PVI vs WACA: • 5 RCTs (% f/u NR in 5 studies, range f/u 6-15 months); N = 500 ***Persistent, paroxysmal, nonparoxysmal, or chronic AF*** RFA with or without additional left-sided ablation lines: • 6 RCTs (%f/u NR in	Overall body of evidence rating and LOE§ categorized using generic system. ***Persistent, paroxysmal, or chronic AF*** RF ablation as 1st-line therapy vs AAD: • 1 RCT of fair quality RF ablation as 2nd -line therapy vs AAD: • 5 RCTs: 4 fair quality, 1 poor quality • 2 non-RCTs, poor quality) ***Persistent or paroxysmal AF*** PVI vs WACA: • 5 RCTs: 4 fair quality, 1 poor quality ***Persistent, paroxysmal, nonparoxysmal, or chronic AF***	**Efficacy** • Moderate evidence that patients receiving RFA as 2nd line therapy had higher chance of maintaining sinus rhythm compared to those treated with medical therapy alone. • Data was insufficient for RFA as 1st line therapy for rhythm control compared with medical therapy alone. • Low level of evidence showing no significant difference in improvement of LAD, LVED, or EF in RFA compared with medical therapy. • Low level of evidence for inconsistent findings on rates of readmissions between patients treated with RFA or medical treatment. • Low level of evidence that type of AF (nonparoxysmal, i.e., chronic or persistent) is predictive of higher rate of AF recurrence. Only 6 out of 17 studies that performed a multivariable analysis of AF type showed statistically significant independent	No studies were found that compared RFA to open surgical procedures. 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.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			6 studies, range f/u 7 – 17 months); N = 1069 ***Paroxysmal AF*** PVI vs PVI with right-sided lines: • 2 RCTs (%f/u NR in 6 studies, range f/u 12 months); N = 214 ***Drug-refractory AF*** PVI using 8 mm vs closed irrigated tip: • 2 RCTs (% f/u NR in 2 studies, range f/u 6 – 12 months); N = 173 PVI using 8 mm vs open irrigated tip: • 2 RCTs (% f/u NR in 2 studies, range f/u 6 – 14 months); N = 233 • 1 non-RCT (% f/u NR, range f/u 12 months); N = 221 Different imaging modalities: • 5 RCTs (% f/u NR in 5 studies, range f/u 6.5 – 13 months); N = 340 • 3 non-RCTs (% f/u NR in 3 studies, range f/u 6 – 10 months); N = 330 ***AF type NR*** Misc. comparisons: • 33 RCTs, non-RCTs, cohort	RFA with or without additional left-sided ablation lines: • 6 RCTs: 4 fair quality, 2 poor quality ***Paroxysmal AF*** PVI vs PVI with right-sided lines: • 2 RCTs: 1 fair quality, 1 poor quality ***Drug-refractory AF*** PVI using 8 mm vs closed irrigated tip: • 2 RCTs of good quality PVI using 8 mm vs open irrigated tip: • 2 RCTs of fair quality • 1 non-RCT of poor quality Different imaging modalities: • 5 RCTs: 3 fair quality, 2 poor quality • 3 non-RCTs, poor quality ***AF type NR*** Misc. comparisons: • 33 RCTs and non-RCTs, cohort studies: 4 of fair quality, 29 of poor quality	association between AF type and AF recurrence. • ***Paroxysmal and persistent AF:*** moderate evidence that WACA resulted in higher rate of freedom from AF recurrence compared with ostial PVI. • Unclear evidence that PVI + left sided ablation lines increases freedom from AF recurrence compared to PVI only. • ***AF and atrial flutter:*** limited evidence that adding a cavotricuspid isthmus ablation line to PVI did not result in a significantly lower recurrence of AF. • High level of evidence that sex, AF duration, and presence of structural heart disease are not associated with AF recurrence. **Safety** • Low level evidence suggests that major adverse events with RFA are uncommon. • No significant difference was seen in risk of cerebrovascular events in patients treated with RFA compared to medical therapy (studies underpowered to small differences). • Insufficient evidence for the superiority of RFA or medical treatment in risk of developing CHF.	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			studies (% f/u NR in 33 studies, range f/u 6 – 17 months or NR in 27 studies); N = 4854		**Economics** NR	
Blue Cross Blue Shield Association TEC Assessment Program (2009)[157] *Radiofrequency catheter ablation of the pulmonary veins for treatment of atrial fibrillation*	March 2006 – January 2009 (to supplement prior search of 1990 – March 2006 for 2006 TEC assessment)	RF catheter ablation for AF: • as first line treatment for recent onset paroxysmal AF compared with AAD • for symptomatic paroxysmal or persistent AF with failed AAD treatment compared with continued AAD or switch to rate control strategy • for class II or III CHF and symptomatic AF, compared with AV nodal ablation and pacemaker	***Paroxysmal AF*** RFA 1st line treatment vs AAD: • 1 RCT (% f/u NR, range f/u 12 months); N = 70 ***Paroxysmal or persistent AF*** RFA 2nd line treatment vs AAD: • 4 RCTs (% f/u NR in 4 studies, range f/u 12 months); N = 593 ***Symptomatic AF and class II or III CHF*** RFA vs AV nodal ablation + pacemaker: • 1 RCT (% f/u NR, range f/u 6 months), N = 146	Quality assessment for controlled trials** categorized using US Preventive Service Task Force Framework. ***Paroxysmal AF*** RFA 1st line treatment vs AAD: • 1 RCT: fair quality ***Paroxysmal or persistent AF*** RFA 2nd line treatment vs AAD: • 4 RCTs: fair quality ***Symptomatic AF and class II or III CHF*** • RFA vs AV nodal ablation + pacemaker: • 1 RCT: good quality	**Efficacy:** • RFA appears to be superior to medications for maintaining sinus rhythm. However, recurrence rate varied widely, indicating differences in absolute efficacy for different AF patient populations. • Because evidence on the most important outcomes is lacking, it is not possible to conclude whether majority of AF patients will benefit from RFA. • ***RFA vs AAD:*** Available data does not establish the degree of symptom improvement of RFA compared with AAD. • ***RFA vs AV nodal ablation + pacemaker*:** Patients with CHF and symptomatic AF have better outcomes following PVI than with AV nodal ablation and pacemaker insertion. **Safety:** Evidence is inadequate to evaluate adverse events. Serious complications can occur but are uncommon. **Economics:** NR	For most patients whose condition is controlled with a rate control strategy, maintenance of sinus rhythm is not by itself sufficient to demonstrate improved outcomes. For these patients, it is necessary to demonstrate improvements on other outcomes to determine benefit; therefore, it is not possible to conclude that catheter ablation improves health outcomes for the broader population of patients with atrial fibrillation.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
Atrial fibrillation and atrial flutter						
Health Technology Assessment, National Institute for Health Research HTA Program (2008)[97] *Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation*	Up to April 2007	For AF and atrial flutter: RF catheter ablation compared with AAD, direct current cardioversion (DCC), AV nodal ablation, electric intracardiac stimulation.	***Atrial fibrillation*** **RFCA vs AAD:** • 5 RCTs; N = 547 • 1 CCT; N = 1171 **RFCA vs direct current cardioversion or AV node ablation with pacing:** • 1 CCT; N = 277 **RFCA vs AAD and cardioversion:** • 1 RCT; N = 146 **RFCA only:** • 53 case series; N = 11908 ***Atrial flutter*** **RFCA vs AAD or AAD + cardioversion:** 2 RCTs; N = 165 **RFCA only** 23 case series; N = 4238	Methodological quality†† categorized using CRD's guidance on undertaking reviews of effectiveness. ***Atrial fibrillation*** **RFCA vs AAD:** • 5 RCTs: 4 satisfactory, 1 poor • 1 CCT rated poor **RFCA vs direct current cardioversion or AV node ablation with pacing:** • 1 CCT rated poor **RFCA vs AAD and cardioversion:** • 1 RCT: good **RFCA only** • 53 case series: 2 good, 3 satisfactory, 48 poor ***Atrial flutter*** **RFCA vs AAD or AAD + cardioversion:** 2 RCTs: satisfactory **RFCA only** 23 case series: 4	**Efficacy:** • ***Atrial fibrillation***: RFCA may be superior to AADs in patients with drug-refractory paroxysmal AF in terms of freedom from arrhythmia at 12 months, but the evidence is insufficient for persistent/ permanent AF or for results beyond 12 months. • ***Atrial flutter:*** The majority of RFCA patients remained free from arrhythmia at 12 months. A limited amount of moderate quality evidence suggests that significantly more RFCA patients are free from atrial flutter during medium term follow-up compared to AAD treatment. **Safety:** • ***Atrial fibrillation:*** Complications are rare for RFCA; no significant relationship seen for mortality. There is a small risk of cardiac tamponade and PV stenosis associated with RFCA. • ***Atrial flutter:*** Complications were rare for RFCA. Current trials were not powered to show any significant relationship between RFCA treatment and mortality. **Economics**:	Risks of complications from RFCA should be balanced against risks of long-term use of antiarrhythmic agents.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
				good, 19 poor	• ***Atrial fibrillation***: RFCA may be cost-effective if the observed quality of life benefits are assumed to continue over the patient's lifetime. • ***Atrial flutter:*** not evaluated.	
Ontario Health Technology Assessment Series (2006)[158] *Ablation for atrial fibrillation: an evidence-based analysis*	1966 – March 2006	For AF and atrial flutter: RF catheter ablation compared with AAD or various ablation techniques	***Atrial fibrillation or atrial flutter*** RFA 1st line treatment: • 2 RCTs (84 – 96% f/u, range f/u 12 – 22 months); N = 131 ***Drug refractory atrial fibrillation*** RFA vs AAD: • 3 RCTs (2 – 100% f/u, range f/u 12 – 18 months); N = 313 SPVI vs CPVI: • 1 RCT (100% f/u, range f/u > 6 months); N = 100 CPVI + CTI vs CPVI + LA: • 1 RCT (100% f/u, range f/u 7 months); N = 70 Superior PV ablation vs 4 PV ablation: • 1 RCT (100% f/u, range f/u > 12 months); N = 52 PV-LAJ + CTI ablation vs PV-LAJ: • 1 RCT (100% f/u, range f/u 13 months); N = 108	Methodological quality categorized using GRADE guidelines; overall critical appraisal NR. ***Atrial fibrillation or atrial flutter*** RFA 1st line treatment: • 2 RCTs, moderate-high or moderate quality ***Drug refractory atrial fibrillation*** RFA vs AAD: • 3 RCTs: 2 high quality, 1 low quality SPVI vs CPVI: • 1 RCT: high quality CPVI + CTI vs CPVI + LA: • 1 RCT: low-moderate quality Superior PV ablation vs 4 PV ablation: • 1 RCT: moderate-high quality PV-LAJ + CTI	**Efficacy:** ***Atrial fibrillation or atrial flutter*** • Catheter ablation significantly improved long-term freedom from arrhythmia and quality of life compared with medical therapy. ***Drug refractory atrial fibrillation*** • Catheter ablation significantly improved long-term freedom from arrhythmia and quality of life compared with medical therapy ***Comparison of ablation techniques:*** • No preference was seen for any particular catheter ablation technique for AF patients. **Safety:** • Conclusions could not be drawn from the RCTs regarding complications, but no procedure-related deaths were reported. **Economics:** • Most individuals with AF treated with RF ablation will survive beyond the time of	Catheter ablation as first line treatment is considered experimental at the time of the report.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
				ablation vs PV-LAJ: • 1 RCT: low quality	recoupment of the up-front costs.	
Atrial flutter and supraventricular tachycardias						
Canadian Coordinating Office for Health Technology Assessment (CCOHTA) (2002)[159] *Radiofrequency catheter ablation for cardiac arrhythmias: a clinical and economic review*	January 1985 to November 2001	RF catheter ablation for supraventricular tachycardias, compared with AAD, rate responsive pacemaker, surgical techniques, or various ablation techniques	***Pre-excitation syndromes (including WPW)*** **Various ablation techniques** • 1 RCT (% f/u NR, f/u range 24 months); N = 500 **RFA only** • 1 survey (% f/u NR, range f/u 24 months); N = 2527 • 11 cohort studies (% f/u NR in 11 studies, range f/u 3 – 18 months); N = 2669 ***AVNRT*** **Slow vs fast pathway ablation** • 1 RCT (% f/u NR, range f/u 3 months); N = 50 • 3 cohort studies (% f/u NR in 3 studies, range f/u 12 months or NR); N = 262 **Slow pathway ablation** • 10 cohort studies (% f/u NR in 10 studies, range f/u NR in 10 studies); N = NR in 10 studies **Slow or fast pathway**	Critical appraisal was not included in this report.	**Efficacy:** • ***Pre-excitation syndromes (including WPW):*** Acute procedural success rate: 87 – 99%, recurrence rate: 0 – 11%; higher failure rate in patients with multiple accessory pathways. Patients report some improvements in QOL and functional capacity. • ***AVNRT:*** Overall success rate: 46 – 100%, with higher success rate for slow pathway ablation (68 – 100%) vs fast pathway ablation (46 – 94%). Patients report decline in symptoms and/or frequency of urgent visits following RFA. • ***Isthmus dependent atrial flutter:*** For patients with lone flutter, acute procedural success rates: 83 – 100% and recurrence rate < 15%; in lower rate of AF (29%) and rehospitalization rate (22%) vs AAD (53% AF, 63% rehospitalization). Clinical benefits of RFA diminished in patients with atrial flutter with concomitant AF. • ***Atrial tachycardias (intra-atrial re-entry, focal, other):*** Limited evidence reports 73 – 100% success rate.	There is a paucity of high quality outcome studies comparing different types of ablation techniques with alternative therapies and a limited number of cost-effectiveness analyses of RFA.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			ablation • 5 cohort studies (% f/u NR in 5 studies, range f/u NR in 5 studies); N = NR in 5 studies **RFA vs AAD** • 1 non-randomized study (% f/u NR, range f/u NR); N = 79 **RFA or treatment NR** • 2 non-randomized studies (% f/u NR in 2 studies, range f/u NR in 2 studies); N = 332 ***Isthmus dependent atrial flutter (lone flutter)*** **RFA vs AAD** • 1 RCT (% f/u NR, range f/u 21 months); N = 61 **RFA only** • 11 cohort studies (% f/u NR in 11 studies, range f/u 5 - 28 months); N = 770 ***Isthmus dependent atrial flutter with concomitant AF*** **RFA vs AAD** • 1 RCT (% f/u NR, range f/u 21 months); N = 61 **RFA only** • 4 cohort studies (%		• ***Sinus node re-entry tachycardia:*** Acute procedural success can be achieved, but long-term efficacy uncertain. • ***Chronic AF:*** RFA with pacemaker treatment is superior to pacemaker alone or drug therapy for controlling ventricular rate and improving symptoms in 2 small studies. • ***Intermittent AF:*** Greater improvement in QOL scores for patients receiving AF + pacemaker vs patients receiving drug therapy. • ***AF:*** Results are conflicting following AV node modification with or without pacemaker. • ***Focal AF:*** Short-term success rates of 62 – 88%, but limited studies exist regarding long-term efficacy of PV ablation. **Safety:** • ***Pre-excitation syndromes (including WPW):*** complication rates of 0 – 11%. • ***AVNRT:*** Lower complication rate for slow pathway ablation (0 – 4%) vs fast pathway ablation (5 – 6%). • ***Isthmus dependent atrial flutter:*** Complications NR. • ***Atrial tachycardias (intra-atrial re-entry, focal, other):*** Low complication rate (details NR).	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			f/u NR in 4 studies, range f/u 5 - 28 months); N = 770 ***Intra-atrial reentrant tachycardia*** **RFA only** • 3 cohort studies (% f/u NR in 3 studies, range f/u NR in 3 studies); N = 77 ***Focal atrial tachycardia*** **RFA only** • 2 cohort studies (% f/u NR in 2 studies, range f/u NR in 2 studies); N = 22 ***Various atrial tachycardias*** **RFA only** • 2 cohort studies (% f/u NR in 2 studies, range f/u NR in 2 studies); N = 100 ***Sinus node re-entry tachycardia*** **RFA only** • 2 cohort studies (% f/u NR in 2 studies, range f/u NR in 2 studies); N = 26 ***Chronic AF*** **RFA + pacemaker vs pacemaker alone or drug therapy**		• ***Sinus node re-entry tachycardia:*** Complications are reported by few studies and included hemi-diaphragm paralysis (1 patient), ectopic atrial tachycardia (1 patient). • ***Chronic AF:*** Complications NR. • ***Intermittent AF:*** Complications NR. • ***AF:*** RFA has at least an acceptable 3-year safety profile; evidence suggests that mortality following RFA is related to patient's underlying heart disease rather than RFA itself. • ***Focal AF:*** Pulmonary vein stenosis ranged from 0 – 42% in 4 studies, with one of the studies additionally reporting an unspecified minor complication in 1 patient. **Economics:** • In patients with **symptomatic PSVT**, RFA is more effective and less costly than drug therapy. At the time of this report, it costs within US $21,000 per QALY gained. • RFA seems to be more cost effective for **WPW** patients of any age compared to other treatment options. • RFA was not cost effective for **asymptomatic WPW** patients of any age.	

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			• 2 RCTs (% f/u NR in 2 studies, range f/u 3 weeks – 12 months); N = 89 • 8 cohort studies (% f/u NR in 8 studies, range f/u 3 – 17 months); N = 396 ***Intermittent AF*** **RFA + pacemaker vs drug therapy** • 2 RCTs (% f/u NR in 2 studies, range f/u 18 months or NR in 1 study); N = 103 ***AF*** **AV node modification + pacemaker vs AV node modification** • 1 RCT (% f/u NR, range f/u 16 months); N = 33 **AV node modification fast vs slow pathway** • 1 RCT (% f/u NR, range f/u 6 months); N = 60 **AV node modification** • 3 cohort studies (% f/u NR in 3 studies, range f/u 3 – 12 months); N = 126 **Safety, RFA only** • 2 cohort studies (% f/u NR in 2 studies, range f/u 3 years or NR in 1 study); N = 585 or NR in 1			

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available (% f/u, length of f/u)	Critical Appraisal	Primary conclusions	Comments
			study **Safety, RFA vs AAD** • 1 matched cohort study (% f/u NR, range f/u 36 months); N = 579 ***Focal AF*** **PV ablation** • 6 cohort studies (% f/u NR in 6 studies, range f/u 4 – 8 months or NR in 1 study); N = 551			

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; APVI: atrium-pulmonary vein isolation; CCT: controlled clinical trial (non-randomized); CFAE: complex fractionated atrial electrogram; CHF: congestive heart failure; CPVA: circumferential pulmonary vein ablation; CPVI: circumferential pulmonary vein isolation; CRD: Centre for Reviews and Dissemination; CTI: cavotricuspid isthmus isolation; CTIB: cavotricuspid isthmus block; EF: ejection fraction; LAA: left atrial ablation; LACA: left atrial circumferential ablation; LAD: left atrial diameter; LVED: left ventricular end diastolic diameter; PSVT: paroxysmal supraventricular tachycardia; PVAI: pulmonary vein antrum isolation; PV: pulmonary vein; PVI: pulmonary vein isolation; PV-LAJ: pulmonary vein – left atrium junctional ablation; QOL: quality of life; QALY: quality adjust life year; RFA: radiofrequency ablation; SPVA: segmental pulmonary vein ablation; SPVI: segmental pulmonary vein isolation; SVCI: superior vena cava isolation; SVT: supraventricular tachycardia; WACA: wide area circumferential ablation; WPW: Wolff-Parkinson-White syndrome.

Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

*Combinations of various ablation methods were compared including: CPVA, SPVA, CPVI, SPVI, CTIB, CTI, PVI, APVI, segmental ostial PVI, circumferential extraostial PVI, PVAI, PV-LAJ, CFAE, LAA, LACA, SVCI, small/large area, isolation of 4 PVs[154]

†Assessment of methodological quality using Cochrane guidelines[160] for the following categories: random sequence generation (selection bias), allocation concealment (selection bias), blinding, incomplete outcome data addressed, and adequate sequence generation. Quality is assigned for each category as: high risk, low risk, or unclear risk. [154]

‡Methodology to determine if medical technology improves health outcomes and is safe and effective: criteria is judged to be "met" or "not met": [155, 156]

- Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.
- Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.
- Criterion 3: The technology must improve net health outcomes.
- Criterion 4: The technology must be as beneficial as any of the established alternatives.

- Criterion 5: The improvement must be attainable outside the investigational settings.

§Generic grading system:

- Study quality defined as: good (low risk of bias, only RCTs; must have reported AF recurrence rate off AADs after initial RFA procedure), fair (susceptible to some bias, do not meet all criteria in "good" category), and poor (high risk of bias, all retrospective studies).[5]
- Overall body of evidence defined as: high (high confidence that the evidence reflects the true effect); moderate (moderate confidence that the evidence reflects the true effect); low (low confidence that the evidence reflects the true effect); insufficient (evidence is either unavailable or does not permit estimation of an effect). [5]

**The US Preventive Service Task Force Framework Quality Assessment[161] for controlled trials includes evaluation of initial assembly of comparable groups, maintenance of comparable groups, comparable interventions, comparable measurements, appropriate analysis of outcomes, which are then given an overall quality level of Good (meets all quality indicators), Fair (does not meet all quality criteria, but no fatal flaws), or Poor (description NR).[157]

†† Criteria derived from CRD's guidance use an 18 item checklist to evaluate each study; all items pertain to controlled studies, eight items pertain to case series. Quality is rated as excellent, good, satisfactory, or poor, according to the number of criteria met.[97]

2.10. Medicare and Representative Private Insurer Coverage Policies

There are currently no National Coverage Decisions (NCDs) published from the Centers for Medicare and Medicaid Services (CMS). Three identified national coverage policies are consistent for coverage of catheter ablation. Table 4 provides an overview of policy decisions.

- Medicare

The Centers for Medicare and Medicaid Services does not have a NCD for catheter ablation of supraventricular tachyarryhthmias. A search of the Medicare Coverage Database (MCD) (http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx) for all National Coverage Determinations was conducted on September 5, 2012. Search term used: "ablation".

- AETNA

When certain criteria have been met (see Table 4 for details), Aetna considers catheter ablation medically necessary for the treatment of:

- Primary atrial tachyarrthythmias; *or*
- Atrioventricular nodal reentrant tachycardia (AVNRT); *or*
- Atrial tachycardia, flutter, and fibrillation; *or*
- Accessory pathways (including Wolfe-Parkinson-White)

- Anthem

Anthem covers transcatheter radiofrequency ablation of the pulmonary veins for the treatment of atrial fibrillation when the patient is *both* symptomatic and resistant to one or more antiarrhythmic drugs, or has an intolerance of or contraindication to antiarrhythmic drug therapy.

Anthem does not cover transcatheter radiofrequency ablation of the pulmonary veins as a first line treatment of atrial fibrillation, when patient is asymptomatic, or in the absence of intolerance or contraindication to AAD therapy, because it is considered experimental or investigational.

Anthem does not cover transcatheter cryoablation of the pulmonary veins as it is considered investigational and not medically necessary.

- CIGNA

  Cigna covers transcatheter radiofrequency ablation of the pulmonary veins (pulmonary vein isolation) as medically necessary for the treatment of symptomatic *persistent* atrial fibrillation.

  Cigna covers transcatheter radiofrequency ablation of the pulmonary veins as medically necessary for the treatment of symptomatic *paroxysmal* atrial fibrillation as an alternative to long-term antiarrhythmic drug therapy when both of the following criteria are met: (1) normal or mildly dilated left atria; and (2) normal or mildly reduced left ventricular function.

  Cigna does not cover transcatheter radiofrequency ablation of the pulmonary veins for any other indication or any other method of transcatheter ablation of the pulmonary veins including but not limited to cryoablation/cryoballoon ablation, because it is considered experimental, investigational, or unproven.

Table 4. Payer policies.

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments

Aetna (2012)
 	
Clinical Policy Bulletin: Cardiac Catheter Ablation Procedures
 	
POLICY #: 0165
 	
Effective Date: 06/18/1997
 	
Last Review Date: 04/27/2012
 	
Next Review Date: 02/14/2013
	NR	This policy is based upon 65 references including RCTs, meta-analyses, systematic reviews, HTAs and clinical guidelines.	Aetna covers catheter ablation procedures when medically necessary for treatment of:
			• Atrial tachyarrhythmias for patients who meet any of the following criteria:
			  • Patients resuscitated from sudden cardiac death as the result of atrial flutter or atrial fibrillation with a rapid ventricular response in the absence of an accessory pathway; or
			  • Patients with dual-chamber pacemakers and pacemaker-mediated tachycardia that does not respond to drug therapy or reprogramming of the pacemaker; or
			  • Patients with symptomatic atrial tachyarrhythmias such as those mentioned above, who are intolerant to drugs or
				• If no electrophysiology study has been performed in the previous 3 months prior to ablation, then an electrophysiology study is considered medically necessary. Two electrophysiologists are required to perform the ablation, one to manipulate the catheters, and the other to guide the precise location for the ablation using electrogram analysis and pacing. Temporary pacemaker placement is included if indicated. When ablating the His-bundle, a permanent pacemaker is always placed because the ablation procedure has caused a complete heart block.
				• The use of the CARTO system, which is an intra-cardiac 3-D mapping system, for guiding of radiofrequency ablation for the treatment of atrial fibrillation is considered medically necessary; however, the effectiveness of the CARTO system in diagnosis, treatment of management of other cardiac arrhythmias has not been established and therefore is considered experimental and investigational.
				• Balloon-based ablation systems,

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
			when the patient does not wish to take them, even though ventricular rate can be controlled; or • Patients with symptomatic atrial tachyarrhythmias who have inadequately controlled ventricular rates; or • Patients with symptomatic non-paroxysmal junctional tachycardia that is drug resistant, the patient is drug intolerant, or patient does not wish to take them. • Atrioventricular nodal reentrant tachycardia (AVNRT) in patients who meet any of the following criteria: • Patients with sustained AVNRT identified during electro-physiological study or catheter ablation of another arrhythmia; or • Patients with symptomatic sustained AVNRT that is drug resistant, or the patient is drug-intolerant or does not wish to have long-term drug therapy; or • In patients who are suspected of having AVNRT clinically, the finding of dual atrio-ventricular nodal pathway physiology and atrial echoes but without AVNRT during electrophysiological study • Atrial tachycardia, flutter,	including cryoablation, laser, and high-frequency ultrasound, have not been proven to be as effective as current methods, and further study is needed. CPT codes if selection criteria is met: 33250 – 33251, 33254, 33255 – 33256, +33257, +33258, +33259, 33261, 33265 – 33266, +93613, 93650, 93651 - 93652

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
			and fibrillation in patients who meet any of the following criteria: • Patients with atrial fibrillation and evidence of a localized site or sites of origin when the tachycardia is drug-resistant or the patient is drug intolerant or does not wish for long term drug therapy (e.g. pulmonary vein isolation procedures; or • Patients with atrial flutter that is drug resistant or the patient is drug intolerant or the patient does not wish to undergo long-term drug therapy; or • Patients with atrial flutter/atrial tachycardia that is associated with paroxysmal atrial fibrillation when the tachycardia is drug-resistant or the patient is drug intolerant or the patient does not wish to undergo long-term drug therapy; or • Patients with atrial tachycardia that is drug-resistant, the patient is drug intolerant, or the patient does not wish to undergo long-term drug therapy • Accessory pathways (including Wolfe-Parkinson-White) in patients who meet any of the following criteria: • Asymptomatic patients with ventricular pre-excitation, when their livelihood or profession, important activities, insurability, or mental well-being or public	

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
			safety would be affected by spontaneous tachyarrhythmias or the presence of the electrocardiographic abnormality; or • Patients with a family history of sudden cardiac death; or • Patients with atrial fibrillation or other atrial tachyarrhythmias and a rapid ventricular response via the accessory pathway when the tachycardia is drug-resistant or the patient is drug intolerant or does not wish to undergo long-term drug therapy; or • Patients with atrial fibrillation and a controlled ventricular response via the accessory pathway; or • Patients with AV reentrant tachycardia or atrial fibrillation with rapid ventricular rates identified during electrophysiological study of another arrhythmia; or • Patients with symptomatic AV reentrant tachycardia that is drug-resistant, or the patient is drug-intolerant or the does not wish to undergo long-term drug therapy. Aetna does not cover cardiac ablation procedures for any of the following arrhythmias, as there is insufficient evidence of effectiveness and therefore the procedures are considered experimental and	

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
			investigational: • Hypertrophic cardiomyopathy; or • Multifocal atrial tachycardia; or • Other uses of radiofrequency catheter ablation not indicated above (e.g., AV junction ablation in combination with pacemaker implantation for symptomatic drug-refractory AF); or • Unstable, rapid, multiple or polymorphic VT that cannot be adequately localized by mapping techniques	

Anthem (2011)
Transcatheter Ablation of Arrhythmogenic Foci in the Pulmonary Veins as a Treatment of Atrial Fibrillation (Radiofrequency and Cryoablation)
 	
POLICY #: MED.00064
 	
Effective Date: 01/11/2012
 	
Next Review Date: NR
	NR	This policy is based on 45 references, including RCTs, case controlled trials, and clinical guidelines.	• Anthem considers transcatheter radiofrequency ablation of arrhythmogenic foci in the pulmonary veins medically necessary as treatment for atrial fibrillation when the patient is:
			  • Symptomatic; AND
			  • Is resistant to one or more antiarrhythmic drugs, or has an intolerance of or contraindication to antiarrhythmic drug therapy
			• Anthem considers transcatheter radiofrequency ablation of arrhythmogenic foci in the pulmonary veins investigational and not medically necessary for treatment of atrial fibrillation in ANY of the following circumstances:
			  • As a first-line treatment of atrial fibrillation,
			  • In the absence of resistance to one or more antiarryhthmic drugs, including absence of intolerance or contraindication to antiarrhythmic drug
				• Published literature on radiofrequency pulmonary vein ablation consists primarily of single institution case series. Some studies included only patients with paroxysmal AF, while others included both paroxysmal and persistent AF. The success rate appears greater for paroxysmal AF.
				• For patients with paroxysmal AF, transcatheter radiofrequency pulmonary vein ablation (PVA) may be considered as an alternative for those individuals who are resistant or unable to tolerate AAD therapy. For patients with persistent AF, PVA may be considered as an alternative to either AAD or defibrillator therapy. For patients with permanent AF, PVA may be considered as an alternative to either AAD therapy or ablation of the AV node followed by ventricular pacing. For all types of AF, PVA may not be curative as the sole treatment, but instead might change the underlying myocardial triggers in such a way as to make subsequent pharmacologic therapy more effective.
				• Although there is some published data that suggests that transcatheter cryoablation is feasible and may be an effective treatment for AF, these studies are limited by small numbers and short follow-up. Prospective, randomized, comparative studies are

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
			therapy • Asymptomatic atrial fibrillation • Anthem considers transcatheter cryoablation of arrhythmogenic foci in the pulmonary veins for treatment of atrial fibrillation investigational and not medically necessary.	necessarily to establish the efficacy and safety of this technique. CPT codes if selection criteria is met: 93799, 427.31
Cigna (2011) *Transcatheter Ablation of Arryhthmo-genic Foci in the Pulmonary Veins for the Treatment of Atrial Fibrillation* POLICY #: 0469 Effective Date: 12/15/2011 Next Review Date: 12/15/2012	NR	Radio-frequency catheter ablation: • 4 RCTs • 3 SRs and meta-analyses • 1 HTA • 1 evidence report • 1 Blue Cross/ Blue Shield Technology Evaluation Center (TEC) • 1 guidance document Cryoablation: • 2 case series	• Cigna covers transcatheter radiofrequency ablation of pulmonary veins (pulmonary vein isolation) as medically necessary for the treatment of symptomatic persistent atrial fibrillation. • Cigna covers transcatheter radiofrequency ablation of the pulmonary veins as medically necessary for the treatment of symptomatic paroxysmal atrial fibrillation as an alternative to long-term antiarrhythmic drug therapy when BOTH of the following criteria are met: • Normal or mildly dilated left atria • Normal or mildly reduced left ventricular function • Cigna does not cover transcatheter radiofrequency ablation of the pulmonary veins for any other indication because it is considered experimental, investigational or unproven. • Cigna does not cover any other method of transcatheter ablation of the pulmonary veins for the treatment of atrial fibrillation, including but not limited to cryoablation/cry balloon ablation, because it is considered experimental, investigational or unproven.	• There is Class I, Level of Evidence A that catheter ablation, when performed in experience centers is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease. • There is class I, level of evidence A that indicates that the procedure should be performed, and the benefit outweighs the risk. The procedure is useful and effective, with sufficient evidence from multiple randomized trials or meta-analyses. • There is class IIa, level of evidence indicating that catheter ablation is reasonable to treat symptomatic persistent AF. It is reasonable to perform the procedure and that the benefits outweigh the risks, but additional studies with focused objectives are needed. • There is class IIb, level of evidence A that catheter ablation may be reasonable to treat symptomatic paroxysmal AF in patients with significant left atrial dilation. This procedure may be considered, the benefit is equal to or greater than the risk, but additional studies with broad objectives are needed. The usefulness and efficacy are less well established and greater conflicting evidence exists from multiple randomized trials or meta analyses. • Additional trials are needed to establish the safety and efficacy of

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
				transcatheter cryoablation/cryoballoon ablation, cryothermy, laser balloon catheter, ultrasound balloon catheter and high-density mesh ablator catheter. CPT codes if selection criteria is met: 427.31, 93799

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; **AV:** atrioventricular; AVNRT: Atrioventricular nodal reentrant tachycardia; NR: not reported; PVA: pulmonary vein ablation; RCT: Randomized controlled trial;

3. The Evidence

3.1. Methods of the Systematic Literature Review

3.1.1 Inclusion/exclusion

The focus of this systematic review is on catheter ablation for supraventricular tachyarrhythmia (including atrial fibrillation, atrial flutter, and supraventricular tachyarrhythmia (SVT)). Inclusion and exclusion criteria are summarized in Table 5

- *Population.* Adults with supraventricular tachyarrhythmia including supraventricular tachycardia, atrial flutter, and atrial fibrillation.
- *Intervention.* Catheter ablation including radiofrequency or cryoablation procedures. For atrial fibrillation, we will only consider use of ablation targeting the pulmonary vein or pulmonary vein antrum. For atrial fibrillation and atrial flutter radiofrequency ablation, we will only consider use of 8 mm and irrigated tip catheters, which are considered to be relevant practice according to the AHRQ HTA report[5]. This view was also supported by one of our clinical experts.
- *Comparator.* Medical therapy, Maze or other surgical procedures, therapies intended to control rhythm, different commonly used ablation approaches
- *Outcomes.* For efficacy/effectiveness, outcomes include freedom from recurrence of supraventricular tachyarrhythmia, improvement of symptoms (including palpitation, tachypnea, chest stuffiness, syncope, anxiety), quality of life and other patient-reported outcomes, medication use (e.g., anticoagulants), hospitalization/readmission, repeat ablation, intermediate outcomes (e.g., maintenance of sinus rhythm, chamber size, ejection fraction), and prevention of mortality, embolic events, and congestive heart failure. For safety, outcomes include procedure or treatment related mortality, embolic complications, congestive heart failure, and other reported complications.
- *Study design.* The focus for all key questions will be placed on studies with the least potential for bias.

Table 5. Summary of inclusion and exclusion criteria (PICO):

Study Component	Inclusion	Exclusion

Population	Adults with supraventricular tachyarrhythmia, to include:
	• Atrial fibrillation (AF)
	• Atrial flutter (AFl)
	• Supraventricular tachycardia:
	  • Sinus tachycardia (inappropriate sinus tachycardia and sinus nodal reentrant tachycardia)
	  • Atrioventricular reentrant tachycardia (AVRT), (including Wolff-Parkinson-White (WPW) Syndrome)
	  • Atrioventricular nodal reentrant tachycardia (AVNRT)
	  • Atrial tachycardia (including focal and multifocal)
	  • Focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia
		• Patients < 18 years of age
		• Ventricular tachycardia and paroxysmal ventricular tachycardia
		• Any tachyarrhythmia that does not originate from the sinus node, atrial tissue, or junctional sites between the atria and ventricles
		• Bradycardia
		• Patients with prior catheter ablation

Intervention	• Catheter ablation:
	  • For atrial fibrillation, we will only consider studies evaluating targeting of the pulmonary vein or pulmonary vein antrum and use of irrigated or 8 mm catheter tips
	  • Radiofrequency
	  • Cryoablation
	  • Cryoballoon
		• Ablation as an adjunct to surgery, intraoperative ablation
		• Use of non-FDA approved devices or devices not in final stages for FDA approval
		• For atrial fibrillation, studies in which PV electrical isolation was not the goal of ablation (e.g., standalone RFA of complex fractionated atrial electrograms (CFAE) and linear ablations), as well as studies of ablation of the atrioventricular (AV) junction will be excluded
		• Complete AV node ablation requiring pacemaker implantation

Comparator	• Medical therapy • Maze or other surgical procedures • Therapies intended to control rhythm • For Key Question 2, comparison of common different ablation approaches will be considered (e.g., pulmonary vein isolation versus pulmonary vein isolation with additional areas (lines))	• Comparisons of different techniques used in catheter ablation (i.e., imaging, types of catheter tips, etc.) • Cardioversion alone (ie., in the absence of antiarrhythmic medical therapy)
Outcomes	<u>Efficacy/effectiveness:</u> • Freedom from recurrence of supraventricular tachyarrhythmia • Improvement of symptoms (including palpitation, tachypnea, chest stuffiness, syncope, anxiety) • Quality of life and other patient-reported outcomes • Medication use (e.g. need for anticoagulants) • Hospitalization/ readmission	• Non clinical outcomes

Study Component	Inclusion	Exclusion
	• Repeat ablation • Intermediate outcomes (including maintenance of sinus rhythm, chamber size, ejection fraction) • Prevention of mortality, embolic events, and congestive heart failure. <u>Safety: (procedure or treatment related)</u> • Mortality • Embolic complications (including stroke or ischemic attack) • Congestive heart failure • Other reported complications (including pericardial effusion or cardiac tamponade, pulmonary vein stenosis, atrioesophageal fistula, deep vein thrombosis, peripheral vascular complication (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury) • Radiation exposure	
Study Design	• For all key questions, focus will be placed on studies with the least potential for bias. • Key Question 1: Randomized controlled trials (RCTs) to assess efficacy; nonrandomized studies (for atrial fibrillation only, we will require at least 100 patients and a low risk of bias) will be considered to evaluate effectiveness. If no comparative studies are available for a given condition, prospective case series with N ≥ 50 will be considered. • Key Question 2: RCTs comparing PVI with different ablation approaches for atrial fibrillation only • Key Question 3 (safety), RCTs and non-randomized studies from Key Question 1 will be included. Additional comparative studies and prospective case series designed specifically to evaluate adverse events will also be considered. • Key Question 4 (differential efficacy): RCTs or high quality cohort studies with low risk of bias • Formal, full economic studies will be sought for Key Question 5	• Non-clinical studies, studies of technique, imaging. • Studies with < 10 patients per treatment group. • Studies with less than 80% of patients having first time catheter ablation will be excluded • For Key Questions 1, 2, and 4: studies with less than 6 months' follow-up. • For Key Question 3, retrospective case series and prospective case series with N < 1000 (AF), N < 100 (atrial flutter), or N < 500 (SVTs) will be excluded. • For Key Question 3, case series that evaluated only surgical or medical approaches will be excluded.
Publication	• Studies published in English in peer-reviewed journals, published HTAs or publically available FDA reports • Full, formal economic analyses (e.g. cost-utility studies) published in English in HTAs or in a peer-reviewed journals published after those represented in previous HTAs	• For atrial fibrillation and atrial flutter, studies with a publication date prior to 2000 will be excluded on the basis that they used conventional tips that are obsolete for these diagnoses • Studies reporting only on the technical aspects of ablation (e.g., imaging, type of catheter, etc.)

Study Component	Inclusion	Exclusion
		• Abstracts, editorials, letters • Unpublished studies • Duplicate publications of the same study which do not report on unique outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

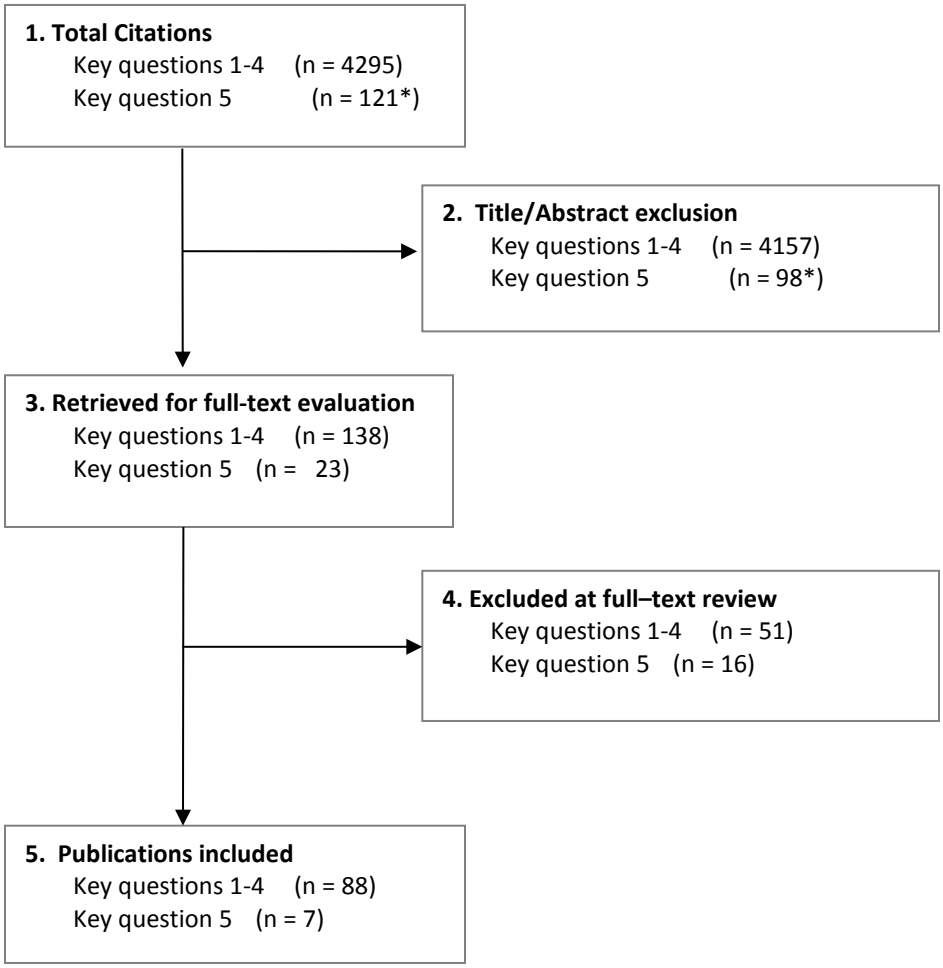
3.1.2 Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search and selection took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Electronic databases searched included PubMed, EMBASE, *The Cochrane Library*, EconLIT, AHRQ, and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports.

For atrial fibrillation, the databases were searched from November 1, 2008 through September 25, 2012. For Key Questions 1 and 2, the search performed in the AHRQ HTA on catheter ablation for atrial fibrillation[5] was accepted and used; this search identified studies published between 2000 and December 2008, thus our search identified relevant studies published after the AHRQ HTA's search period through September, 2012. For atrial flutter, databases were searched from January 2000 through September 27, 2012. For both atrial fibrillation and atrial flutter, the literature search was limited to studies published in 2000 and later in order to restrict studies to those that used catheters relevant to current practice (ie., 8 mm and irrigated tip catheters). For supraventricular tachyarrhythmias (other than atrial fibrillation or atrial flutter), databases were searched from January 1985 through September 27, 2012Reference lists of all eligible studies were also searched. The search strategies for PubMed are shown in Appendix B. Figure 2 shows a flow chart of the results of all searches for primary studies. Articles excluded at full-text review are listed in Appendix C.

Figure 2. Flow chart showing results of literature search



* Key Question 5 studies are a subset of the 4295 studies identified for Key Questions 1-4.

3.1.3. Data extraction

Reviewers extracted the following data from the included clinical studies: study location, study funding, study design, patient demographics, study interventions, inclusion/exclusion criteria, follow-up time, study outcomes, and complications/adverse events. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. For comparative studies for key questions 1 and 2, data abstraction from the recent AHRQ HTA on catheter ablation for atrial fibrillation was accepted and used; thus we did not re-abstract efficacy or effectiveness data from the studies included in that report. We did re-abstract safety data, however. For economic studies, study funding and location, population characteristics, treatments evaluated, methods used (including perspective, model used, and time horizon), evidence base and assumptions, cost estimates, economic parameters and

perspectives, and results for base-case and any sensitivity analyses were abstracted. Detailed abstraction tables may be found in Appendix F.

3.2. Methods of Data Analysis and Evidence Synthesis

3.2.1 Data analysis and synthesis of evidence

The results were grouped according to patient diagnosis: atrial fibrillation, atrial flutter, and supraventricular tachyarrhythmias (AVNRT, AVRT and WPW Syndrome, sinus tachycardia, atrial tachycardia, focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia, and mixed populations). The results were further subdivided by the comparator treatment. Study characteristics and outcomes were summarized in text and/or summary tables. For Key Question 1, when possible we pooled data from RCTs: requirements for pooling include similar methodology, similar clinical characteristics (including study population, interventions, and how the outcome was determined)[162], and similar follow-up in at least three RCTs. Data were not pooled from nonrandomized trials.

Since the primary focus of catheter ablation should be the improvement in clinical health outcomes (e.g. freedom from recurrence, mortality, and stroke) and since such outcomes have been a primary focus in most technology assessments, they are the primary outcomes reported in this assessment. The following table (Table 6) presents a description of these and other less commonly reported measures from the comparative studies included in this HTA.

Table 6. Description of outcomes instruments used in comparative studies evaluating clinical health outcomes.

Outcome measure	Clinician or patient reported	Instrument type	Components	Score range	Interpretation
Kansas City Cardiomyopathy Questionnaire (KCCQ)[163, 164]	Patient	Congestive heart failure	Subscales (# items) Physical limitation (6) Symptoms (8) Self-efficacy and knowledge (2) QoL/mood (3) Social limitation (4) Two summary scores: Functional Status Clinical Summary	0 - 100	Higher scores indicate better health
Minnesota Living with Heart Failure Questionnaire (MLHFQ)[164, 165]	Patient	Heart failure	Subscales (# items) Physical aspects of daily life (9) Emotional/psychological (5) Social/economic (7) Physical and emotional domains can be summed.	0 - 105	Lower scores indicate better quality of life
Short-Form 36 (SF-36) (Short Form 36 health survey questionnaire) [166]Ware, 1992 #742}	Patient	Generic	8 subscales (# items) Physical functioning (10) Role limitations due to physical health problems (4) Bodily pain (2) General health (5) Vitality (4) Social functioning (2) Role limitations due to emotional problems (3) Mental health (5)	0–100 for each subscale (total score not used)	Lower score indicate greater disability
Symptom Checklist-Frequency and Severity Scale[167]	Patient	AF-specific	Symptom frequency	0–64	Lower scores = less symptomatic
			Symptom severity	0-48	

AF: atrial fibrillation; QoL: quality of life

Outcomes from formal economic analyses may include various incremental cost effectiveness ratios and related parameters, e.g. cost per quality of life year gained.

3.2.2. Study quality assessment: Level of evidence (LoE) evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine, precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group, and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).

Details of the Level of Evidence (LoE) and overall strength of evidence (SoE) methodology are found in Appendix D. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Appendix D. Standardized guidelines were used to determine the LoE for each study included in this assessment.

3.3. Quality of Literature Available

Quality of studies retained.

The systematic search of bibliographic data bases produced 4295 citations using the search strategy in Appendix B.

For Key Question 1:

- *Atrial fibrillation:* Overall, a total of nine RCTs (ten studies) and five cohort studies met our inclusion criteria. Twelve studies were excluded at full-text review (see Appendix C for details). The included studies were classified as follows:
    - PVI versus AADs: Nine RCTs (10 studies)[6-16] and four cohort studies[17-20] which compared pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) were included. One RCT was included which compared cryoablation with AADs[21]. All RCTs were considered to be at moderately low risk of bias (Class of Evidence II), and all cohort studies were considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.
    - PVI versus Cox-Maze surgery: One retrospective cohort study[22] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

- *Atrial flutter:* One RCT met our inclusion criteria. Three studies were excluded at full-text review (see Appendix C for details). The included study was classified as follows:
    - Catheter ablation versus AADs*:* One RCT[23] met our inclusion criteria. The study was considered to be at moderately low risk of bias (Class of Evidence

II) after methodological evaluation. No cohort studies were identified that met our inclusion criteria.

- *Supraventricular tachycardias:* Overall, one RCT and six cohort studies met our inclusion criteria. Four studies were excluded at full-text review (see Appendix C for details). The included studies were classified as follows:
  - *AVNRT*
    - Catheter ablation versus AADs*:* One prospective cohort study[24] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.
    - Catheter ablation versus open perinodal dissection surgery: Two cohort studies[25, 26] met our inclusion criteria, both of which were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation.
    - Catheter ablation versus no treatment: One cohort study[27] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.
  - *AVRT, including WPW Syndrome*
    - Catheter ablation versus AADs or surgery: One small retrospective cohort study[28] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.
    - Catheter ablation versus no treatment: One RCT[29] was identified that met our inclusion criteria and was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation.
  - Mixed populations
    - Catheter ablation versus AADs: One prospective cohort study[30] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

No other comparative studies on any other diagnosis of interest met our inclusion criteria for Key Question 1.

For Key Question 1a:

- *Atrial fibrillation:* No studies met our inclusion criteria; no studies were reviewed at full-text level.

- *Atrial flutter:* Four RCTs[31-34] were included that compared radiofrequency ablation with cryoablation in patients with typical atrial flutter. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. One study was excluded at full-text review (see Appendix C for details).

- *SVTs:* Four RCTs[35-38] were included that compared these procedures in patients with SVT. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. Two studies were excluded at full-text review (see Appendix C for details).

For Key Question 2:

- *Atrial fibrillation:* Thirty-five RCTs[39-73] met our inclusion criteria and reported outcomes related to freedom from recurrence for AF using different approaches of PVI. We identified studies that compared the following approaches: PVI versus wide-area circumferential ablation (WACA), PVI with or without additional left sided ablation lines, PVI with or without additional right sided ablation lines, PVI with or without complex fractionated electrograms, and a variety of miscellaneous comparisons were also found. One study was considered to have a low risk of bias (Class of Evidence I) and the remaining 34 studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. Fifteen studies were excluded at full-text review (see Appendix C for details).

For Key Question 3:

- *Atrial fibrillation:* All adverse events and complications from the comparative studies included in Key Question 1 were reported. In addition, we identified six prospective case series[74-79] that were specifically designed to evaluate adverse events in at least 1000 patients who underwent PVI for atrial fibrillation. We also identified four prospective case series[80-83] that evaluated the incidence of procedure-related esophageal lesions in at least 100 AF patients. These studies were included as this PVI-related complication was not reported in any of the comparative or larger prospective case series. All case series are considered to have a high risk of bias (Class of Evidence IV). Eight case series were excluded at full-text review (see Appendix C for details).

- *Atrial flutter:* All adverse events and complications from the comparative studies included in Key Question 1 were reported. In addition, we identified six prospective case series[84-89] that were specifically designed to evaluate adverse events in at least 100 patients who underwent catheter ablation for atrial flutter. All case series are

considered to have a high risk of bias (Class of Evidence IV). No case series were excluded at full-text review.

- *SVTs:* All adverse events and complications from the comparative studies included in Key Question 1 were reported. In addition, six case series[87-92] that were specifically designed to evaluate adverse events following catheter ablation in at least 500 patients with SVT were also identified for inclusion. All case series are considered to have a high risk of bias (Class of Evidence IV). Six case series were excluded at full-text review (see Appendix C for details).

For Key Question 4:
All comparative studies included in Key Question 1 were evaluated for analysis of the differential efficacy/effectiveness or safety of catheter ablation compared to other treatments. No additional studies were identified for inclusion.

For Key Question 5:

- *Atrial fibrillation:* Five studies[93-97] were identified that met our inclusion criteria. Six studies were excluded at full-text review (see Appendix C for details).
- *Atrial flutter:* No studies were identified that met our inclusion criteria. One study was excluded at full-text review (see Appendix C for details).
- *SVTs:* Two studies[98, 99] were identified that met our inclusion criteria. Nine studies were excluded at full-text review (see Appendix C for details).

Tables summarizing the level of evidence and additional aspects of critical appraisal can be found in APPENDICES D and E.

4. Results

4.1. Key Question 1: Does catheter ablation improve patient outcomes in persons with supraventricular tachyarrhythmias compared with other treatment options: What is the evidence for comparative efficacy and effectiveness over the short term and longer term?

4.1.1 Atrial fibrillation

Pulmonary vein isolation (PVI) versus Anti-Arrhythmic Drugs (AADs)

Summary

Studies. Nine RCTs (10 studies)[6-16] and four cohort studies[17-20] which compared pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) were included. One RCT was included which compared cryoablation with AADs[21]. All RCTs were considered to be at moderately low risk of bias (Class of Evidence II), and all cohort studies were considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

Summary.

Freedom from recurrence: There is moderate quality evidence that radiofrequency PVI results in significantly more freedom from recurrence in both the short- and long-term. In the short-term, this conclusion is supported by data from 7 RCTs and PVI is associated with a 50% (95% CI, 43%, 58%) decrease in risk of recurrence compared with AADs. In the long-term, the conclusion is supported by data from 1 RCT and PVI is associated with a 61% (95% CI, 48%, 70%) decrease in risk of recurrence compared with AADs. There is low quality evidence that cryo-PVI results in significantly more freedom from recurrence in the short- term as supported by data from 1 RCT. Cryo-PVI is associated with a 63% (95% CI, 52%, 70%) decrease in risk of recurrence compared with AADs.

Mortality, stroke, and congestive heart failure (not procedure-related): There is low quality evidence that suggests that there is no difference between radiofrequency PVI and AADs in the 12 month rates of mortality (1 RCT), stroke (2 RCTs), and congestive heart failure (1 RCT) not attributed to any treatment given. There is similarly low quality evidence that suggests that there is no difference between cryo-PVI and AADs in the 12 month rates of mortality, stroke, and congestive heart failure not attributed to any treatment given based on data from 1 RCT.

Randomized controlled trials (RCTs) (Efficacy)

Ten RCTs (11 studies) which compared pulmonary vein isolation with medical therapy in patients with atrial fibrillation were identified for inclusion[6-16, 21]. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the

Appendix contains the details on the methodological quality grading for each study. The majority of studies failed to meet more than one criterion for a good quality RCT.

Demographics

A total of 1216 patients were enrolled in these ten RCTs[6-16, 21]. Nine trials utilized radiofrequency ablation[6-16], while one employed cryoablation[21]. Study enrollment ranged from 30 to 245 patients. Mean patient age ranged from 51 to 64 years, and 57% to 84% of patients were male. Two studies limited enrollment to patients with paroxysmal atrial fibrillation (PAF)[7, 11, 12], and in a third study, 96% of patients had PAF[15]. Three studies included a mix of patients with PAF (41% to 67%) and persistent[6, 8] or permanent[14] AF, and two studies only enrolled patients with persistent[9] or chronic[10] AF. Two studies did not specify the nature of the atrial fibrillation[16, 21]. Mean symptom duration ranged from 5 to 73 months. One study included only patients with type 2 diabetes mellitus[6], and another limited enrollment to those with advanced heart failure[9]. Only the RCT by Wazni and colleagues[15] specifically stated that patients were receiving ablation or medical treatment for rate control as a first-line therapy; six of the remaining RCTs required documented failure of at least one anti-arrhythmic drug (AAD) for inclusion[6, 8, 11, 12, 14, 16, 21]. All but one study reported short-term outcomes only: the majority of studies followed patients for 12 months, though one study reported outcomes at six months[9] and another at nine months[16]. One study reported outcomes at both 12 and 48 months[12]. Follow-up ranged from 93% to 100%, except in one study for which the percent of patients with complete follow-up could not be determined[16]. See Table 7.

Table 7. Study population overview: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Mean age (years)	% male	Paroxysmal AF (%)	Symptom duration (months)	Comorbidities	Follow-up duration (% followed)	Study funding
RF PVI							
Forleo (2009)[6] N = 70	64	61 %	41%	38.9 (mean) (range, 17-66)	Diabetes mellitus type 2 (100%)	12 months (100%)	NR (last author receives lecture fees from St. Jude Medical and serves on the advisory board of Biosense-Webster)
Jais (2008)*[7] N = 112	51	84 %	100%	66 (median)	none	12 months (96%)	Biosense Webster, St. Jude Medical, Bard, Medtronic, Biotronik, Canada Research Chair in Electrophysiolo

Study	Mean age (years)	% male	Paroxysmal AF (%)	Symptom duration (months)	Comorbidities	Follow-up duration (% followed)	Study funding
							gy and Adult Congenital Heart Disease, Canadian Institute of Health Research, Fonds de Recherche en Sante, Boston Scientific, CryoCath Technologies
Krittayaphong (2003)*[8] N = 30	52	63 %	67%	56 (mean)	none	12 months (93%)	Faculty of Medicine, Siriraj Hospital
MacDonald (2011)[9] N = 41	63.3	78 %	0%	53.3 (mean)	Advanced heart failure: NYHA functional class: II: 10%; III: 90%; IV: 0%	6 months (93%)	Chief Scientist Office, Scotland (grant number CZB4475)
Oral (2006)*[10] N = 146	56	65 %	0%	54 (mean)	none	12 months (100%)	Ellen and Robert Thompson Fibrillarion Research Fund Other conflict of interest includes Ablation Frontier, Biosense Webster, St. Jude Medical, Guidant, and Medtronic
Pappone (2006/2011)*[11, 12] N = 198	56	67 %	100%	72	none	12 months (2006) (100%) 48 months (2011) (95%)	Arrhythmology Department, San Raffaele University Hospital (Italy); note that Dr. Pappone has advisory board appointments at Johnson & Johnson, St. Jude Medical, Medtronic Inc., Boston Scientific Co., and Biotronik SE

Study	Mean age (years)	% male	Paroxysmal AF (%)	Symptom duration (months)	Comorbidities	Follow-up duration (% followed)	Study funding
Stabile (2006)*[14] N = 137	62	57 %	67%	73 (mean)	none	12 months (97%)	Biosense-Webster, Italy
Wazni (2005)*[15] N = 70	54	NR	96%	5 (mean)	none	12 months (96%)	"Supported in part by an unrestricted educational grant from Acuson, a division of Siemens Medical Solutions", which did not participate in any part of the study.
Wilber (2010)*[16] N = 167	55.7	66.5%	NR	68 (mean)	none	9 months % f/u NR	Biosense Webster
Cryo-PVI							
STOP AF Pivotal Trial (2010)[21] N = 245	56.6	77.1%	NR	NR	none	12 months (93%)	Medtronic

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; NYHA: New York Heart Association; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency

Intervention details (Table 8)

Ablation group. While the approaches and techniques used by the included studies varied, all employed pulmonary vein isolation (PVI), and eight ablated additional lines[6-12, 14, 16]. Anti-arrhythmic drugs were permitted after ablation in eight of the studies [6, 8-12, 14, 16, 21], many limited their use to the first one to three months post-ablation. The most commonly utilized drug was amiodarone. Cardioversion was applied periprocedurally in two trials in order to convert patients in atrial fibrillation to sinus rhythm; 13% to 95% of patients in these studies underwent cardioversion[8, 9]. Three studies permitted cardioversion upon early recurrence; 3% to 25% of patients received this treatment[6, 10, 14]. Repeat ablation was permitted in six RCTs; 6% to 43% of patients underwent repeat ablation in these studies[7, 9-12, 16, 21]. Timing of repeat ablation varied; while most studies allowed reablation only within the blanking period, others required that patients wait until after the blanking period to be considered for repeat ablation.

Anti-arrhythmic drug (AAD) group. Medical therapy protocols varied. Patients were treated with a previously unused AAD in seven of the trials[6-8, 11, 12, 15, 16, 21]. One study

enrolled patients with chronic AF and did not specify that patients receive a new to them AAD[10], while another specifically stated that patients receive "continued medical therapy for rate control"[9]. One study treated nearly a third of patients in the control group with a drug that had previously failed[14]. Cardioversion was used in half of the studies, usually if persistent atrial fibrillation was present or if the patient had early recurrence[6, 8, 10, 14, 15]. Further details are available in Table 8.

Table 8. Treatment overview: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Treatment group	Addi-tional lines?	Isolation success (% of pts)	AADs (Duration)	Reablation? (% of pts, time period)	Cardioversion? (% of pts)	Crossover? (% of pts, time period)	Blanking period? (Duration)
RF PVI								
Forleo (2009)[6]	RF cPVI (n = 35)	Yes	100%	New AAD (1 – 3 months)	None	If early recurrence (3%)	Not permitted	5 weeks
	AADs (n = 35)	-	-	New AAD(s) (NR)	-	If persistent AF present or early recurrence (NR)		
Jais (2008)*[7]	RF cPVI (n = 53)	Yes	94 – 100%*	None	≤ 2 permitted (43%, ≤ 90 days)	None	Yes, if failure (9%, ≥ 3 mos.)	90 days
	AADs (n = 59)	-	-	New AAD(s) (NR)	-		(63%, ≥ 3 mos.)	
Krittayaphong (2003)*[8]	RF cPVI (n = 15)	Yes	NR	New AAD (amiodarone) (3 months)	None	Periprocedural to convert AF to SR (13%)	NR	NR
	AADs ± cardioversion (n = 15)	-	-	New AAD (amiodarone) (study duration)	-	If persistent AF present (NR)		
MacDonald (2011)[9]	RF cPVI (n = 22)	Yes	NR	Amiodarone (3 months)	Permitted (29%, ≥ 3 mos.)	Periprocedural to convert AF to SR (95%)	NR	3 months
	AADs (n = 19)	-	-	"continued medical treatment for rate control" (NR)	-	NR		
Oral (2006)*[10]	RF cPVI (n = 77)	Yes	100%	Amiodarone (3 months)	If recurrent AF or flutter (32%, mean 204 days)	If early recurrence and persistence of AF (23%)	-	None
	AADs (n = 69)	-	-	Amiodarone (3-6 months)	-	If not in SR at study initiation and/or at 6 wks (97%)	Yes, if failure (77%, > 3 mos.)	

Study	Treatment group	Addi-tional lines?	Isolation success (% of pts)	AADs (Duration)	Reablation? (% of pts, time period)	Cardioversion? (% of pts)	Crossover? (% of pts, time period)	Blanking period? (Duration)
Pappone (2006/2011)*[1, 12]	RF cPVI (n = 99)	Yes	NR	AADs (6 weeks)	If recurrent symptomatic AF at end of blanking period (6%, ≥ 6 days)	NR	-	6 days
	AADs (n = 99)	-	-	New AAD(s) (amiodarone, flecanide, and/or solatol (≤ 2 drugs)) (NR)	-		If failure after 2 trials of AADs (42%, > 6 weeks)	
Stabile (2006)*[14]	RF cPVI (n = 68)	Yes	100%	Amiodarone (NR)	None	If recurrence (25%, < 1 month)	NR	1 month
	AADs (n = 69)	-	-	AADs (preferably amiodarone) (NR)	-	If recurrence (22%, < 1 month)		
Wazni (2005)*[15]	RF PVI (first-line therapy) (n = 33)	No	100%	NR	None	None	NR	2 months
	AADs (first-line therapy) (n = 37)	-	-	New AADs (duration of study)	-	If recurrence (54%, < 2 mos.)		
Wilber (2010)*[16]	RF cPVI (n = 106)	Yes	100%	Previously ineffective AAD permitted	≤ 2 permitted (12.6%, ≤ 80 days)	NR	-	3 months
	AADs (n = 61)	-	-	New AAD (NR)	-		If treatment failure (59%, mean 3.9 mos.)	14 days
Cryo PVI								
STOP AF Pivotal Trial (2010)[21]	Cryo cPVI (n = 163)	NR	> 95%	Previously failed AF drug (8%, ≥ 90 days)	1 permitted (29%, ≤ 90 days)	NR	-	90 days

Study	Treatment group	Addi-tional lines?	Isolation success (% of pts)	AADs (Duration)	Reablation? (% of pts, time period)	Cardioversion? (% of pts)	Crossover? (% of pts, time period)	Blanking period? (Duration)
	AADs (n = 82)	-	-	New AAD (flecainide, propafenone, or solatol) (NR)	-		If chronic treatment failure (76%, NR)	

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: Circumferential pulmonary vein isolation; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized control trials; RF: radiofrequency; SR: sinus rhythm; - : not applicable
* varied by pulmonary vein

Cohort studies (Effectiveness)

Two prospective[17, 18] and two retrospective[19, 20] cohort studies met our inclusion criteria. All studies were considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for each study.

Study details are provided in Table 9; see Appendix Table F1 for more detailed information.

Table 9. Study population overview: Cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Mean age (years)	% male	Paroxysmal AF (%)	Symptom duration (months)	Co-morbidities	Follow-up duration (% followed)	Treatment groups	Study funding
RF PVI								
Lan (2009)[17] N = 240 Prospective	59	79 %	100%	31.4 (mean)	None	12 months (100%)	RF circumferential OR segmental PVI (n = 120) AAD (n = 120)	Grant from Health Research Foundation (Health bureau of Chongqing); authors stated no relationships with MSD and Sanofi-Synthelabo; and that they receive no honoraria or consulting fees from Biosense Webster.
Pappone (2003)[18] N = 1171 Prospective	65	58 %	70%	55.2 (mean)	None	mean 30 months (98.4%)	RF cPVI (n = 589) AAD ± cardioversion (n = 582)	NR
Rossillo (2008)[19] N = 170 Retrospective	62	84 %	16%	96 (mean)*	None	15 ± 7 months (% f/u NR)	RF PVI (n = 85) AAD + cardioversion (n = 85)	NR
Sonne (2009)[20] N = 351 Retrospective	67	68 %	26%	NR	None	mean 69 months (82%)	RF PVI (n = 146) AAD + cardioversion (n = 205)	NR

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: Circumferential pulmonary vein isolation; NR: not reported; PVI: pulmonary vein isolation; RF: radiofrequency

* data reported for ablation group only

Primary Outcomes

Freedom from recurrence (Table 10)

Efficacy (8 RCTs)
Cumulative freedom from recurrence of AF or atrial arrhythmias was described as a primary outcome in eight RCTs. Note that the definition of freedom from recurrence varied by study (see Table 10 footnotes for detailed definitions).

Seven RCTs consistently reported that the percentage of patients who had freedom from recurrence in the short-term (through 6 to 12 months) was greater post-RFA compared with medical therapy; this difference was statistically meaningful in all seven studies (Table 10a, c)[6-8, 11, 14-16, 21]. One RCT reported similar long-term results, with 73% of patients who underwent PVI still free from recurrence at 48 months follow-up, while only 12% of patients in the control group had remained free from recurrence (and had not crossed over and received ablation)[12] (Table 10b). Nearly all of the studies employed a "blanking period", a period ranging from 6 days to 3 months following treatment during which arrhythmia recurrence was not evaluated (see Table 8 for details)[6, 7, 9, 11, 12, 14-16, 21]. Following ablation, scars need time to form, thus recurrences of AF may be a transient phenomenon. This period was used by some studies to perform repeat ablation, cardioversion, and adjust anti-arrhythmic drug(s) and doses.

Meta-analysis of recurrence in the short-term (≤12 months) was performed (Figure 3). One study was not included in the meta-analysis for the following reason: patients who underwent reablation during the blanking period could be considered to have freedom from recurrence (1 study)[7]. For this analysis, six RCTs[6, 8, 11, 12, 14-16] involving a total of 672 patients were included and the data showed that patients were nearly three times as likely to have cumulative freedom from recurrence after the blanking period at one year if they had been treated with radiofrequency ablation compared with anti-arrhythmic drug treatment (risk ratio, 2.89 (95% confidence interval (2.05, 4.09)); $P < .00001$). Similar results were seen in the subset of 61 patients in one study who received first-line therapy (relative risk, 2.36 (95% CI, 1.50, 3.70); $P = .0002$) and in the 550 patients who received second-line therapy (relative risk, 3.05 (95% CI, 2.00, 4.67); $P < .00001$).

In the long-term (≤48 months), results from one study suggested that the risk of having symptomatic recurrence up to 48 months follow-up was six times less likely following radiofrequency ablation compared with AAD treatment (73% versus 12%, respectively; $P < .001$) (Table 10b)[12].

One RCT similarly found that patients randomized to receive cryoablation had significantly greater freedom from recurrence compared with those patients randomized to receive AADs alone (69.9% versus 7%, respectively; $P < .001$) (Table 10c)[21].

Table 10. Freedom from recurrence: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

a. Short-term outcomes: radiofrequency ablation versus AADs

Study	Outcome*	Time period	Reablation?	Patients who achieved outcome		p-value†
				Ablation	AAD	
Forleo (2009)[6] N = 70	Freedom from recurrence	Cumulative ‡ (≤ 12 mos.)	None	80% (28/35)	43% (15/35)	0.001
Jais (2008)*[7] N = 112	Freedom from recurrence	Cumulative ‡ (≤ 12 mos.)	≤ 2 permitted (43%, ≤ 90 days)	88% (46/52)	24% (13/55)	<.0001
Krittayaphong (2003) [8] N = 30	Freedom from recurrence	Cumulative (≤ 12 mos.)	None	79% (11/14)	40% (6/15)	.018
Pappone (2006/2011)[11, 12] N = 198	Freedom from symptomatic recurrence or failure (including reablation and crossovers)	Cumulative ‡ (≤ 12 mos.)	If recurrent symptom-atic AF at end of blanking period (6%, ≥ 6 days)	89% (85/99)	22% (24/99)	<0.001
Stabile (2006) [14] N = 137	Freedom from recurrence	Cumulative ‡ (≤ 12 mos.)	None	56% (38/68)	9% (6/69)	<0.001 (adjusted HR: 3.2 (95% CI, 2.0, 5.1)
Wilber (2010) [16] N = 167	Freedom from recurrence or failure (including reablation)	Cumulative ‡ (≤ 9 mos.)	≤ 2 permitted (12.6%, ≤ 80 days)	63% (67/106)	17% (10/61)	<0.001
Wazni (2005) [15] N = 70 FIRST LINE THERAPY	Freedom from recurrence	Cumulative ‡ (≤ 12 mos.)	None	88% (28/32)	37% (13/35)	<0.001

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; HR: hazard ratio; NR: not reported; PVI:pulmonary vein isolation; RCTs: randomized controlled trials

b. Long-term outcomes: radiofrequency ablation versus AADs

Study	Outcome*	Time period	Reablation?	Patients who achieved outcome		p-value†
				Ablation	AAD	
Pappone (2006/2011)[11, 12] N = 198	Freedom from symptomatic recurrence or failure (including reablation and crossovers)	Cumulative ‡ (≤ 48 mos.)	If recurrent symptom-matic AF at end of blanking period (6%, ≥ 6 days)	73% (72/99)	12% (12/99)	<0.001

AADs: anti-arrhythmic drugs; AF: atrial fibrillation

b. Short-term outcomes: cryoablation versus AADs

Study	Outcome*	Time period	Reablation?	Patients who achieved outcome		p-value†
				Ablation	AAD	
STOP AF Pivotal Trial (2010)[21] N = 245	Freedom from recurrence or failure (including reablation)	Cumulative ‡ (≤ 12 mos.)	1 permitted (29%, ≤ 90 days)	69.9% (114/163)	7% (6/82)	<.001

AADs: anti-arrhythmic drugs; AF: atrial fibrillation

*Outcome definitions varied by study:

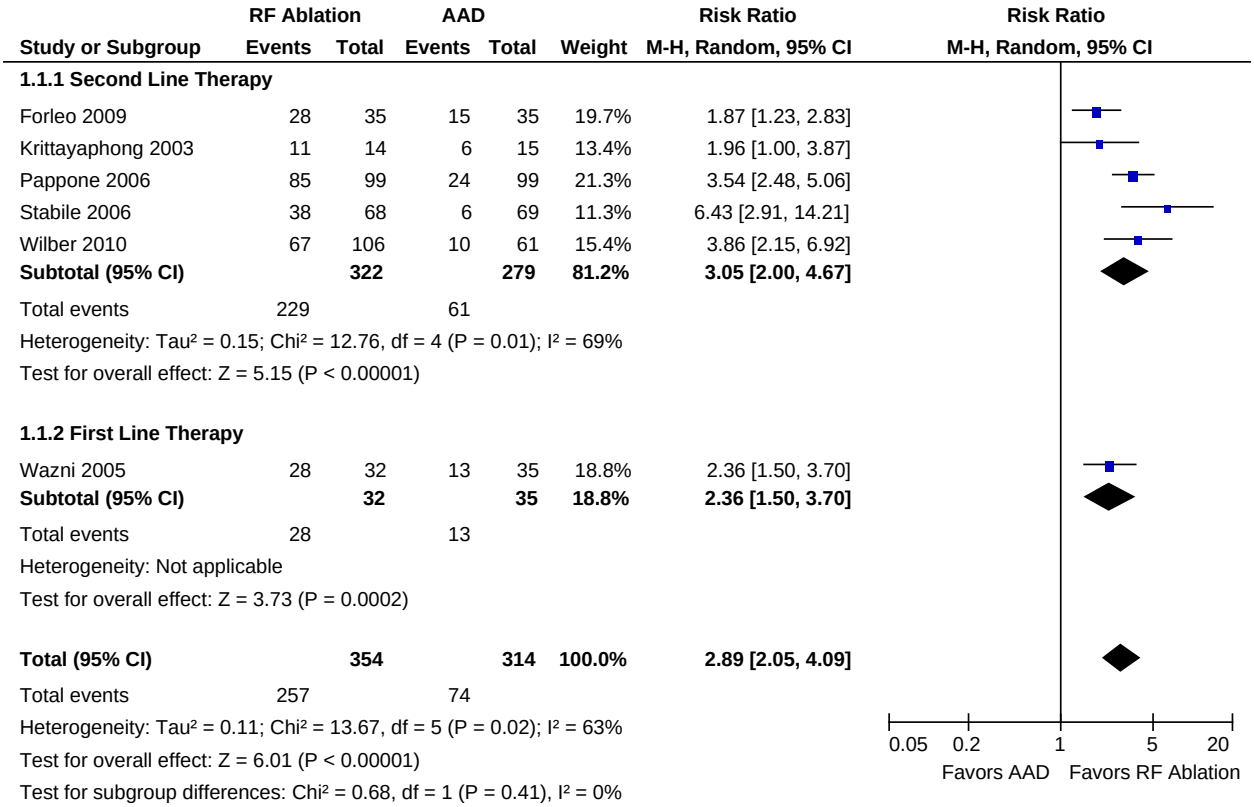
- Forleo (2009), freedom from AF recurrence, "any electrocardiographically confirmed episode of AF or atypical atrial flutter lasting more than 30 seconds…[after 5 weeks and up to] 12 months."
- Jais (2008), freedom from recurrence: "any recurrent AF between months 3 and 12…last[ing] at least 3 minutes and were documented by ECG or reported by the patient as AF, even in the absence of ECG confirmation."
- Krittayaphong (2003), freedom from recurrence was not clearly defined.
- Pappone (2006/2011), "freedom from documented recurrent atrial tachycardia during a 12-month follow-up… The endpoint was reached with the first episode of atrial tachycardia, and cases with a second AAD or repeat ablation procedure were considered failures. Recurrence of atrial tachycardia was defined as atrial tachycardia that lasted at least 30 seconds."
- Stabile (2006), "absence of any recurrence of atrial arrhythmia lasting more than 30 seconds in the one year follow-up period, after the one-month blanking period." (Implied that this would be confirmed by ECG or Holter recordings.)
- Wazni (2005), "recurrence of symptomatic AF or asymptomatic AF lasting longer than 15 seconds during Holter or event monitoring in the one-year follow-up period."
- Wilber (2010), "freedom from protocol-defined treatment failure, which included documented symptomatic paroxysmal AF [between 3 and 12 months]. Patients in the ablation group with repeat ablation after day 80 after the initial ablation, absence of entrance block confirmed in all four pulmonary veins at the end of the ablation procedure, or changes in specified drug regiment postblanking (including class I/III drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and atrioventricular nodal

blocker) were also considered treatment failures, even if they remained free from symptomatic paroxysmal AF. In the AAD group, an adverse event requiring discontinuation of the assigned drug was also considered a treatment failure."

† unadjusted (unless specified)

‡ after blanking period

Figure 3. Meta-analysis: Short-term freedom from recurrence: RCTs comparing radiofrequency pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF.



AADS: anti-arrhythmic drugs; AF: atrial fibrillation; PVI: pulmonary vein isolation; RCTs: randomized controlled trials

Legend: A meta-analysis of six studies was performed to compare the effect of pulmonary vein isolation (PVI) versus anti-arrhythmic drugs (AAD) on maintaining sinus rhythm. The Mantel-Haenszel method was implemented to weight the studies and a random effects model was assumed. The effect size was measured by the relative risk. A distinction was made between "first line" therapy studies and "second line" therapy studies. The results are given above with 95% confidence intervals.

Effectiveness (2 cohort studies) (Table 11)

Two prospective cohort studies also reported on freedom from recurrence. The larger of these studies (N = 1171) reported that nearly twice as many patients had cumulative freedom from symptomatic recurrence (lasting more than 10 minutes) up to a median of 30 months follow-up following ablation compared with AAD treatment (79.6% versus

41.6%, respectively). This difference was statistically significant, with an adjusted hazard ratio of 0.30 (95% CI, 0.24, 0.37; $P < .001$)[18]. In contrast, a second study found a similar percentage of patients had achieved cumulative freedom from recurrence (lasting more than 30 seconds) through 12 months follow-up following ablation versus medical treatment (35% versus 32%; P-value not reported).

The larger study by Pappone and colleagues also reported that the average number of relapse episodes per year after the first recurrence was lower in the ablation group compared with the medical treatment group (2.1 versus 5.4, respectively), with a risk ratio of 0.38 (95% CI, 0.32, 0.56; *P*-value not reported).

Table 11. Freedom from recurrence: cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Outcome	Time period	Reablation?	Patients who achieved outcome		p-value*
				Ablation	AAD	
RF PVI						
Lan (2009)[17] N = 240	Freedom from recurrence (> 30 seconds, ECG/Holter documented)	Cumulative (1 – 12 mos.)	NR	35% (42/120)	32% (38/120)	NR
Pappone (2003)[18] N = 1171	Freedom from symptomatic recurrence (> 10 minutes, ECG documented)	Cumulative (≤ median 30 mos.)	If recurrent symptom-atic AF at end of blanking period (6%, ≥ 6 days)	79.6% (469/589)	41.6% (242/582)	NR (adjusted HR: 0.30 (95% CI, 0.24, 0.37; *P* < .001)

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; HR: hazard ratio; NR: not reported; PVI: pulmonary vein isolation; RF: radiofrequency
* unadjusted (unless specified)

Mortality (not procedure/ treatment-related) (Table 12)

Efficacy (5 RCTs)

Four RCTs reported overall mortality rates up to 9 to 12 months follow-up[7, 10, 14, 16]. In the radiofrequency PVI groups, data from three RCTs suggest that 1.7% (3/178) of patients died during the follow-up period of causes not related to the ablation procedure (range, 1% to 3% of RF PVI patients per study)[10, 14, 16]. Cause of death included: pneumonia seven months post-PVI[10], brain hemorrhage nine months post-PVI (note that the patient had experienced a periprocedural stroke)[14], and acute myocardial infarction nine months post-PVI. In the AAD control group, data from two RCTs suggest a mortality rate of 3.2% (4/128) (3% in both studies)[7, 14]; again, these are deaths not attributed to the treatment given. Cause of death included myocardial infarction[7], acute myeloid leukemia[7], sudden death[14], and cancer[14]. As evidenced by the data in Table 12, only one RCT reported mortality rates for both treatment groups: Stabile reported that death unrelated to treatment[14] occurred in 1% (1/68) of patients randomized to receive radiofrequency PVI and in 3% (2/69) of patients randomized to receive AADs. The remaining three RCTs reported mortality in only one of the two treatment groups but gave no data for the other treatment group[7, 10, 16]. This lack of data makes it difficult to draw conclusions regarding the incidence of death following PVI compared with AADs.

One RCT reported that death not attributed to the procedure or treatment occurred in 0.6% of patients randomized to receive cryo-PVI (1/163) and in 0% of patients randomized to the AAD group (0/82). The cause of death in the cryo-PVI group was myocardial infarction and multiple organ failure ten months post-procedure[21].

The remaining RCTs did not report any data regarding mortality.

Table 12. Mortality rates: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study (length f/u)	Treatment group	Thromboembolic-related deaths	Cardio-related deaths	Other causes of death	Mortality summary*
RF PVI					
Forleo (2009)[6] 12 months	RF cPVI (n = 35)	NR	NR	NR	NR
	AADs (n = 35)	NR	NR	NR	NR
Jais (2008)[7] (12 months)	RF cPVI (n = 53)	NR	NR	NR	NR
	AADs (n = 59)	NR	Myocardial infarction (MI) (n = 1)	Acute myeloid leukemia (n = 1)	3% (2/59)
Krittayaphong (2003)[8] (12 months)	RF cPVI (n = 15)	NR	NR	NR	NR
	AADs ± cardioversion (n = 15)	NR	NR	NR	NR
MacDonald (2011)[9] (6 months)	RF cPVI (n = 22)	NR	NR	NR	NR
	AADs (n = 19)	NR	NR	NR	NR
Oral (2006)[10] 12 months	RF cPVI (n = 77)	NR	NR	Pneumonia (7-months post-procedure) (n = 1)	1% (1/77)
	AADs (n = 69)	NR	NR	NR	NR
Pappone (2006/2011)[11, 12] (12 months)	RF cPVI (n = 99)	NR	NR	NR	NR
	AADs (n = 99)	NR	NR	NR	NR

Study (length f/u)	**Treatment group**	**Thromboembolic-related deaths**	**Cardio-related deaths**	**Other causes of death**	**Mortality summary***
(48 months)	RF cPVI (n = 99)	NR	NR	NR	NR
	AADs (n = 99)	NR	NR	NR	NR
Stabile (2006)[14] (12 months)	RF cPVI (n = 68)	Brain hemorrhage (at 9 months)- patient had periprocedural stroke (n = 1)	NR	NR	1% (1/68)
	AADs (n = 69)	NR	"Sudden death" (n = 1)	Cancer (n = 1)	3% (2/69)
Wazni (2005)[15] (12 months)	RF PVI (first-line therapy) (n = 33)	NR	NR	NR	NR
	AADs (first-line therapy) (n = 37)	NR	NR	NR	NR
Wilber (2010)[16] (9 months)	RF cPVI (n = 106)	NR	Acute MI (9 months post-procedure) (n = 1)	NR	0.9% (1/106)
	AADs (n = 61)	NR	NR	NR	NR
Cryo PVI					
STOP AF Pivotal Trial (2010)[21] (12 months	Cryo PVI (n = 163)	0% (0/163)	MI and multiple organ failure (10 months post-procedure) (n = 1)	0% (0/163)	0.6% (1/163)
	AADs (n = 82)	0% (0/82)	0% (0/82)	0% (0/82)	0% (0/82)

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; CPVI: circumferential pulmonary vein isolation; f/u: follow-up; MI: myocardial infarction; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency

* not including treatment- or procedure-related deaths, which are reported in Key Question 3.

Effectiveness (3 cohort studies) (Table 13)

One prospective[18] and two retrospective[19, 20] studies reported that death was less common following ablation compared with medical treatment; these results were shown to be statistically meaningful in the two studies that performed statistical analysis.

In a large prospective study of 1171 patients designed to evaluate mortality following radiofrequency PVI compared with medical therapy, Pappone and colleagues (2003) found that at the latest follow-up (mean of 30 months), significantly fewer patients in the ablation group had died compared with those in the medical group (6.5% versus 14.3%, respectively), with an all-cause mortality hazard ratio of 0.46 (95% CI, 0.31, 0.68; $P <$ .001). Similar differences were found for death resulting from cardiac- or stroke-related events (3.1% versus 10.1%, respectively), with a hazard ratio of 0.45 (95% CI, 0.31, 0.64; $P <$ .001). Further, the observed survival probabilities were significantly higher following ablation compared with medical therapy at one (98% versus 96%), two (95% versus 90%), and three (92% versus 86%) years, respectively ($P <$ .001)[18].

Sonne and colleagues found that patients treated with antiarrhythmic drugs and cardioversion had a much higher risk of death compared with those who underwent PVI (16.5% versus 2.1%), with an adjusted hazard ratio of 4.9 ($P =$ .001)[20].

Finally, Rossillo et al reported that fewer patients in the ablation group died during the follow-up period (mean of 15 months) compared with those in the control group (0% versus 2%, respectively), however no statistical analysis was performed[19].

Table 13. Mortality rates: cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study (length f/u)	**Treatment group**	**Thromboembolic-related deaths**	**Cardio-related deaths**	**Other causes of death**	**All-cause mortality***
RF PVI					
Lan (2009)[17] 12 months	RF circumferential OR segmental PVI (n = 120)	NR	NR	NR	NR
	AAD (n = 120)	NR	NR	NR	NR
Pappone (2003)[18] Mean 30 months	RF cPVI (n = 589)	0.4% (2/589) Ischemic stroke (n = 2)	2.7% (16/589) Congestive heart failure (n = 8) MI (n = 8) Sudden (n = 0)	3.4% (20/589) Respiratory failure (n = 5) Cancer (n = 8) Infection (n = 3) "Other" (n = 4)	6.5% (38/589)
	AAD ± cardioversion (n = 582)	2.4% (14/582) Ischemic stroke (n = 14)	7.7% (45/582) Congestive heart failure (n = 23) MI (n = 10) Sudden (n = 12)	4.1% (24/582) Respiratory failure (n = 7) Cancer (n = 9) Infection (n = 2) "Other" (n = 6)	14.3% (83/582) ($P < .001$)
Rossillo (2008)[19] 15 ± 7 months	RF PVI (n = 85)	0% (0/85)	NR	NR	0% (0/85)
	AAD + cardioversion (n = 85)	2% (2/85) Stroke (> 30 days after start of study) (n = 2)	NR	NR	2% (2/85)

Study (length f/u)	**Treatment group**	**Thromboembolic-related deaths**	**Cardio-related deaths**	**Other causes of death**	**All-cause mortality***
Sonne (2009)[20] mean 69 months	RF PVI (n = 146)	0% (0/146) Stroke (n = 0)	2.1% (3/146) Congestive heart failure (n = 1) MI (n = 2) Sudden (n = 0)	0% (0/146) Respiratory failure (n = 0) Cancer (n = 0) Infection (n = 0) "Other" (n = 0)	2.1% (3/146)
	AAD + cardioversion (n = 205)	1.5% (3/205) Stroke (n = 3)	9.8% (20/205) Congestive heart failure (n = 20) MI (n = 0) Sudden (n = 0)	5.4% (11/205) Respiratory failure (n = 3) Cancer (n = 3) Infection (n = 2) "Other" (n = 3)	16.5% (34/205) (*P* = .001)

AADS: anti-arrhythmic drugs; AF: atrial fibrillation; CPVI: circumferential pulmonary vein isolation; f/u: follow-up; MI: myocardial infarction; NR: not reported; PVI: pulmonary vein isolation; RF: radiofrequency
* not including treatment- or procedure-related deaths, which are reported in Key Question 3.

Stroke (not procedure/ treatment-related; including death from thromboembolic events)

Efficacy (4 RCTs) (Table 14)

Two RCTs reported no thromboembolic events in either the radiofrequency PVI (0/68) or AAD (0/72) treatment groups through 12 months follow-up[6, 15]. One RCT reported that thromboembolic events occurred in 1% of patients randomized to the AAD treatment group (1/69), but did not report any data for the PVI group. The patient in the AAD group experienced a transient ischemic attack[14].

One RCT found that 0.6% (1/163) of patients randomized to receive cryo-PVI and 0% (0/82) experienced a thromboembolic event not related to the treatment received. The difference was not statistically significant (P = 1.0).

Table 14. Stroke rates: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study (length f/u)	**Treatment group**	**Thromboembolic events (not treatment-related)**
RF PVI		
Forleo (2009)[6] 12 months	RF cPVI (n = 35)	0% (0/35)
	AADs (n = 35)	0% (0/35)
Jais (2008)[7] (12 months)	RF cPVI (n = 53)	NR
	AADs (n = 59)	NR
Krittayaphong (2003)[8] (12 months)	RF cPVI (n = 15)	NR
	AADs ± cardioversion (n = 15)	NR
MacDonald (2011)[9] (6 months)	RF cPVI (n = 22)	NR
	AADs (n = 19)	NR
Oral (2006)[10] 12 months	RF cPVI (n = 77)	NR
	AADs (n = 69)	NR
Pappone (2006/2011)[11, 12] (48 months)	RF cPVI (n = 99)	NR
	AADs (n = 99)	NR

Study (length f/u)	Treatment group	Thromboembolic events (not treatment-related)
Stabile (2006)[14]	RF cPVI (n = 68)	NR
(12 months)	AADs (n = 69)	1% (1/69) (transient ischemic attack)
Wazni (2005)[15]	RF PVI (first-line therapy) (n = 33)	0% (0/33)
(12 months)	AADs (first-line therapy) (n = 37)	0% (0/37)
Wilber (2010)[16]	RF cPVI (n = 106)	NR
(30 days)	AADs (n = 61)	NR
Cryo PVI		
STOP AF Pivotal Trial (2010)[21]	Cryo cPVI (n = 163)	0.6% (1/163)
(12 months	AADs (n = 82)	0% (0/82) (P = 1.0)

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; CPVI: circumferential pulmonary vein isolation; f/u: follow-up; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency

Effectiveness (2 cohort studies) (Table 15)

Two cohort studies reported on thromboembolic events that were not procedure-related. Pappone et al. (2003) reported 14 procedure-unrelated thromboembolic events (including two hemorrhagic strokes, four ischemic strokes, and eight transient ischemic attacks) occurred in the radiofrequency PVI group (14 events in 589 patients). There were 49 thromboembolic events in the AAD group (49 events in 582 patients), which consisted of seven hemorrhagic strokes, 15 ischemic strokes, and 27 transient ischemic attacks. Patients were followed for a mean of 30 months. No statistical analysis was performed[18].

Rossillo and colleagues reported that no PVI patients experienced a procedure-related thromboembolic event (0/85), while 5% of AAD patients experienced such an event (4/85) (cerebrovascular accident and fatal stroke in two patients each)[19].

Table 15. Stroke rates: cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study (length f/u)	**Treatment group**	**Thromboembolic events** (not treatment-related)
RF PVI		
Lan (2009)[17] 12 months	RF circumferential OR segmental PVI (n = 120)	NR
	AAD (n = 120)	NR
Pappone (2003)[18] Mean 30 months	RF cPVI (n = 589)	14 events Hemorrhagic stroke (2 events) Ischemic stroke (4 events) Transient ischemic attack (n = 8)
	AAD ± cardioversion (n = 582)	49 events Hemorrhagic stroke (7 events) Ischemic stroke (15 events) Transient ischemic attack (27 events) (P = NR)
Rossillo (2008)[19] 15 ± 7 months	RF PVI (n = 85)	0% (0/85)
	AAD + cardioversion (n = 85)	5% (4/85) Cerebrovascular accident (n = 2) Stroke (fatal) (n = 2) (P = NR)
Sonne (2009)[20] mean 69 months	RF PVI (n = 146)	NR*
	AAD + cardioversion (n = 205)	NR*

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; CPVI: circumferential pulmonary vein isolation; f/u: follow-up; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency
* this study only reported stroke as a cause of mortality but did not report the total rate of stroke or other thromboembolic events.

Congestive heart failure

Efficacy (2 RCTs)
Two RCTs reported the incidence of congestive heart failure following PVI compared with medical treatment. Because of heterogeneity in patient populations, ablation techniques, and length follow-up, meta-analysis was not performed.
The STOP AF Trial reported that 0.6% (1/163) in the ablation group and none in the medical therapy group (0/82) was hospitalized for congestive heart failure through the 12 months follow-up[21].

In a four-year follow-up study of 198 patients, Pappone et al (2011) reported that there were no cases of new-onset heart failure in any patient following either ablation or medical treatment[12].

Effectiveness (1 prospective cohort study)
Pappone and colleagues (2003) reported that the incidence of heart failure was lower in those who had received ablation compared with patients treated with medical therapy (5.4% (32/589) versus 9.8% (57/582), respectively; *P*-value not reported)[18].

Secondary Outcomes

Improvement of symptoms (including palpitation, tachypnea, chest stuffiness, syncope, anxiety)

Efficacy (3 RCTs) (Table 16)
Three RCTs reported on improvement of symptom severity and/or frequency (aside from symptomatic AF recurrence, which was reported above). Two trials reported scores from the patient-reported atrial fibrillation Symptom Checklist- Frequency and Severity Scale. Three RCTs reported on symptom frequency. Krittayaphong et al. found no difference in the mean reduction in the number of symptomatic episodes per month following ablation compared with medical therapy (42 versus approximately 25 fewer episodes per month; P = .335)[8]. Two trials reported AF symptom frequency scores[7, 16]. While both studies found that patients in the ablation group had a greater improvement in symptom frequency compared with those in the medical treatment groups (as seen by lower scores), the difference was only statistically significant in one of those studies[16]. Both trials found a statistically significant greater improvement in symptom severity scores following treatment with ablation compared with medical treatment ($P \leq .001$).

Table 16. AF Symptom Frequency and Severity Checklist scores: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Outcome	Follow-up duration	Score difference from baseline*		p-value†
			Ablation	AAD	
RF PVI					
Jais (2008)[7] N = 112	Symptom frequency checklist score	12 months	-14.0	-12.2	.10
Wilber (2010)[16] N = 167	Symptom frequency checklist score	12 months	-11.1	-.07	< .001
Jais (2008)[7] N = 112	Symptom severity checklist score	12 months	-11.5	-8.8	.001
Wilber (2010)[16] N = 167	Symptom severity checklist score	12 months	-9.4	0.0	<.001

AADs: anti-arrhythmic drugs; AF: atrial fibrillation;PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency
* lower score difference equals lower severity of symptoms

Effectiveness

No cohort studies reported on symptoms (outside of symptomatic recurrence, which was reported above).

Quality of life and other patient-reported outcomes

Efficacy (7 RCTs) (Table 17)

SF-36 subscale scores were reported in seven[6-9, 12, 15, 16] of the included trials. In general, there was greater improvement from baseline in these scores in patients randomized to receive radiofrequency PVI compared with those randomized to receive AADs, though the differences between treatment groups were not always statistically significant. Follow-up ranged from 6 to 12 months, except for one study in which it was 48 months. The study which reported SF-36 outcomes at 48 months found no statistically significant differences in improvements from baseline in SF-36 scores between treatment groups[12]. The physical component score was significantly more improved from baseline in the ablation group than in the medical treatment group in three of four studies reporting. The mental component score and physical functioning scores were both more improved from baseline following ablation versus medical treatment in two of four studies reporting,

while general health scores were similarly improved in two of three studies reporting. Bodily pain, social functioning, and role emotional subscales were each reported by two studies and had significantly greater improvements following ablation versus AADs in one study. There were no statistically significant differences in score improvements from baseline between treatment groups for the mental health (2 studies), role physical (1 study), or vitality (1 study) subscales.

MacDonald and colleagues also measured quality of life using two additional questionnaires- the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). There were no statistically significant differences between treatment groups in either outcome at 6 months follow-up[9].

Table 17. SF-36 Outcomes: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

		SF-36 Subscale Score: Improvements from baseline									
Study	**Treatment group**	**Physical component score**	**Mental component score**	**Physical functioning**	**Bodily pain**	**General health**	**Social functioning**	**Role physical**	**Role emotional**	**Mental health**	**Vitality**
RF PVI											
Forleo (2009)[6] (12 months)	RF cPVI (n = 35)	NR	NR	8.4 points higher in PVI group ($P < .05$)	5.3 points higher in PVI group ($P < .05$)	8.9 points higher in PVI group ($P < .05$)	7.7 points higher in PVI group ($P < .05$)	NR	6.8 points higher in PVI group ($P < .05$)	NR	NR
	AADs (n = 35)										
Jais (2008)[7] (12 months)	RF cPVI (n = 53)	7.2	9.7	NR	NR	NR	NR	NR	NR	NR	NR
	AADs (n = 59)	6.0 (*P*-value NR, but P = .001 between groups for final scores)	9.1 (*P*-value NR, but P = .001 between groups for final scores)								
Krittayaphong (2003)[8] (12 months)	RF cPVI (n = 15)	NR	NR	23*	NR	20	NR	NR	NR	NR	NR
	AADs ± cardioversion (n = 15)			-3* ($P = .691$)		2 ($P = .048$)					
MacDonald (2011)[9]	RF cPVI (n = 22)	4	0.4	NR	NR	NR	NR	NR	NR	NR	NR

		SF-36 Subscale Score: Improvements from baseline									
Study	**Treatment group**	**Physical component score**	**Mental component score**	**Physical functioning**	**Bodily pain**	**General health**	**Social functioning**	**Role physical**	**Role emotional**	**Mental health**	**Vitality**
(6 months)	AADs (n = 19)	-1 (*P* = .042)	5.9 (*P* = .07)								
Pappone (2011)[11, 12]	RF cPVI (n = 99)	7.9	9.2	16	12	14	19	19	16	15	15
(48 months†)	AADs (n = 99)	6.9 (*P* > .05)	7.5 (*P* > .05)	14 (*P* > .05)	11 (*P* > .05)	10 (*P* > .05)	20 (*P* > .05)	19 (*P* > .05)	14 (*P* > .05)	11 (*P* > .05)	13 (*P* > .05)
Wazni (2005)[15]	RF PVI (first-line therapy) (n = 33)	NR	NR	26	NR	NR	NR	NR	NR	0	NR
(12 months)	AADs (first-line therapy) (n = 37)			6 *P* = .001						4 (*P* = .62)	
Wilber (2010)[16]	RF cPVI (n = 106)	8.5	6.9	NR	NR	NR	NR	NR	NR	NR	NR
(9 months)	AADs (n = 61)	1.6 (*P* < .001)	0.4 (*P* < .001)								

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; CPVI: circumferential pulmonary vein isolation; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency

* values estimated from graph

† data not reported at 12 months

Effectiveness (1 cohort study)
One prospective study found greater improvements following ablation compared with medical therapy from baseline to 12 months in the SF-36 physical component scores (~11 versus ~1 (estimated from graphs); *P*-value not reported) and mental component scores (~7 versus ~3 (estimated from graphs); *P*-value not reported)[18]. The authors used multivariate analysis to show that recurrence in AF was independently associated with significant reductions in both physical and mental functioning in the medical therapy group ($P < .001$).

Maintenance of sinus rhythm

Efficacy (4 RCTs) (Table 18)
Three RCTs found that a greater percentage of patients were in sinus rhythm at 6 to 12 months follow-up; however these results were not statistically meaningful in the one study that assessed these data[9-11] nor in the meta-analysis (risk ratio, 2.2 (95% CI, 0.92, 4.89; $P = .08$) (Figure 4). One of these RCTs reported that a greater proportion of patients randomized to receive ablation was in sinus rhythm at 48 months follow-up compared with those randomized to receive AADs (73% versus 57%; $P = .017$). This is despite the fact that the majority of patients in the AAD treatment group in sinus rhythm at final follow-up had crossed over and received ablation (44 of 56 patients)[12].

Jais and colleagues reported that patients randomized to PVI experienced a significantly greater reduction in AF burden by the end of the 12-month follow-up period, with a median within-subject reduction of 10.0 minutes and 3.2 minutes, respectively ($P < .0001$)[7].

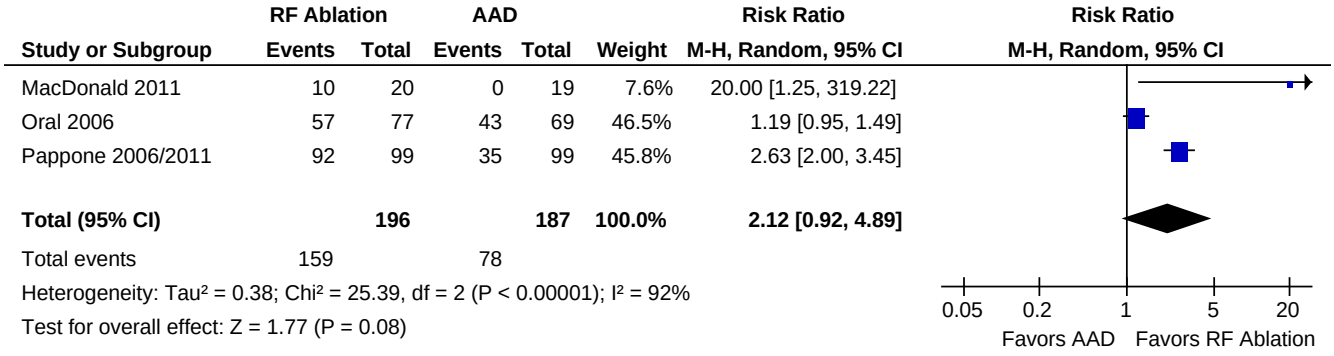
Table 18. Sinus rhythm at last follow-up: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Outcome*	Time period	Reablation?	Patients who achieved outcome		p-value*
				Ablation	AAD	
MacDonald (2011)[9] N = 41	Sinus rhythm	at 6 mos.	Permitted (29%, ≥ 3 mos.)	50% (10/20)	0% (0/19)	NR
Oral (2006) [10] N = 146	Sinus rhythm in absence of AADs	at 12 mos.	If recurrent AF or flutter (32%, mean 204 days)	74% (57/77)	62% (43/69)	.05

Study	Outcome*	Time period	Reablation?	Patients who achieved outcome		p-value*
				Ablation	AAD	
Pappone (2006/2011)[11, 12]	Sinus rhythm	at 12 mos.	If recurrent symptom-matic AF at end of blanking period (6%, ≥ 6 days)	93% (NR)	35% (NR)	NR
N = 198		at 48 mos.		73% (72/99)	57%† (56/99)	.017

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency
* unadjusted (unless specified)
† 44 of the 56 patients in SR at last follow-up had crossed over and undergone RFA.

Figure 4. Meta-analysis: Sinus rhythm at last follow-up: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF



AADs: anti-arrhythmic drugs; AF: atrial fibrillation; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency

Legend: A meta-analysis of three studies was performed to compare the effect of pulmonary vein isolation (PVI) versus anti-arrhythmic drugs (AAD) on sinus rhythm at final follow-up. The Mantel-Haenszel method was implemented to weight the studies and a random effects model was assumed. All studies are considered "second line" therapy studies. The results are given above with 95% confidence intervals.

Effectiveness (1 cohort study)

One retrospective cohort study found that twice as many patients were in sinus rhythm at a mean of 15 ± 7 months following ablation compared with AAD treatment (82% (70/85) versus 40% (34/85), respectively; *P*-value not reported)[19].

Anticoagulant use

Efficacy (2 RCTs)
Two RCTs reported the percentage of patients who achieved discontinuation of anticoagulation therapy by 12 months follow-up. Jais and colleagues found that more patients were able to discontinue this therapy after treatment with ablation compared with medical treatment alone (60% (31/52) versus 34% (18/53); $P = .02$)[7]. Forleo et al. reported that 83% (29/35) of ablation patients were able to discontinue anticoagulants by 12 months, but didn't report this information for the control group. In this study, all patients were treated with anticoagulants, which could be discontinued after 6 months in the absence of recurrence[6].

Effectiveness
No cohort studies reported on hospitalizations or readmissions.

Hospitalization/readmission

Efficacy (4 RCTs)
Hospital readmission was reported by a total of four RCTs, all of which found that hospitalizations were less common in the ablation group than in the medical treatment group. Due to differences in reporting (i.e., readmission for any reason versus for only cardiac-related causes), ablation technique (i.e., radiofrequency versus cryo), and length, follow-up meta-analysis was not performed.

In the short term, two studies reported on hospitalizations following radiofrequency PVI. Forleo and colleagues reported that significantly fewer patients in the ablation group required readmission (for any reason) in the 12 month follow-up period than did those in the ablation group (9% versus 34%, $P = .01$)[6]. Stabile et al. (2006) reported that the median number of hospitalizations (for any reason) per patient in the 12 months follow-up was lower in the ablation group compared with the AAD group (1 versus 2). This difference, however, was not statistically significant and the range of visits per patient was the same in both treatment groups (1 to 2 visits per patient)[14].

Pappone et al. (2011) reported that the total number of hospitalizations up to 48 months' follow-up for cardiac-related causes (and the corresponding number of visits per patient) was much lower in the ablation group than in the control group (0.61 versus 3.3 visits per patient; *P*-value not reported)[12]. These numbers included those who underwent ablation after the beginning of study due to repeat ablation (6% of those in the ablation group) or crossover (42% of those in the AAD group).

Finally, the STOP AF Pivotal trial for cryoablation compared with medical treatment reported that while fewer patients required hospitalization for any reason in the ablation group, the difference was not statistically significant (1.8% versus 7.3%; $P = .064$). However, statistically fewer patients in the ablation group were readmitted specifically

for AF recurrence or ablation compared with the control group (0.6% (1/163) versus 6.1% (5/82); $P = .017$)[21].

Effectiveness
No cohort studies reported on hospitalizations or readmissions.

Repeat ablation

Efficacy (6 RCTs) (see Table 8)
Repeat ablation for recurrent arrhythmia was permitted in six of the ten included RCTs[7, 9-12, 16, 21]. Three of these trials only permitted repeat ablation during the blanking period of 80 to 90 days; the percentage of patients who underwent repeat ablation in these studies ranged from 12.6% to 43%[7, 16, 21]. Two of the remaining studies allowed repeat ablation only after the blanking period of 6 days to 3 months; 6% to 29% of patients underwent a repeat procedure. One study did not employ a blanking period, and 32% of patients received repeat ablation at a mean of 204 days following the first procedure. Overall, a range of 6% to 43% of patients randomized to receive ablation underwent a repeat ablation procedure.

Effectiveness
No cohort studies reported on repeat ablation procedures.

Measures of cardiac function: atrial size and ventricular ejection fractions

Efficacy (3 RCTs) (Table 19)
Changes in left atrial diameter (LAD) were evaluated by two RCTs. While one study found a significantly lower final LAD in the ablation group compared with the AAD group (4.0 ± 0.5 versus 4.5 ± 6 cm; $P < .001$) (both groups had the same mean LAD at baseline)[10], the other study reported no difference in the mean change in LAD from baseline between treatment groups[7].

As reported by one RCT, left ventricular end-diastolic dimension (LVED) was not different between treatment groups at final follow-up (P = .35), with a mean change from baseline of -0.2 and 0.0 cm in the ablation and AAD treatment groups, respectively[7]. Two studies evaluated left ventricular ejection fraction (LVEF) and found no difference in the change from baseline to 6 to 12 months' follow-up between treatment groups. However, one of these studies also reported LVEF as measured by radionuclide ventriculography (instead of cardiovascular magnetic resonance (CMR)) and saw a significantly greater change from baseline to 6 months in the ablation group compared with the AAD group (8.2 ± 12.0% versus 1.4 ± 5.9%; $P = .032$). The authors commented that they were unsure how to interpret the discrepancy between the CMR and radionuclide measurements. CMR yields images that are a composite of the cardiac cycles acquired during a single breath-hold, while radionuclide ventriculography measures LVEF on a composite beat from 20 minutes of recorded heartbeats[9]. Regardless, the sample size of this study was

quite small, with 22 patients enrolled in the ablation group and 19 in the medical therapy group.

There was no difference in the change in right ventricular ejection fraction (RVEF) between the PVI and AAD group as reported by one small RCT[9].

Table 19. Measures of cardiac function: RCTs comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Study	Treatment group	LAD (cm)	LVED (cm)	LVEF (method NR) (%)	LVEF (CMR) (%)	Radionuclide LVEF (%)	RVEF (%)
Jais (2008)[7] (12 months)	RF cPVI (n = 53)	-0.1	-0.2	2%	NR	NR	NR
	AADs (n = 59)	-0.1 (*P* = NS)	0.0 (*P* = NS)	-1% (*P* = NS)			
MacDonald (2011)[9] (6 months)	RF cPVI (n = 22)	NR	NR	NR	4.5 ± 11.1%	8.2 ± 12.0%	4.3 ± 8.1%
	AADs (n = 19)				2.8 ± 6.7% (*P* = .6)	1.4 ± 5.9% (*P* = .032)	1.2 ± 4.9% (*P* = .17)
Oral (2006) [10] (12 months)	RF cPVI (n = 77)	-0.5	NR	NR	NR	NR	NR
	AADs (n = 69)	0.0 (*P* = NR)*					

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; CMR: cardiovascular magnetic resonance; CPVI: circumferential pulmonary vein isolation; f/u: follow-up; LAD: left atrial diameter; LVED: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency; RVEF: right ventricular ejection fraction
* p-value was statistically significant for differences in measurements between treatment groups at final follow-up, but was not assessed for the change from baseline between groups.

Effectiveness (1 cohort study)
One retrospective cohort study by Lan and colleagues reported a small mean decrease from baseline in LAD 12 months following PVI (-0.017 cm) and a slight increase in the AAD group (0.112 cm)[17]. A direct statistical analysis comparing results between the PVI and AAD treatment groups was not performed.

Pulmonary vein isolation (PVI) versus Cox-Maze surgery

Summary
Studies. One retrospective cohort study[22] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

Summary.
Freedom from recurrence: There is insufficient evidence that radiofrequency PVI results in significantly less freedom from recurrence in the absence of AADs compared with Cox Maze surgery (mean follow-up: 54 months). This conclusion is supported by data from 1 cohort study and PVI is associated with a 26% increase in risk of recurrence compared with Cox Maze surgery. There is insufficient evidence that radiofrequency PVI results in similar rates of freedom from recurrence in the presence of AADs compared with Cox Maze surgery (74% versus 84%, respectively; mean follow-up: 54 months). This conclusion is supported by data from 1 cohort study.

Stroke: There is insufficient evidence that radiofrequency PVI results in similarly low rates of stroke compared with Cox Maze surgery (1.7% versus 2%, respectively; mean follow-up: 54 months). This conclusion is supported by data from 1 cohort study.

Randomized controlled trials (RCTs) (Efficacy)
No RCTs were identified that met our inclusion criteria.

Cohort studies (Effectiveness)
One retrospective cohort study by Stulak and colleagues (2011)[22] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for each study.
Study details are provided in Table 20; see Appendix Table F1 for more detailed information. Note that 10.0% (29/289) of patients had undergone previous ablation: 11% (21/194) in the ablation group and 6% (8/97) in the Cox-Maze surgery group. In addition, the mean length follow-up was significantly shorter in the ablation group compared with the Cox-Maze group (3.1 versus 5.6 years, respectively; $P < .001$).

Table 20. Study population overview: Cohort studies comparing pulmonary vein isolation (PVI) with Cox-Maze Surgery in patients with AF

Study	**Mean age** (years)	**% male**	**Paroxysmal AF** (%)	**Symptom duration** (months)	**Co-morbidities**	**Follow-up duration** (% followed)	**Treatment groups**	**Study funding**
Stulak (2011)[22] N = 289 Retro-spective	54 (median)	70%	71% "intermittent"	49 (mean)	None	RFA: 3.1 yrs (median) Cox-Maze: 5.6 yrs (median) (*P* < .001) (92%)	RF PVI (n = 194 patients matched 2:1 to Cox-Maze patients) Cox-Maze Surgery (n = 97)	NR

AF: atrial fibrillation; PVI: pulmonary vein isolation; RF: radiofrequency

Primary Outcomes

Freedom from recurrence

Effectiveness (1 cohort study)
At last follow-up (median of 3.1 years in the ablation group and of 5.6 years in the Cox-Maze surgery group), there was not a statistically significant difference in the overall freedom from atrial fibrillation between treatment groups (74% versus 84%; $P = .078$)[22]. However, significantly fewer patients in the ablation group had freedom from AF without taking AADs (56% versus 82%; $P < .001$). Note that the authors did not report the outcome in the Cox-Maze group at a median of 3.1 years follow-up, making the data difficult to interpret.

The authors did report that at 5 years follow-up, significantly fewer patients in the ablation group had freedom from AF recurrence compared with those in the Cox-Maze group (28% versus 87%; $P < .001$)[22].

Note that a second ablation procedure was performed in 24% of ablation and in 7% of Cox-Maze surgery patients ($P < .001$) (see section on repeat ablation below for additional details)[22].

Mortality

Effectiveness
This cohort study did not report mortality rates.

Stroke

Effectiveness
A total of 3 patients in the ablation group suffered a thromboembolic event (stroke in 2 patients and transient ischemic attack in 1 patient) (1.7%) compared with 2 patients in the Cox-Maze surgery group (stroke in 1 patient and transient ischemic attack in 1 patient) (2%). Statistical analysis was not performed. In the ablation group, one of the stroke events occurred immediately following the procedure, and the transient ischemic attack was related to the procedure. In the Cox-Maze surgery group, both events took place 1.5 to 2 months following surgery[22].

Congestive heart failure

Effectiveness
This cohort study did not report incidence of congestive heart failure.

Secondary Outcomes

Improvement of symptoms (including palpitation, tachypnea, chest stuffiness, syncope, anxiety)

Effectiveness
This cohort study did not report on improvement of symptoms.

Quality of life and other patient-reported outcomes

Effectiveness
This cohort study did not report quality of life or other patient-reported outcomes.

Maintenance of sinus rhythm

Effectiveness
This cohort study did not report the percentage of patients in sinus rhythm at last follow-up.

Anticoagulant used

Effectiveness (1 cohort study)
Use of warfarin was significantly higher in the ablation group than in the Cox-Maze surgery group at final follow-up (median of 3.1 years in the ablation group and of 5.6 years in the Cox-Maze surgery group) (55% versus 12%; $P < .001$)[22]. However, the authors did not report the use of anticoagulants in the Cox-Maze group at a median of 3.1 years follow-up, so the data are difficult to interpret.

Hospitalization/readmission

Effectiveness

This cohort study did not report hospitalization/readmission.

Repeat ablation

Effectiveness (1 cohort study)
A second ablation procedure was performed in 24% (41/172) of those patients with complete follow-up in the ablation group, and 8 of these 41 patients underwent a third ablation procedure. Catheter ablation was performed in 7% (6/93) of patients in the Cox-Maze surgery group) ($P < .001$)[22].

Measures of cardiac function: atrial size and ventricular ejection fractions

Effectiveness
This cohort study did not report measures of cardiac function.

4.1.2 Atrial flutter

Catheter Ablation versus Antiarrhythmic Drugs (AADs)

Summary
Studies. One RCT[23] met our inclusion criteria. The study was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. No cohort studies were identified that met our inclusion criteria.

Summary.
Freedom from recurrence: There is moderate quality evidence that catheter ablation results in significantly more freedom from recurrence in the short-term. This conclusion is based on data from 1 RCT, in which ablation is associated with a 26% (95% CI, 13%, 43%) decrease in risk of recurrence compared with AADs.

Mortality: There is low evidence that catheter ablation results in similarly low rates of mortality not attributed to treatment given compared with AADs (11% versus 16%, respectively; mean follow-up: 13 months) based on data from 1 RCT.

Randomized controlled trials (RCTs) (Efficacy)
One RCT was identified that met our inclusion criteria.

This trial compared radiofrequency ablation with medical therapy in patients with atrial flutter[23]. The study was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for the study, which met all but two criteria for a good quality RCT.

Demographics
A total of 104 patients were enrolled in this RCT. For inclusion, patients had to be at least 70 years of age, as these patients represented a population deemed to be at higher risk for atrial fibrillation. Mean patient age was 79 years, and 81% of patients were male. Only patients with one documented episode of symptomatic typical atrial flutter (AFL) who had not received previous antiarrhythmic treatment were included. Approximately one-quarter of patients had a history of atrial fibrillation, and 62% had structural heart disease. At the time of randomization, all patients were in AFL and symptomatic. Patients were followed for a mean of 13 ± 6 months, and 99% of patients were available for complete follow-up. See Table 21; see Appendix Table F2 for more detailed information.

Table 21. Study population overview: RCTs comparing ablation with anti-arrhythmic drugs (AADs) in patients with AFL

Study	Mean age (years)	% male	Type of atrial flutter	Symptom duration (months)	Comorbidities	Follow-up duration (% followed)	Study funding
Da Costa (2006)[23] N = 104	78.5 (age ≥ 70 years)	80.8%	History of one episode of atrial flutter (100%)	NR	Structural heart disease (61.5%)	18 months (mean, 13 ± 6 months) (99%)	Ministère français de la Santé (Projet Hospitalier de Recherche Clinique 2002)

AADs: anti-arrhythmic drugs; AFL:atrial flutter; NR: not reported; PVI: pulmonary vein isolation; RCTs: randomized controlled trials; RF: radiofrequency

Intervention details (Table 22)

Ablation group. Patients underwent radiofrequency catheter ablation with either an 8-mm-tip electrode or an irrigated 5-mm-tip thermocouple catheter. The procedure was terminated upon complete bidirectional isthmus block. No information was provided regarding anti-arrhythmic drugs or cardioversion, thus it is likely that patients in this treatment group did not receive these treatments[23].

Conversion to sinus rhythm control group. Patients were first treated with a loading dose of amidarone for at least one week. Twelve patients (24%) converted to sinus rhythm. The remaining patients then underwent electric intracardiac stimulation following validation of right cavotricuspid isthmus AFL validation; this procedure restored sinus rhythm in 17 patients (33%). For the remaining patients external (n = 12; 24%) or internal (n = 10; 20%) cardioversion was performed, which successfully converted flutter to sinus rhythm. Amiodarone was administered at a loading dose for a minimum of four weeks total, and then the dose was cut in half.

Table 22. Treatment overview: RCTs comparing ablation with conversion to sinus rhythm control group in patients with AFL

Study	**Treatment group**	**Additional lines?**	**Isolation success** (% of pts)	**AADs** (Duration)	**Reablation?** (% of pts, time period)	**Cardioversion?** (% of pts)	**Crossover?** (% of pts, time period)	**Blanking period?** (Duration)
Da Costa (2006)[23]	RF ablation (n = 52)	NR	100%	None	2% (NR)	None	If AF occurrence, then AAD treatment (12%, NR)	NR
	Conversion to sinus rhythm (n = 52)	-	-	Amiodarone	-	Intracardiac atrial overdrive pacing: 76% (if not successful in restoring SR, then-) Cardioversion: 43%	Yes, upon recurrence (30%, NR)	NR

AAD: anti-arrhythmic drugs; NR: not reported; RF: radiofrequency; RCTs: randomized controlled trials; n/a: not applicable

Cohort Studies (Effectiveness)

No comparative cohort studies were identified that met our inclusion criteria.

Primary Outcomes

Freedom from recurrence

Efficacy (1 RCT)
Recurrence of AFL was significantly lower in patients who received radiofrequency ablation compared with those treated with medical therapy to convert to sinus rhythm at a mean of 13 ± 6 months following treatment initiation (4% versus 30%, respectively; $P < .0001$)[23].

There was no difference between ablation and the medical therapy treatment groups in the occurrence of atrial fibrillation of more than 10 minutes duration (25% versus 18%, respectively; P = .3)[23]. Similar results were found when all AF episodes were considered (including those less than 10 minutes' duration) (29% versus 20%, respectively; $P = .4$).

Mortality (not procedure/ treatment-related)

Efficacy (1 RCT) (Table 23)
Death not attributed to treatments received occurred in 11% of patients randomized to receive radiofrequency ablation (6/52) compared with 16% of those randomized to the control group (8/52), a difference which was not statistically significant ($P = .7$)[23]. Cause of death in the ablation group included but was not limited to refractory heart failure and sudden death, and in the control group included but was not limited to massive pulmonary embolism and coronary artery bypass graft surgery. Other causes of death were not reported according to treatment group and included cancer, acute infectious respiratory disease, multivisceral failure, digestive occlusion, and septic shock.

Table 23. Mortality rates: RCTs comparing ablation with anti-arrhythmic drugs (AADs) in patients with AFL

Study (length f/u)	Treatment group	Thromboembolic-related deaths	Cardio-related deaths	Other causes of death	Mortality summary*
Da Costa (2006)[23] 15 ± 6 months	RF ablation (n = 52)	NR	4% (2/52): Refractory heart failure (n = 1); Sudden (n = 1, patients had severe ischemic myocardio-myopathy 9 months postablation)	8%† (4/52)	11% (6/52)
	Conversion to sinus rhythm (n = 51)	2% (1/51) Massive pulmonary embolism (n = 1)	2% (1/51) Death during coronary artery bypass graft surgery (n = 1)	12%† (6/51) Unknown (n = 2)	16% (8/51) (P = .7)

AAD: anti-arrhythmic drugs; AFL: atrial flutter; NR: not reported; RF: radiofrequency; RCTs: randomized controlled trials

* not including treatment- or procedure-related deaths, which are reported in Key Question 3.

† Noncardiovascular causes of death were not reported for each treatment group, but included: cancer (n = 3), acute infectious respiratory disease (n = 2), multivisceral failure (n = 1), digestive occlusion (n = 1), and septic shock (n = 1).

Stroke (not procedure/ treatment-related; including death from thromboembolic events)

Efficacy

As reported in Table 23, thromboembolic-related deaths occurred in 2% of patients in the control group (1/51): one patient experienced a fatal massive pulmonary embolism. Data were not reported for the ablation group[23].

Congestive heart failure

Efficacy

As reported in Table 23, 2% of patients in the ablation group (1/52) experienced refractory heart failure. Data were not reported for the control group[23].

Secondary Outcomes

Maintenance of sinus rhythm

Efficacy
At a mean of 13 ± 6 months follow-up, 94% of patients in both treatment groups were in sinus rhythm. Of the remaining patients, three were in chronic atrial fibrillation (4% (ablation) versus 2% (medical therapy); P = NS) and three were in atrial flutter rhythm (2% (ablation) versus 1% (medical therapy); P = NS)[23].

Repeat ablation

Efficacy
In the ablation group, 2% of patients (1/52) underwent a repeat ablation procedure (and another asymptomatic patient declined to undergo repeat ablation). In the medical therapy group, all patients with recurrence underwent ablation (30% (15/51)). All additional procedures were successful in treating recurrences[23].

The following secondary outcomes of interest were not reported by this RCT:
- Improvement of symptoms (including palpitation, tachypnea, chest stuffiness, syncope, anxiety)
- Quality of life and other patient-reported outcomes
- Anticoagulant use
- Hospitalization/ readmission
- Measures of cardiac function: atrial size and ventricular ejection fractions

4.1.3. Supraventricular tachycardias (SVTs)

4.1.3.1 Atrioventricular nodal reciprocating tachycardia (AVNRT)

Catheter Ablation versus Antiarrhythmic Drugs (AADs)

Summary
Studies. One prospective cohort study[24] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation. No RCTs were identified that met our inclusion criteria.

Summary.
Patient-reported freedom from symptoms: There is insufficient evidence that catheter ablation results in significantly more freedom from recurrence compared with AADs. This conclusion is based on data from 1 cohort study with 1 to 8 years follow-up, in which ablation is associated with a 39% decrease in risk of recurrence compared with chronic use of AADs and in a 55% decrease in risk of recurrence compared with short-term or no use of AADs.

Randomized controlled trials (RCTs) (Efficacy)
No RCTs were identified that met our inclusion criteria that compared catheter ablation to medical therapy in patients with atrioventricular nodal reciprocating tachycardia (AVNRT).

Cohort studies (Effectiveness)
One prospective cohort study[24] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for each study.

The authors prospectively enrolled 93 consecutive patients with atrioventricular node reentrant tachycardia (AVNRT). During the follow-up period, 18 patients received ablation one to eight years after baseline, 24 patients were treated with chronic AADs, and 38 received either AADs for only a few months (n = 35) or no treatment (n = 3)[24]. Study details are provided in Table 24; see Appendix Table F3 for more detailed information.

Table 24. Study population overview: Cohort studies comparing radiofrequency ablation with anti-arrhythmic drugs (AADs) in patients with AVNRT

Study	Mean age (years)	% male	Paroxysmal SVT (%)	Symptom duration (months)	Follow-up duration (% followed)	Treatment groups	Study funding
D'Este (2007)[24] N = 93 Prospective	34	28%	NR	3.7 – 7.1 years (mean)*	13.2 years (mean) (11.4 – 16.1 years) (86%)	RF ablation (n = 18)† (performed 1-8 yrs after baseline)	NR
						Chronic AADs (n = 24)†	
						Brief (or no) AAD: (n = 38)† (3/38 pts rec'd no treatment, remaining patients received AADs for a few months)	

AAD: anti-arrhythmic drugs; AVNRT: Atrioventricular nodal reentrant tachycardia; SVT: supraventricular tachyarrhythmia; RF: radiofrequency
* more precise information was not reported
† after loss to follow-up; treatment was given during (rather than at the beginning of) the follow-up period

Primary Outcomes
The following primary outcomes of interest were not reported by this study:
- Freedom from recurrence
- Mortality rates

- Stroke rates
- Rates of congestive heart failure

Secondary Outcomes

Improvement of symptoms

Effectiveness (1 cohort study)
At baseline, symptoms of AVNRT (not defined) were more frequent in the patients who ended up being treated with radiofrequency ablation one to eight years after baseline compared with those patients who were treated with chronic or short-term AADs (7.8 ± 3.7 versus 3.5 ± 2.3 versus 2.3 ± 1.9 episodes per month, respectively; $P < .015$ for ablation versus short-term AADs). At final follow-up, 100% of patients treated with radiofrequency ablation reported being free from symptoms for the previous three years compared with 61% of those treated with chronic AADs and 45% of those who received AADs for only a few months. No statistical analysis was performed.

The following secondary outcomes of interest were not reported by this study:
- Quality of life and other patient-reported outcomes
- Maintenance of sinus rhythm at last follow-up
- Anticoagulant use
- Hospitalization/ readmission
- Repeat ablation
- Measures of cardiac function: atrial size and ventricular ejection fractions

Catheter Ablation versus Open Perinodal Dissection Surgery

Summary
Studies. Two cohort studies[25, 26] met our inclusion criteria, both of which were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation. No RCTs were identified that met our inclusion criteria.

Summary
Freedom from recurrence: There is insufficient evidence that catheter ablation results in similar rates of freedom from recurrence as open perinodal dissection surgery (85-95% versus 88-94%) based on data from two cohort studies.

Randomized controlled trials (Efficacy)
No RCTs were identified that met our inclusion criteria.

Cohort studies (Effectiveness)
One prospective cohort study[25] and one retrospective cohort study[26] met our inclusion criteria. Both were considered to be at moderately high risk of bias (Class of Evidence

III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for this study. These two studies treated AVNRT patients by modifying (but not completely destroying) the atrioventricular node. In patients who received radiofrequency catheter ablation, the fast, slow, or combined slow and fast pathways were targeted. Surgical atrioventricular (AV) node modification ("skeletonization") interrupts all atrial inputs of the AV node except the deep left atrial node, which preserves atrioventricular conduction while blocking the sources of the tachycardia. Although these therapies target the AV node, pacemaker implantation was not typical: in the study by Kimman and colleagues it was only needed in 3.3% of the ablation patients and 8% of the surgery patients[25], while in the Natale study 2% of ablation patients and 2% of surgery patients had inadvertent complete AV block and required a pacemaker[26]. Study details are provided in Table 25; see Appendix Table F3 for more detailed information.

Table 25. Study population overview: Cohort studies comparing radiofrequency ablation with skeletonization surgery in patients with AVNRT

Study	Mean age (years)	% male	Paroxysmal SVT (%)	Symptom duration (months)	Follow-up duration (% followed)	Treatment groups	Study funding
Kimman (1999)[25] N = 146 Prospective	44.1	27%	NR	13.9 years (mean)	28 months (mean) (100%)	RF ablation (n = 120)	NR
					53 months (mean) (100%)	Perinodal dissection surgery (n = 26)	
Natale (1993)[26] N = 96 Retrospective	36	18%	NR	NR	10 months (mean) (100%)	RF ablation (n = 43)	Heart and Stroke Foundation of Ontario, Toronto, Canada.
					38 months (mean) (100%)	Perinodal dissection surgery (n = 53)	

AAD: anti-arrhythmic drugs; AVNRT: Atrioventricular nodal reentrant tachycardia; SVT: supraventricular tachyarrhythmia; RF: radiofrequency

Primary Outcomes

Freedom from recurrence

Effectiveness (2 cohort studies)

Kimman et al. (1999) reported freedom from AVNRT recurrence in 85% (102/120) of ablation patients compared with 88% (23/26) of patients who underwent open perinodal dissection ("skeletonization") surgery[25]. Natale and colleagues (1993) found that patients

had similar rates of freedom from tachycardia recurrence regardless of whether they were treated with radiofrequency catheter ablation or open perinodal surgery (95% (41/43) versus 94% (50/53), respectively)[26]. Statistical analysis was not performed in either study, and no blanking period was used.

The following primary outcomes of interest were not reported by this study:

- Mortality (not procedure/ treatment-related)
- Stroke (not procedure/ treatment-related)
- Congestive heart failure

Secondary Outcomes

Repeat ablation

Effectiveness (1 cohort study)

Kimman et al. treated patients with confirmed AVNRT recurrence with ablation (15% of ablation patients and 12% of surgery patients)[25]. These late ablation procedures were eventually successful in all patients who received them, although some patients required up to four procedures to achieve freedom from recurrence.

The following secondary outcomes of interest were not reported by this study:

- Improvement of symptoms
- Quality of life and other patient-reported outcomes
- Maintenance of sinus rhythm at last follow-up
- Anticoagulant use
- Hospitalization/ readmission
- Measures of cardiac function: atrial size and ventricular ejection fractions

Catheter Ablation versus no treatment

Summary

Studies. One cohort study[27] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation. No RCTs were identified that met our inclusion criteria.

Freedom from recurrence: There is insufficient evidence that catheter ablation results in significantly greater freedom from recurrence compared with no treatment (100% versus 36%) based on data from one small cohort study.

Randomized controlled trials (Efficacy)

No RCTs were identified that met our inclusion criteria.

Cohort studies (Effectiveness)
One prospective cohort study[27] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for this study.

The study enrolled patients with paroxysmal SVT and dual AV node pathways were included. The tachycardias were documented but noninducible. Radiofrequency catheter ablation targeted the slow pathway. Study details are provided in Table 26; see Appendix Table F3 for more detailed information.

Table 26. Study population overview: Cohort studies comparing radiofrequency ablation with no treatment in patients with AVNRT

Study	Mean age (years)	% male	Paroxysmal SVT (%)	Symptom duration (months)	Follow-up duration (% followed)	Treatment groups	Study funding
Lin (1998)[27] N = 27 Prospective	42	70%	100%	≥ 12 months (mean NR)	23 ± 13 (range, 1-54) (% f/u NR)	RF ablation (n = 16)	NR
					13 ± 14 months (range, 1-45) (% f/u NR)	No treatment (n = 11)	

AVNRT: Atrioventricular nodal reentrant tachycardia; RF: radiofrequency; NR: not reported

Primary Outcomes

Freedom from recurrence

Effectiveness (1 cohort study)
Lin and colleagues found that patients who received catheter ablation of the slow pathway were more likely to have freedom from recurrence of clinical tachycardia compared with patients who received no treatment (100% (16/16) versus 36% (4/11), respectively; $P < .03$)[27]. Nearly all instances of recurrence (6/7) occurred within 9 months following the initiation of the study. No blanking period was reported.

The following primary outcomes of interest were not reported by this study:
- Mortality (not procedure/ treatment-related)
- Stroke (not procedure/ treatment-related)
- Congestive heart failure

Secondary Outcomes

The following secondary outcomes of interest were not reported by this study:

- Improvement of symptoms
- Quality of life and other patient-reported outcomes
- Maintenance of sinus rhythm at last follow-up
- Anticoagulant use
- Hospitalization/ readmission (data for ablation group not reported)
- Repeat ablation
- Measures of cardiac function: atrial size and ventricular ejection fractions

4.1.3.2. AVRT, including Wolff-Parkinson-White (WPW) Syndrome

Catheter Ablation versus AADs or surgery

Summary

Studies. One small retrospective cohort study[28] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation

Patient-reported freedom from symptoms: There is insufficient evidence that catheter ablation results in significantly greater freedom from symptoms compared with AADs (90% versus 8%) based on data from one small cohort study. There is insufficient evidence that catheter ablation results similar rates of freedom from symptoms compared with surgery (90% versus 100%) based on data from one small cohort study.

Randomized controlled trials (Efficacy)

No RCTs were identified that met our inclusion criteria.

Cohort studies (Effectiveness)

One small retrospective cohort study[28] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for each study.

As part of a cost-estimate analysis, authors reviewed data from 52 patients with "incapacitating" SVT related to an accessory atrioventricular pathway. Patients were treated with radiofrequency ablation (n = 20), long-term AADs (n = 12), or surgical division of accessory pathways (n = 20). Patients who received catheter ablation were only followed for a mean of 8 months, compared with 58 and 54 months in the AAD and surgery groups, respectively. Study details are provided in Table 27; see Appendix Table F3 for more detailed information.

Table 27. Study population overview: Cohort studies comparing radiofrequency ablation with anti-arrhythmic drugs (AADs) in patients with AVRT

Study	Mean age (years)	% male	Paroxysmal SVT (%)	Symptom duration (months)	Follow-up duration (% followed)	Treatment groups	Study funding
Weerasooriya (1994)[28] N = 52 Retrospective	38	56%	NR	NR	8.4 ± 1.6 months	RF ablation (n = 20)	National Health and Medical Research Council of Australia, National Heart Foundation of Australia and Royal Perth Hospital Medical Research Foundation
					58 months (mean)	Long-term AADs (n = 12)	
					54 ± 15 months	Surgery (n = 20)	

AADs: anti-arrhythmic drugs; AVNRT: Atrioventricular nodal reentrant tachycardia; RF: radiofrequency; NR: not reported

Primary Outcomes

The following primary outcomes of interest were not reported by this study:

- Freedom from recurrence
- Mortality (not procedure/ treatment-related)
- Stroke (not procedure/ treatment-related)
- Congestive heart failure

Secondary Outcomes

Improvement of symptoms

Effectiveness (1 cohort study)

Through the final follow-up of 8.4 ± 1.6 months, 90% of ablation patients (18/20) remained asymptomatic. Similar results were seen during the mean 54 ± 15 months of follow-up in the surgery group, with 100% of patients (20/20) remaining symptom-free. In those patients who received long-term treatment of AADs, only 8% (1/12) of patients were symptom-free during the mean 58 ± 23 months of follow-up. While these results suggest that surgery was more effective than long-term AADs, it is difficult to draw conclusions regarding the effectiveness of ablation in reducing symptoms compared with the other treatment groups due to the much shorter follow-up period (8.4 months compared with 54 and 58 months)[28].

The following secondary outcomes of interest were not reported by this study:

- Quality of life and other patient-reported outcomes
- Maintenance of sinus rhythm at last follow-up
- Anticoagulant use
- Hospitalization/ readmission
- Repeat ablation
- Measures of cardiac function: atrial size and ventricular ejection fractions

Catheter Ablation versus no treatment

Summary

Studies. One RCT[29] was identified that met our inclusion criteria and was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation.

Summary.

Freedom from recurrence: There is moderate quality evidence from 1 RCT that catheter ablation results in significantly greater freedom from recurrence in both the short- and long-term versus no treatment. In the short-term, PVI is associated with a 55% (95% CI, 35%, 70%) decrease in risk of recurrence compared with no treatment. In the long-term, PVI is associated with a 55% (95% CI, 34%, 70%) decrease in risk of recurrence compared with no treatment.

Mortality (not treatment-related): There is low quality evidence from 1 RCT that there is no difference in mortality rates following catheter ablation compared with no treatment. There were no deaths in either group.

Randomized controlled trials (RCTs) (Efficacy)

One RCT was identified that met our inclusion criteria[29]. This trial compared radiofrequency ablation with no treatment in patients with Wolff-Parkinson-White (WPW) Syndrome. The study was considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for the study, which met all but two criteria for a good quality RCT.

Demographics

A total of 76 WPW patients were enrolled in this RCT. For inclusion, patients had to be classified as being at high risk for arrhythmias based on electrophysiological testing, that is, patients had to have reproducibly inducible arrhythmias and be less than 36 years of age. The median patient age was 23 years, with patients' ages ranging from 15 to 30 years, and 50% of patients were male. Approximately one-third of patients had multiple accessory pathways, and none had structural heart disease. Patients were followed for a median of 24 months (ranging from 9 to 60 months) and 95% of patients were available for complete follow-up[29]. See Table 28.

Table 28. Study population overview: RCTs comparing ablation with no treatment in patients with WPW Syndrome

Study	Mean age (years)	% male	Characteristics of WPW Syndrome	Symptom duration (months)	Comorbidities	Follow-up duration (% followed)	Study funding
Pappone, Santinelli (2003)[29] N = 76	23 (median) (15-30 years)*	50%*	Patients considered to be at high risk for arrhythmia based on electrophysiological tests Multiple accessory pathways (33%) Inducible arrhythmia (100%)	NR	Structural heart disease (0%)	24 months (median) (9 – 60 months) (95%)	NR

RCT: randomized controlled trials; RF: radiofrequency; NR: not reported; WPW: Wolff-Parkinson-White syndrome
* after loss to follow-up

Intervention details (Table 29)

Ablation group. Patients underwent radiofrequency catheter ablation of the left-sided and/or the right-sided accessory pathway. The treatment concluded once conduction in the accessory pathways was eliminated and no longer inducible. Anti-arrhythmic drugs were not given[29].

No treatment group. Patients in the control group did not receive any treatment[29].

Blanking period. The authors did not report that there was a blanking period following ablation before recurrences were documented.

Table 29. Treatment overview: RCTs comparing ablation with no treatment in patients with WPW Syndrome

Study	Treatment group	Isolation success (% of pts)	AADs (Duration)	Reablation? (% of pts, time period)	Cardioversion? (% of pts)	Crossover? (% of pts, time period)	Blanking period? (Duration)
Pappone, Santinelli (2003)[29]	RF ablation (n = 38)	100%	None	5% (2/37) due to AVNRT, underwent successful slow-pathway ablation (NR)	None	-	NR
	No treatment (n = 38)	-	None	-	3% (1/35) (as treatment for cardiac arrest due to ventricular fibrillation)	None	NR

AADs: anti-arrhythmic drugs; NR: not reported; RF: radiofrequency; - : not applicable; RCT: randomized controlled trials; WPW: Wolff-Parkinson-White syndrome

Cohort Studies (Effectiveness)
No comparative cohort studies were identified that met our inclusion criteria.

Primary Outcomes

Freedom from recurrence

Efficacy (1 RCT)
Patients with inducible WPW at high risk for recurrence had a lower rate of arrhythmia recurrence if they were treated with ablation than if they received no treatment. In the ablation group, two patients (5%) had recurrence of arrhythmia during the median follow-up period of 27 months (range of 9 to 60 months)[29]. These events occurred at 9 months and 27 months, and both patients were found to have AVNRT and received successful slow ablation of the slow pathway. In the no treatment group, 60% of patients (21/35) had recurrence of arrhythmias within a median follow-up period of 15 months (range of 8 to 53 months). The arrhythmia was caused by SVT (15/21), AF (5/21), and ventricular fibrillation (1/21). All patients in this group exhibited ventricular pre-excitation during the follow-up period. Among those patients with 5-year follow-up, patients treated with ablation had a risk reduction of 92% compared with the no treatment group in terms of recurrence rates (93% (35/37) versus 23% (14/35), respectively; $P < .001$). No blanking period was reported.

Mortality (not procedure/ treatment-related)

Efficacy (1 RCT)
No patients died during the follow-up period in either treatment group.

The following primary outcomes of interest were not reported by this study:
- Stroke (not procedure/ treatment-related)
- Congestive heart failure

Secondary Outcomes

Repeat ablation

Efficacy (1 RCT)
As described above, two patients in the ablation group (5%) received repeat ablation due to arrhythmic events during the follow-up period. Recurrence was due to AVNRT in both patients, and they underwent successful ablation of the slow pathway[29].

The following secondary outcomes of interest were not reported by this study:
- Improvement of symptoms
- Quality of life and other patient-reported outcomes
- Maintenance of sinus rhythm at last follow-up

- Anticoagulant use
- Hospitalization/ readmission
- Measures of cardiac function: atrial size and ventricular ejection fractions

4.1.3.3. Mixed populations

Catheter Ablation versus AADs

Summary
Studies. One prospective cohort study[30] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation.

Patient-reported freedom from symptoms: There is low quality evidence from 1 cohort study that catheter ablation results in significantly greater freedom from symptoms compared with AADs (85% versus 55%) based on data from one cohort study.

Randomized controlled trials (RCTs) (Efficacy)
No RCTs were identified that met our inclusion criteria.

Cohort studies (Effectiveness)
One prospective cohort study[30] met our inclusion criteria. The study was considered to be at moderately high risk of bias (Class of Evidence III) after methodological evaluation (see Appendix Table D1 for definitions). Table E1 in the Appendix contains the details on the methodological quality grading for each study.

Goldberg and colleagues evaluated long-term outcomes in patients with newly diagnosed paroxysmal SVT as part of a costing analysis. Patients with AF and atrial flutter were excluded, but no other diagnostic restrictions were placed. Patients chose to be treated with radiofrequency ablation (n = 39) or medical therapy (n = 44). Half of the patients in the medical therapy eventually underwent catheter ablation between one and five years after baseline. Study details are provided in Table 30; see Appendix Table F3 for more detailed information.

Table 30. Study population overview: Cohort studies comparing radiofrequency ablation with anti-arrhythmic drugs (AADs) in patients with SVT

Study	Mean age (years)	% male	Paroxysmal SVT (%)	Symptom duration (months)	Follow-up duration (% followed)	Treatment groups	Study funding
Goldberg (2002)[30] N = 95 Prospective	51*	30%*	100%	38 months (mean)	1 year (87%) 5 years (87%)	RF ablation (n = 39)* AADs (n = 44)*	NR

AADs: anti-arrhythmic drugs; RF: radiofrequency; SVT: supraventricular tachyarrhythmia
* after loss to follow-up

Primary Outcomes

The following primary outcomes of interest were not reported by this study:

- Freedom from recurrence
- Mortality (not procedure/ treatment-related); NOTE that 1/95 patients died but the patient was excluded from follow-up and the treatment group was not noted. The death was reported to be from an unrelated cause[30]
- Stroke (not procedure/ treatment-related)
- Congestive heart failure

Secondary Outcomes

Improvement of symptoms

Effectiveness (1 cohort study)

At one year follow-up, approximately 85% of patients treated with ablation were free from disease-related symptoms (palpitations and dizziness) compared with approximately 55% of patients who received medical therapy (P- value not reported). No patients had crossed over at this point.

Freedom from symptoms (palpitations and dizziness) through 5 years follow-up was more prevalent in patients initially treated with ablation compared with those initially treated with medical therapy, half of which eventually crossed over and received ablation (approximately 92% versus approximately 50%, respectively; P-value not reported).

Quality of life and other patient-reported outcomes

Effectiveness (1 cohort study)

In general, patients who received ablation treatment had greater improvement in all the subdomains of the SF-36 quality of life scale compared with those treated with medical therapy at one year follow-up (Table 31). Statistical analysis was not performed.

At 5 year follow-up, improvements in all SF-36 quality of life subdomain scores fell in both treatment groups compared with those reported for 1 year, with many subscales showing lower scores than those at baseline (Table 31). Patients initially treated with ablation were doing better (as compared with baseline) in the SF-36 physical functioning and social functioning subscales than those initially treated with medical therapy (physical functioning: improvement of 10 versus 2 points from baseline, respectively; social functioning: improvement of 8 versus 1 points from baseline, respectively), although half the medical therapy patients crossed over and received ablation between 1 and 5 years follow-up. In contrast, patients initially treated with ablation were doing worse than those initially treated with medical therapy in the change in the SF-36 role emotional subscale (improvement of -1 versus 6 points from baseline, respectively). No statistical comparisons were performed[30].

Table 31. SF-36 Outcomes: Cohort studies comparing radiofrequency ablation with anti-arrhythmic drugs (AADs) in patients with SVT

		SF-36 Subscale Score: Improvements from baseline									
Study	**Treatment group**	**Physical component score**	**Mental component score**	**Physical functioning**	**Bodily pain**	**General health**	**Social functioning**	**Role physical**	**Role emotional**	**Mental health**	**Vitality**
Goldberg (2002)[30] (1 year)	RF ablation (n = 39)	NR	NR	15	5	11	11	32	16	10	15
	AADs (n = 44)			8	-5	6	8	29	10	10	7
(5 years)	RF ablation (n = 39)	NR	NR	10	-7	-3	8	8	-1	1	3
	AADs (n = 44) 50% of these patients received ablation between years 1 and 5			2	-9	-3	1	8	6	4	2

AADs: anti-arrhythmic drugs; NR: not reported; RF: radiofrequency; SF-36: Short Form 36; SVT: supraventricular tachyarrhythmia

Repeat ablation

Effectiveness (1 cohort study)
One patient in the ablation group underwent a successful repeat ablation due to recurrent arrhythmia (3% (1/39))[30].

The following secondary outcomes of interest were not reported by this study:

- Maintenance of sinus rhythm at last follow-up
- Anticoagulant use
- Hospitalization/ readmission
- Measures of cardiac function: atrial size and ventricular ejection fractions

4.1.3.4. Sinus tachycardia, atrial tachycardia, and focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia

No comparative studies were identified that evaluated catheter ablation in patients with sinus tachycardia, atrial tachycardia, focal junctional ectopic tachycardia or nonparoxysmal junctional tachycardia.

4.1. Key Question 1a: If catheter ablation is efficacious compared with other treatment options, is there differential efficacy between radiofrequency ablation versus cryoablation?

Overview

Eight RCTs[31-38] met our inclusion criteria and reported outcomes related to freedom from recurrence following radiofrequency ablation versus cryoablation. We did not identify any RCTs that compared radiofrequency ablation to cryoablation in patients with atrial fibrillation. Four RCTs[31-34] were included that evaluated radiofrequency ablation versus cryoablation in patients with typical atrial flutter, and four RCTs[35-38] were included that compared these procedures in patients with SVT. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). All studies failed to meet more than one criterion for a good quality RCT.

4.2.1. Atrial fibrillation

No RCTs were identified that compared radiofrequency ablation to cryoablation in patients with atrial fibrillation.

4.2.2. Atrial flutter

Summary

Studies. Four RCTs[31-34] were included that compared radiofrequency ablation with cryoablation in patients with typical atrial flutter. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). All studies failed to meet more than one criterion for a good quality RCT.

Summary

Freedom from recurrence: There is low quality evidence from 3 RCTs that there is no difference in the rate of freedom from recurrence between radiofrequency ablation and cryoablation (63% versus 57%, respectively) in patients with atrial flutter as measured at 5 to 15 months follow-up.

Persistent bidirectional conduction block: There is low quality evidence from 1 RCT that atrial flutter patients treated with radiofrequency ablation had significantly higher rates of persistent birdirectional conduction block compared with those treated with cryoablation at 3 months follow-up, with a risk difference of 19% (95% CI, 4%, 33%).

Results

Four RCTs[31-34] were included that compared radiofrequency ablation with cryoablation in patients with typical atrial flutter. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). All studies failed to meet more than one criterion for a good quality RCT.

A total of 325 patients were randomized, and follow-up ranged from 3 to a mean of 15 months. Three studies[31-33] evaluated patients with typical atrial flutter, while one study[34] included patients with typical atrial flutter with or without atrial fibrillation (76% of patients had history of atrial fibrillation). One study reported that patients randomized to receive radiofrequency had significantly greater persistent bidirectional conduction block compared with those in the cryoablation group (85% versus 66%, respectively; $P = .014$). However, follow-up data were available for only 64% of patients, which may have been due in part to the fact that invasive testing was required for complete follow-up[32]. The remaining three studies reported similar rates of freedom from recurrence in both treatment groups[31, 33, 34]. See Table 32 for further study details.

Table 32. RCTs comparing radiofrequency ablation to cryoablation for atrial flutter: outcomes

Investigator (year) Country, CoE	N Diagnosis	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Collins (2006)[31] Australia CoE II	• N = 32 • Typical atrial flutter	• Freedom from arrythmia recurrence (atrial flutter or AF) 14 (9-19) months	• RF ablation (n = 15)	93% (14/15)	NR
			• Cryoablation (n = 13)	85% (11/13)	
Kuniss (2009)[32] Germany CoE II	• N = 191 • Typical atrial flutter	• Persistent bidirectional conduction block 3 months	• RF ablation (n = 91)	85% (51/60 who complied with invasive f/u testing)	.014
			• Cryoablation (n = 90)	66% (42/64 who complied with invasive f/u testing)	
Malmborg (2009)[33] Sweden CoE II	• N = 40 • Typical atrial flutter	• Freedom from recurrence of atrial flutter 15 (6-23) months	• RF ablation (n = 20)	85% (17/20)	.45
			• Cryoablation (n = 20)	80% (16/20)	
Thornton (2008)[34] The Netherlands CoE II	• N = 62 • Typical atrial flutter ± atrial fibrillation (76% of patients had history of atrial fibrillation)	• Freedom from recurrence of arrhythmia (after successful procedure) 4.6 (3-13.7) months	• RF ablation (n = 30)	33% (10/30)	NS
			• Cryoablation (n = 32)	31% (10/32)	

AF: atrial fibrillation; NR: not reported; RF: radiofrequency; RCT: randomized controlled trials

4.2.3. Supraventricular tachyarrhythmia

Summary

Studies. Four RCTs[35-38] were included that compared these procedures in patients with SVT. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). All studies failed to meet more than one criterion for a good quality RCT.

Freedom from recurrence : There is moderate quality evidence from 3 RCTs patients treated with radiofrequency ablation had significantly higher rates of freedom from recurrence compared with those treated with cryoablation at 6 to 12 months follow-up, with a risk difference of 5% (95% CI, 1%, 9%).

Results

Four RCTs[35-38] were included that compared radiofrequency ablation with cryoablation in patients with supraventricular tachycarrhythmia. All studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). All studies failed to meet more than one criterion for a good quality RCT. A total of 802 patients were randomized, and follow-up ranged from 6 to 12 months. Three studies[35, 37, 38] evaluated patients with AVNRT, while one study[36] included patients AVNRT (57%) or AVRT (43%). The largest RCT found that patients in the radiofrequency ablation group had significantly higher rates of freedom from documented arrhythmia recurrence at six months compared with those in the cryoablation group (95.6% (238/249) versus 90.7% (223/246), respectively; P = .029)[35]. The second largest study similarly reported that more patients who were randomized to radiofrequency ablation had a combination of procedural success, freedom from AVNRT recurrence, and freedom from permanent complete AV block versus those randomized to receive cryoablation (97% (97/100) versus 89% (89/100), respectively; P = .03)[38]. The other two studies did not evaluate statistical significance of freedom from recurrence between treatment groups, though results from one study favored radiofrequency ablation while the other favored cryoablation[36, 37]. See Table 33 for further study details.

Table 33. RCTs comparing radiofrequency ablation to cryoablation for SVT: outcomes

Investigator (year) Country, CoE	N Diagnosis	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Deisenhofer (2010)[35] Germany CoE II	• N = 509 • Inducible AVNRT (slow-fast in 98% of patients)	• Freedom from documented arrhythmia recurrence 6 months	• RF ablation (slow pathway)	95.6% (238/249)	.029
			• Cryoablation (slow pathway)	90.7% (223/246)	
Kardos (2007)[36] Hungary CoE II	• N = 30 • AVNRT: 57% (17/30) • AVRT: 43% (13/30)	• Freedom from inducible arrhythmia recurrence 12 months	• RF ablation (n = 17)	71%	NS
			• Cryoablation (using ice mapping) (n = 13)	77%	
Kimman (2006)[37] The Netherlands CoE II	• N = 63 • AVNRT	• Freedom from palpitations (patient-reported) 12 months	• RF ablation (slow pathway) (n = 33)	70%	NR
			• Cryoablation (slow pathway) (using ice mapping) (n = 30)	57%	
Zrenner (2004)[38] Germany CoE II	• N = 200 • AVNRT	• Freedom from AVNRT recurrence (details NR) mean 8 months	• RF ablation (slow pathway) (n = 100)	99%	NR
			• Cryoablation (slow pathway) (n = 100)	92%	
		• Procedural success, and freedom from AVNRT recurrence and permanent complete AV block* (details NR) mean 8 months	• RF ablation (slow pathway) (n = 100)	97%	.03
			• Cryoablation (slow pathway) (n = 100)	89%	

AADs: anti-arrhythmic drugs; AV: atrioventricular ;AVNRT: Atrioventricular nodal reentrant tachycardia; CoE: class of evidence; NR: not reported; RF: radiofrequency; RCT: randomized controlled trials; SVT: supraventricular tachyarrhythmia
*no patient experienced permanent complete AV block.

4.3 Key Question 2: What is the evidence regarding the comparative efficacy of various approaches to radiofrequency catheter ablation?

Summary

Studies. Thirty-five RCTs[39-73] met our inclusion criteria and reported outcomes related to freedom from recurrence for AF using different approaches of PVI. We identified studies that compared the following approaches: PVI versus wide-area circumferential ablation (WACA), PVI with or without additional left sided ablation lines, PVI with or without additional right sided ablation lines, PVI with or without complex fractionated electrograms, and a variety of miscellaneous comparisons were also found. One study was considered to have a low risk of bias (Class of Evidence I) and the remaining 34 studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions).

Summary

Freedom from recurrence : There is low quality evidence from 5 RCTs that patients treated with PVI had significantly lower rates of freedom from recurrence compared with those treated with WACA at 3 to 13 months follow-up, with a risk difference of 10% (95% CI, 1%, 18%). There is moderate quality evidence from 8 RCTs that there is no difference in freedom from recurrence at 7 to 36 months follow-up in patients treated with PVI compared with those who received PVI plus additional left sided ablation lines (65.5% versus 70.3%, respectively). There is moderate quality evidence from 4 RCTs that there is no difference in freedom from recurrence at 8 to 12 months follow-up in patients treated with PVI compared with those who received PVI plus additional right sided ablation lines (68.2% versus 70.8%, respectively). There is moderate quality evidence from 6 RCTs that patients that treated with PVI had significantly lower rates of freedom from recurrence compared with those treated with PVI plus CFE at 12 to 23 months follow-up, with a risk difference of 17% (95% CI, 9%, 25%).

Overview

Thirty-five RCTs[39-73] met our inclusion criteria and reported outcomes related to freedom from recurrence for AF using different approaches of PVI. Sixteen[39, 48, 51-53, 56, 57, 60-64, 68, 71-73] of these studies were reported in and summarized by the AHRQ HTA; we have added results from an additional 19[40-47, 49, 50, 54, 55, 58, 59, 65-67, 69, 70] studies published since the search period from that HTA. We identified studies that compared the following approaches: PVI versus wide-area circumferential ablation (WACA), PVI with or without additional left sided ablation lines, PVI with or without additional right sided ablation lines, PVI with or without complex fractionated electrograms, and a variety of miscellaneous comparisons were also found. One study[64] was considered to have a low risk of bias (Class of Evidence I) and the remaining 34 studies were considered to be at moderately low risk of bias (Class of Evidence II) after methodological evaluation (see Appendix Table D1 for definitions). Table E3 in the Appendix contains the details on the methodological quality grading for each study. The majority of studies failed to meet more than one criterion for a good quality RCT.

4.3.1. PVI versus WACA

Five RCTs evaluated the efficacy of ostial PVI compared with wide-area circumferential ablation (WACA) (with or without additional lines), all five of which were identified and evaluated by the AHRQ HTA[39, 53, 57, 60, 63, 168]. A total of 480 patients were randomized, and follow-up ranged from 3 to 15 months. Two studies enrolled only patients with paroxysmal AF[57, 63], while the other three enrolled a mixed population of patients with paroxysmal and persistent/permanent AF[39, 53, 60] (range, 51% to 89% paroxysmal AF). Overall, the results are unclear, with three studies[39, 60, 63] reporting statistically improved rates of freedom from AF following WACA compared with PVI, one study[57] showing similar results between groups, and one study[53] favoring PVI compared with WACA. The AHRQ HTA report concluded that WACA may result in lower rates of recurrence compared with ostial PVI in AF patients[168]. Two studies reported freedom from recurrence in patients who were not taking AADs and who only received one procedure: both studies found that significantly more patients treated with WACA had freedom from recurrence compared to those patients treated with ostial PVI (Arentz: 67% versus 49%, respectively; $P \leq .05$; Oral 2003: 88% versus 67%, respectively; $P = .02$). Of the three studies that reported freedom from recurrence after repeat ablation[53, 57, 60], two[53, 60] similarly found that patients treated with WACA had a better outcome compared with those who received PVI (Table 34).

Table 34. RCTs comparing PVI to WACA for atrial fibrillation: outcomes

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Studies included in the AHRQ HTA[168]					
Arentz (2007)[39] Germany CoE II	• 61%	• Freedom from AF (no AAD, after one ablation) 15 months	• PVI (ostia) n = 55	49%	≤ .05
			• WACA n = 55	67%	
Oral (2003)[63] US CoE II	• 100%	• Absence of symptomatic AF (off AAD, no repeat procedure) 6 months	• PVI (ostia) n = 40	67%	0.02 (log rank)
			• WACA + MIL + posterior line n = 40	88%	
		• Repeat ablation NR	• PVI (ostia) n = 40	17.5%	NR
			• WACA + MIL + posterior line n = 40	0%	

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Nilsson (2006)[60] Denmark CoE II	• 51%	• Freedom from symptomatic AF or left AT (not on AADs) (74 pts had 1 re-ablation) 12 months	• PVI (ostia) n = 54	31%	.02
			• WACA n = 46	57%	
Karch (2005)[53] Germany CoE II	• 89%	• Freedom from atrial tachyarrhythmia (AT) (no repeat procedure) 6 months	• PVI (ostia) n = 50	54%	NR
			• WACA n = 50	34%	
		• Freedom from AT (with repeat procedure) 6 months	• PVI (ostia) n = 50	66%	.02
			• WACA n = 50	42%	
		• Repeat ablation procedure within 6 months	• PVI (ostia) n = 50	16%	NS
			• WACA n = 50	24%	
Liu, Long (2006)[57] China CoE II	• 100%	• No AT 3-9 months after the last procedure (No AADs) 9 months	• Stepwise PVI (add roof line if inducible, then add MIL if inducible) n = 55	78%	.63
			• WACA n = 55	84%	
		• Repeat ablation within 3-5 months of original procedure 3-5 months	• Stepwise PVI (add roof line if inducible, then add MIL if inducible) n = 55	13%	NR
			• WACA n = 55	9%	

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
			• non-encircling LA roof, septum, anterior wall, mitral isthmus and annulus lines n = 40	33%	

AAD: antiarrythmic drug treatment; AF: atrial fibrillation; AT: atrial tachycardia;CoE: class of evidence; LA: left atrium; MIL: mitral isthmus line; NR: not reported; ns: not statistically significant ($P \geq .05$); PV: pulmonary vein; PVI: pulmonary vein isolation; WACA: wide area circumferential ablation

4.3.2. PVI versus PVI with additional left-sided ablation lines

Ten RCTs[48, 49, 51, 52, 58, 59, 64, 67, 68, 73] evaluated the efficacy of PVI versus PVI with additional left-sided lines (for example, mitral-isthmus, roof or posterior left atrium lines), six[48, 51, 52, 64, 68, 73] of which were identified and evaluated by the AHRQ HTA[168]. A total of 1530 patients were randomized, and follow-up ranged from 7 to 36 months. Four studies[52, 59, 67, 68] enrolled only patients with paroxysmal AF, three[48, 49, 64] enrolled a mixed population of patients with paroxysmal and persistent/permanent AF (range, 63% to 71% paroxysmal AF), and two[58, 73] included only patients with persistent/permanent AF (one study[51] did not report this information). Overall, three[48, 52, 73] of the ten identified studies found that patients who were treated with additional left sided ablation lines were significantly more likely to have freedom from recurrence compared with those who did not receive left sided ablation lines; an additional two studies[49, 51] reported greater freedom from recurrence with the addition of left sided ablation lines but did not assess statistical significance. Five studies[58, 59, 64, 67, 68] showed no statistically significant differences between treatment groups (Table 35).Three of six studies reported in the AHRQ HTA found significantly improved rates of freedom from recurrence or stable sinus rhythm at follow-up patients randomized to receive additional left sided ablation lines[168]. Specifically, Willems et al.[73] reported that significantly more patients with persistent AF were in sinus rhythm at seven months' follow-up (69% versus 20%; $P = .001$); two other studies[48, 51, 52] found similar results in a mixed population of paroxysmal/persistent AF patients. One study reported results that favored additional left ablation lines but did not assess the statistical significance[51]. None of the four additional studies published after the AHRQ search period reported a significant difference in recurrence rates following PVI compared with PVI with additional left-sided ablation lines.

Table 35. RCTs comparing PVI to PVI with or without additional left-sided ablation lines for atrial fibrillation: outcomes

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Studies included in the AHRQ HTA[168]					
Willems (2006)[73] Germany CoE II	0%	SR (Lack of any symptomatic or asymptomatic AF episode (>30 s); some pts on AADs(?)) 7 months	PVI (antrum) + CTI n = 30	20%	0.0001
			PVI (antrum) + CTI + left atrial linear lines n = 32	69%	
Pappone (2004)[64] Italy CoE I	63%	Freedom from recurrent AF (3 pts had reablation for AF) 12 months	WACA n = 280	87% (est.)	0.57
			WACA + posterior left atrial lines + MIL n = 280	88% (est.)	
Fassini (2005)[48] Italy CoE II	67%	Stable SR (after this procedure) 12 months	PVI n = 92	53 ± 5%	0.01
			PVI + MIL n = 95	71 ± 5%	
		Continual use of AAD 12 months	PVI n = 92	56%	NS
			PVI + MIL n = 95	50%	
Haissaguerre (2004)[51] France CoE II	NR	Freedom from AF or flutter (no AAD; included reablation) 7 months	PVI + CTI n = 35	74%	NR
			PVI + CTI + MIL n = 35	83%	
Sheikh (2006)[68] USA CoE II	100%	SR (no AAD; 3 had AFL ablation) 9 months	PVI (ostia) n = 50	28%	NS
			PVI + superior PV line + LIPV to MV annulus line n = 50	28%	
Hocini (2005)[52] France CoE II	100%	No atrial arrhythmia and off AAD 14 months	PVI (antrum) + CTI n = 45	69%	0.04
			PVI (antrum) + CTI + roof line n = 45	87%	

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Studies published after the AHRQ HTA search period					
Gaita (2008)[49] Italy CoE II	61%	Freedom from recurrence after single operation (after 2 months blanking period) 12 months	PVI n = 67	39%	NR
			PVI + left linear lesions n = 137	53%	
		Freedom from recurrence after repeat operation in those who had recurrence and consented to procedure (48.5% of total patients) 36 months	PVI n = 67	49%	NR
			PVI + left linear lesions n = 137	72%	
		Repeat ablation due to recurrence 12-36 months	PVI n = 67	67% (rec'd to 75%)	NR
			PVI + left linear lesions n = 137	47% (rec'd to 51%)	
Mikhaylov (2010)[58] Russia, Netherlands CoE II	0%	Freedom from recurrence (29% of patients underwent repeat procedure) 13 months	PVI n = 17	47%	NS
			PVI + LA n = 17	41%	
		Repeat ablation 13 months	PVI n = 17	29.4%	NS
			PVI + left atrial septal lines n = 17	29.4%	
Sawhney (2010)[67] USA CoE II	100%	Freedom from recurrence after single operation 16 ± 6 months	Segmental PVI n = 33	58%	0.62
			cPVI + left atrial linear ablation n = 33	52%	
		Freedom from recurrence after mean of 1.3 operations 24 months	Segmental PVI n = 33	85%	NS
			cPVI + left atrial linear ablation n = 33	85%	
Mun (2012)[59] South Korea CoE II	100%	Freedom from recurrence 15 ± 5 months	cPVI n = 52	12%	NS
			cPVI + left atrial roof line n = 52	21%	

AAD: antiarrythmic drug treatment; AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; CoE: class of evidence; cPVI: circumferential PVI; CTI: cavo tricuspid isthmus; LA: left atrium; LIPV: left inferior pulmonary vein; MIL: mitral isthmus line; MV: mitral valve; NR: not reported; ns: not statistically significant ($P \geq .05$); NS: not statistically significant ($P \geq .05$); PV: pulmonary vein; PVI: pulmonary vein isolation; SR: sinus rhythm; WACA: wide area circumferential ablation

4.3.3. PVI versus PVI with additional right-sided ablation lines

Four RCTs[42, 66, 71, 72] evaluated the efficacy of PVI versus PVI with additional right-sided lines (for example, cavotricuspid isthmus ablation, superior vena cava ablation), two[71, 72] of which were identified and evaluated by the AHRQ HTA[168]. A total of 683 patients were randomized, and follow-up ranged from 8 to 12 months. Overall, there was no statistically significant difference in the rate of freedom from recurrence between treatment groups as reported by all four studies. One study[71] enrolled only patients with paroxysmal AF, while the remaining three[42, 66, 72] enrolled a mixed population of patients with paroxysmal and persistent/permanent AF (range, 59% to 74% paroxysmal AF). The AHRQ HTA report found no statistically significant difference in the rates of freedom from recurrence in AF patients who received PVI alone or with additional right sided ablation lines[168]. The results from both of the additional studies[42, 66] published after the AHRQ search period were in accordance with these conclusions (Table 36).

Table 36. RCTs comparing PVI to PVI with additional right-sided ablation lines for atrial fibrillation: outcomes

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Studies included in the AHRQ HTA[168]					
Wazni (2003)[72] USA, Germany, Italy CoE II	59%	No AF recurrence > 8 weeks	PVI (ostia-antrum) n = 59	90%	NS
			PVI (ostia-antrum) + CTI n = 49	86%	
		No AF recurrence (9% had repeat procedure; 3% on AADs) 12 months	PVI (ostia-antrum) n = 53	100%	NS
			PVI (ostia-antrum) + CTI n = 42	100%	
Wang (2008)[71] China CoE II	100%	Freedom from recurrent AT (after 1 procedure; some on AADs) 4.6 months (12 months?)	WACA n = 54	78%	0.75
			WACA + SVC n = 52	81%	
		Freedom from recurrent AT (included reablation; some on AADs) 12 months	WACA n = 54	93%	0.73
			WACA + SVC n = 52	94%	
Studies published after the AHRQ HTA search period					
Corrado (2010)[42]	46%	Freedom from recurrence 12 months	PVI (antrum) n = 160	74%	NS

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
USA, Italy CoE II			PVI (antrum) + Superior Vena Cava Isolation n = 134	81%	
Pontoppidan (2012)[66] Denmark CoE II	54%	Freedom from AF 12 months	cPV ablation n = 73	32%	0.71
			cPV ablation + CVI block n = 73	34%	
		Freedom from AFl 12 months	cPV ablation n = 73	84%	0.61
			cPV ablation + CVI block n = 73	88%	
		Repeat Circumferential PV ablation procedures 12 months	cPV ablation n = 73	36%	<.01
			cPV ablation + CVI block n = 73	18%	

AAD: antiarrhythmicdrug treatment; AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; CoE: class of evidence; cPV: circumferential pulmonary vein; cPVI: circumferential PVI; CTI: cavotricuspid isthmus; LA: left atrium; LIPV: left inferior pulmonary vein; MV: mitral valve; NR: not reported; ns: not statistically significant ($P \geq .05$); PV: pulmonary vein; PVI: pulmonary vein isolation; RCT: randomized controlled trials; SR: sinus rhythm; SVC: superior vena cava; WACA: wide area circumferential ablation

4.3.4. PVI versus complex fractionated electrogram (CFE) ablation (± PVI): outcomes

Seven RCTs[40, 43-47, 70] evaluated the efficacy of PVI versus complex fractionated electrogram ablation with or without PVI, all of which were published after the AHRQ HTA's search period. A total of 778 patients were randomized, and follow-up ranged from 12 to 23 months. Overall, four studies[43, 44, 46, 70] reported that freedom from recurrence was significantly more likely in patients randomized to receive PVI + CFE compared with either PVI alone and/or CFE alone, while two studies[45, 47] found no difference in this outcome between PVI + CFE versus PVI or CFE groups. One study[40] did not evaluate the effects of PVI + CFE but did report significant difference between PVI and CFE treatment groups.

Three studies[40, 43, 44] enrolled only patients with paroxysmal AF. One reported significantly greater freedom from recurrence in patients treated with PVI compared with CFE ablation alone (89% versus 23%, respectively; $P < .001$)[44]; another reported data with a similar trend but the results were not statistically significant (72% versus 57%, respectively; $P = .075$)[40]. Furthermore, significantly greater freedom from recurrence was demonstrated in patients from one study that received PVI plus CFE ablation in comparison to those who received PVI alone (83% versus 74%, respectively; $P = .017$),

while another study[44] reported data with no difference between these two treatment groups (91% versus 89%, respectively; *P*-value not reported). One study[70] enrolled a mixed population of patients with paroxysmal and persistent/permanent AF (64% paroxysmal AF), and similarly found that CFE ablation plus PVI conferred significantly greater freedom from recurrence compared with PVI alone (74% versus 48% (after one procedure), respectively; $P = .03$). Of the three studies that included only patients with persistent/permanent AF[45-47], CFE ablation plus PVI performed similarly to PVI alone (see Table 37 for details).

Table 37. RCTs comparing PVI to complex fractionated electrogram (CFE) ablation (± PVI) for atrial fibrillation

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Studies published after the AHRQ HTA search period					
Chen (2011)[40] China CoE II	• 100%	• Freedom from recurrence (after 3 months blanking period) off AAD (49% of patients crossed over and received both PVI + CFE during initial procedure) 22.6 ± 6.4 months	• PVI (antrum) n = 60	72%	0.075
			• CFE n = 58	57%	
Deisenhofer (2009)[43] Germany CoE II	• 100%	• Freedom from recurrence (after 1 month blanking period) (34% underwent repeat ablation using same approach) 19 ± 8 months	• PVI n = 46	74%	.017
			• PVI + CFE n = 48	83%	
		• Repeat ablation (same as original procedure)	• PVI n = 46	33%	ns
			• PVI + CFE n = 48	35%	
Di Biase (2009)[44] USA, Italy, China, Egypt, Canada, Singapore CoE II	• 100%	• Freedom from recurrence (after 2 month blanking period) (28% underwent second ablation procedure) 12 months	• PVI (antrum) n = 35	89%	< .001
			• CFE n = 34	23%	
			• PVI + CFE n = 34	91%	
		• Repeat ablation (PVI (antrum) approach) 12 months	• PVI (antrum) n = 35	20%	NR
			• CFE n = 34	65%	

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
			• PVI + CFE n = 34	21%	
Elayi (2008)[46] France, Italy, USA, Canada, Singapore, Egypt, China CoE II	• 0%	• Freedom from recurrence after 1 procedure 16 months (mean)	• cPVI (antrum) n = 47	11%	< .001
			• PVI (antrum) n = 48	40%	
			• CFE + PVI (antrum) n = 49	61%	
		• Freedom from recurrence after 1-2 procedures, with AADs 16 months (mean)	• PVI (antrum) n = 48	28%	<.001
			• CPVA n = 47	56%	
			• PVI + CFE n = 49	80%	
		• Repeat ablation 12 months	• PVAI n = 48	29%	NR
			• CPVA n = 47	26%	
			• PVI + CFAE n = 49	20%	
Elayi (2011)[45] USA, Italy CoE II	• 0%	• Freedom from recurrence (7 pts in each group were on AADs) 17 ± 5 months	• PVAI n = 48	69%	NS
			• PVAI + CFAE n = 50	72%	
Estner (2011)[47] Germany CoE II	• 0%	• Freedom from recurrence after one procedure 12 months	• cPVI + additional lines ("linear ablation") n = 59	37%	0.9
			• CFE + PVI ("spot ablation") n = 57	39%	
		• Freedom from recurrence after all procedures (no AADs) 12 months after last ablation procedure	• cPVI + additional lines ("linear ablation") n = 59	54%	0.7
			• CFE + PVI ("spot ablation") n = 57	56%	
		• Repeat ablation 23 months (mean)	• cPVI + additional lines ("linear ablation") n = 59	25%	NR

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
			• CFE + PVI ("spot ablation") n = 57	28%	
Verma (2010) Canada, Italy, Norway, Spain CoE II	• 64%	• Freedom from recurrence after one procedure (after 3 month blanking period) (94% of all patients were off AADs) 12 months	• PVI n = 32	48%	.03 (vs. PVI + CFE)
			• CFE n = 34	29%	<.001 (vs. PVI + CFE)
			• PVI + CFE n = 34	74%	Favors PVI + CFE over PVI or CFE
		• Freedom from recurrence after two procedures (after 3 month blanking period) (94% of all patients were off AADs) 12 months	• PVI n = 32	68%	.04 (vs. PVI + CFE)
			• CFE n = 34	38%	.<.001 (vs. PVI + CFE)
			• PVI + CFE n = 34	88%	
		• Reablation 12 months	• PVI n = 32	31%	.07 (vs. PVI + CFE)
			• CFE n = 34	47%	.008 (vs. PVI + CFE) (ns vs PVI)
			• PVI + CFE n = 34	15%	

AAD: antiarrhythmic drug treatment; AF: atrial fibrillation; AFL: atrial flutter; cPVI: circumferential PVI; CoE: class of evidence; CFAE; complex fractionated atrial electrogram; CFE: complex fractionated electrogram ablation; NR: not reported; ns: not statistically significant ($P \geq .05$); PVAI; pulmonary vein antrum ablation with isolation ;PVI: pulmonary vein isolation; RCT: randomized controlled trials

4.3.5. Miscellaneous comparisons

Ten additional studies were identified that evaluated a variety of miscellaneous approaches (see Table 38 for details):

- As reported in the AHRQ HTA[5]:
  - Liu and colleagues[56] found that in patients who received wide-area circumferential ablation (WACA), significantly more had freedom from recurrence when a more aggressive approach was utilized compared with a modified approach (82% versus 58%, respectively; $P = .01$).

- Oral (2004)[62] reported that patients whose AF was not terminated or inducible after WACA/posterior left ablation lines/mitral isthmus line ablation that then were randomized to receive additional ablation lines had 86% freedom from recurrence compared with 67% of those who did not receive additional treatment; these results did not reach statistical significance ($P = .05$).
- Oral (2005)[61] showed that the rate of recurrence was similar in patients with chronic AF treated with WACA/posterior (or roof line) left atrial ablation/mitral isthmus line ablation compared with those who received non-encircling left atrial roof/septum/anterior wall/mitral isthmus/annulus lines ablation (48% versus 33%, respectively; $P = .20$).

- As reported after the AHRQ HTA's search period:
  - Kim[55] reported no difference in freedom from recurrence between patients randomized to receive WACA alone versus WACA with PVI and ablation of residual potentials (81% versus 80%, respectively).
  - Tamoborero et al. found no difference between freedom from recurrence after a single procedure in patients treated with circumferential PVI plus linear lesions along the left atrial roof (45%) compared with those treated with circumferential PVI plus left atrial posterior wall isolation (45%)[69].
  - Two studies[41, 59] reported similar results in patients treated with PVI alone versus box isolation (in the presence or absence of PVI).
  - In a small RCT, Gavin and colleagues[50] found significantly more freedom from recurrence after a single procedure in patients randomized to receive PVI (antrum) alone compared with PVI (antrum) plus coronary sinus ablation (77% versus 50%, respectively; $P < .01$). These results were no longer statistically significant once patients were permitted to undergo reablation.
  - Katritis[54] reported that significantly more patients who underwent PVI plus autonomic ganglia modification had freedom from recurrence compared with those who received PVI alone (85% versus 65%, respectively; $P = .019$).
  - Pokushalov[65] demonstrated greater freedom from recurrence following anatomic compared with selective ganglionated plexi ablation (78% versus 43%, respectively; $P = .02$) (see Table 38 for procedural details).

Table 38. RCTs comparing various approaches for atrial fibrillation: outcomes

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Studies included in the AHRQ HTA[168]					
Liu, Dong (2006)[56] China CoE II	75%	No AT beyond 3 months after initial procedure (no AADs) 13 months	WACA, then closing gaps in pts with residual PV conduction (aggressive) n = 50	82%	0.01
			WACA, then PVI inside circular lines in pts with residual PV conduction (modified) n = 50	58%	
Oral (2004)[62] USA CoE II	100%	Freedom from AF (no AADs; no additional reablation) 6 months	WACA + posterior LA lines + MIL n = 30	67%	0.05
			WACA + posterior LA lines + MIL + additional lines n = 30	86%	
Oral (2005)[61] USA CoE II	0%	Freedom from AF or AFL, no AAD, single procedure 10 months	WACA + posterior LA (or roof line) + MIL + ablation of amplitude >0.2 mv within the circles but outside the PV n = 40	48%	0.20
			non-encircling LA roof, septum, anterior wall, mitral isthmus and annulus lines n = 40	33%	
Studies published after the AHRQ HTA search period					
Kim (2010)[55] South Korea CoE II	100%	Freedom from recurrence 23 ± 8 months	Wide area circumferential PV ablation with n = 49	81%	.845

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
			Wide area circumferential PV ablation with PVI and ablation of residual potentials n = 53	80%	
Tamborero (2009)[69] Spain CoE II	60%	Freedom from recurrence after a single procedure 10 ± 4 months	Circum-ferential PVI (antrum) + linear lesions along the left atrial roof n = 60	45%	.943
			Circum-ferential PVI (antrum) left atrial posterior wall isolation n = 60	45%	
Chilukuri (2011)[41] USA CoE II	79%	Freedom from recurrence in the absence of AADs 10 ± 2 months	PVI n = 13	15%	.52
			Box isolation* n = 16	25%	
Mun (2012)[59] South Korea CoE II	100%	Freedom from recurrence 15 ± 5 months	Circum-ferential PVI n = 52	88%	NS
			Circum-ferential PVI + PostBox ablation* n = 52	81%	
Gavin (2012)[50] Australia CoE II	100%	Freedom from recurrence without AADs after single procedure 18 months	PVI (antrum) n = 22	77%	< .01
			PVI (antrum) + Coronary Sinus n = 20	50%	
		Freedom from recurrence without AADs after mean of 1.2 procedures 18 months	PVI (antrum) n = 22	82%	NR
			PVI (antrum) + Coronary Sinus n = 20	80%	
		Repeat ablation 18 months	PVI (antrum) n = 22	9%	NR
			PVI (antrum) + Coronary Sinus n = 20	40%	

Investigator (year) Country, CoE	Paroxysmal AF (% of patients)	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Katritsis (2011)[54] Greece, USA, UK CoE II	76%	Freedom from recurrence (19% of patients underwent repeat ablation) 12 months	PVI n = 33	61%	.019
			PVI + autonomic ganglia modification n = 34	85%	
		Repeat ablation 12 months	PVI n = 33	21.2%	NR
			PVI + autonomic ganglia modification n = 34	17.6%	
Pokushalov (2009)[65] Russia, Greece	100%	Freedom from recurrence 13 ± 2 months	Selective GP ablation† n = 40	43%	.02
			Anatomic GP ablation† n = 40	78%	

AAD: antiarrhythmicdrug treatment; AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; GP: ganglionated plexi; LA: left atrium; MIL: mitral isthmus line; NR: not reported; ns: not statistically significant ($P \geq .05$); PV: pulmonary vein; PVI: pulmonary vein isolation; RCT: randomized controlled trials; WACA: wide area circumferential ablation

*Box ablation:

- Chilukuri: continuous lesions created at anterior portions of ipsilateral superior and inferior PVs, subsequent linear lesions joining the two superior PVs (roof line) and the two inferior PVs (bottom line) created to complete isolation of the posterior LA.
- Mun: "PostBox lesion generated by an additional posterior inferior line connecting the lower margins of the right and left CPVI lines to a left atrial roof line."

†Ganglionated plexi (GP) ablation details (Pokushalov):

- Selective GP ablation: ablation in left atrium, adjacent to and in the antral region of the pulmonary veins and the region of the left atrial crux, and in the right atrium, adjacent to the superior vena cava and septum, and at the inferior vena cava near the coronary sinus ostium.
- Anatomic GP ablation: ablation at sites of presumed GP clusters to include GP clusters near the pulmonary vein-left atrial junctions at various sites.

4.4 Key Question 3: What is the evidence of the safety of catheter ablation?

4.4.1. Atrial Fibrillation

Summary

Studies. We evaluated safety data from all comparative studies included in Key Question 1. In total, nine RCTs[6-12, 14-16], two prospective cohort studies[17, 18] and two retrospective cohort studies[19, 20] comparing radiofrequency PVI to AADs, one retrospective cohort study[22] comparing radiofrequency PVI to Cox-Maze surgery, and one RCT comparing cryoablation to AADs[21]. In addition, we identified six prospective case series[74-79] that were specifically designed to evaluate adverse events in at least 1000 patients who underwent PVI for atrial fibrillation. We also identified four prospective case series[80-83] that evaluated the incidence of procedure-related esophageal lesions in at least 100 AF patients. These studies were included as this PVI-related complication was not reported in any of the comparative or larger prospective case series. Case series data are briefly summarized here; more detailed information can be found in Appendix F.

Summary.

Procedure- or treatment-related mortality: There is low quality evidence from 1 RCT that there is no difference in procedure- or treatment-related mortality rates following RF PVI compared with AADs. There were no treatment-related deaths in either group.

Procedure- or treatment-related thromboembolic events: There is low quality evidence from 3 RCTs that there is no difference in procedure- or treatment-related thromboembolic event rates following RF PVI compared with AADs (0.7% versus 0.6%, respectively).

Pericardial effusion or cardiac tamponade: There is low quality evidence from 2 RCTs that there is no difference in pericardial effusion or cardiac tamponade rates following RF PVI compared with AADs (1.3% versus 0.8%, respectively). There is low quality evidence from 1 RCT that there is no difference in pericardial effusion or cardiac tamponade rates following cryo-PVI compared with AADs (0.6% versus 1%, respectively).

Pulmonary vein stenosis: There is low quality evidence from 3 RCTs that there is no difference in pulmonary vein stenosis rates following RF PVI compared with AADs, with no reported cases in either group. There were no treatment-related deaths in either group. There is low quality evidence from 1 RCT that there is no difference in pulmonary vein stenosis rates following cryo-PVI compared with AADs (1.2% versus 2%, respectively).

Studies
We evaluated safety data from all comparative studies included in Key Question 1. In total, nine RCTs[6-12, 14-16], two prospective cohort studies[17, 18] and two retrospective cohort studies[19, 20] comparing radiofrequency PVI to AADs, one retrospective cohort study[22] comparing radiofrequency PVI to Cox-Maze surgery, and one RCT comparing cryoablation to AADs[21].

In addition, we identified six prospective case series[74-79] that were specifically designed to evaluate adverse events in at least 1000 patients who underwent PVI for atrial fibrillation. We also identified four prospective case series[80-83] that evaluated the incidence of procedure-related esophageal lesions in at least 100 AF patients. These studies were included as this PVI-related complication was not reported in any of the comparative or larger prospective case series. Case series data are briefly summarized here; more detailed information can be found in Appendix F.

Procedure- or treatment-related mortality (Table 39)

Radiofrequency PVI versus AADs (2 RCTs)
Two RCTs reported no cases of radiofrequency PVI-related mortality (0%, total n = 159)[7, 16]. One of these studies also noted that there were no instances of treatment-related death in the AAD group (0%, n = 59)[7]. The remainder of the comparative studies did not report any data.

Radiofrequency PVI versus Cox-Maze surgery
No data were reported from this cohort study[22].

Cryo-PVI versus AADs (1 RCT)
One RCT reported a 0% 30-day mortality rate in both the cryoablation (n = 163) and AAD (n = 82) treatment groups[21].

PVI (4 case series)
There were no cases of procedure-related mortality in 4589 AF patients following PVI as reported by four case series. The overall 30-day mortality rate was 0.044% (2/4589) [74-76, 78]. One patient died five days following a procedural stroke; the patient had a fatal myocardial infarction attributed to in-stent thrombosis and had a history of ischemic heart disease and coronary stents[78]. The second patient died from a combination of hospital-acquired pneumonia and cardiac failure ten days post-ablation; the patient had a history of ischemic heart disease and severe left ventricular systolic dysfunction and underwent periprocedural tamponade draining[78].

Table 39. Procedure-related mortality: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Jais (2008)[7] N = 112 RCT	12 months (96%)	Treatment-related death	RF cPVI (n = 53) AADs (n = 59)	0% (0/53) 0% (0/59)	 NR
Wilber (2010)[16] N = 167 RCT	30 days % f/u NR	Procedure-related death	RF cPVI (n = 106) AADs (n = 61)	0% (0/106) n/a	 n/a
Cryo-PVI versus AADs					
STOP AF Pivotal Trial (2010)[21] N = 245 RCT	12 months (93%)	Procedure-related death	Cryo cPVI (n = 163) AADs (n = 82)	0% (0/163) n/a	 n/a
		30-day mortality	Cryo cPVI (n = 163) AADs (n = 82)	0% (0/163) 0% (0/82)	 NR

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

Procedure- or treatment-related embolic complications (including stroke or ischemic attack) (Table 40)

PVI versus AADs (6 RCTs, 2 cohort studies)

Six RCTs reported that procedure-related strokes occurred in a total of four patients following radiofrequency PVI (mean 1.5% (range, 0% to 7%) of patients; total 4/272)[6, 8, 9, 11, 14, 15]. One stroke occurred during left atrium ablation and the patient died of brain hemorrhage nine months later[14]. One stroke[8] and one transient ischemic attack[11] occurred shortly following the ablation procedure. Finally, one stroke occurred six days postablation, after which the patient withdrew from study participation[9]. Two of the RCTs also reported no drug-related thromboembolic events (0%, total n = 70)[6, 15].

No ablation-related thromboembolic events were reported by two cohort studies (0%, total n = 674)[18, 19], though one patient in the ablation group had a stroke immediately following cardioversion[19]. For the AAD group, one of the cohort studies reported a 30-day stroke rate of 1% (1/85); one patient experienced a fatal stroke[19].

Radiofrequency PVI versus Cox-Maze surgery
No data were reported from this cohort study[22].

Cryo-PVI versus AADs
No cryoablation-related thromboembolic events occurred in one RCT (n = 163)[21].

PVI (6 case series)
As reported by six case series for 14,093 AF patients, the mean incidence of procedure-related thromboembolic complications was 0.525% (74/14,093) (range, 0.31% to 0.85% of patients per study)[74-79].

Table 40. Procedure-related embolic complications: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Forleo (2009)[6] N = 70 RCT	12 months (100%)	Procedure-related thrombo-embolic events	RF cPVI (n = 35) AADs (n = 35)	0% (0/35) 0% (0/35)	 --
Krittayaphong (2003)[8] N = 30 RCT	12 months (93%)	Treatment-related cerebral infarction	RF cPVI (n = 15) AADs ± cardioversion (n = 15)	7% (1/15) (occurred immediately after procedure) NR	 n/a
MacDonald (2011)[9] N = 41 RCT	6 months (93%)	Treatment-related stroke	RF cPVI (n = 22) AADs (n = 19)	5% (1/22) (6 days postablation; patient then withdrew) NR	 n/a
Pappone (2006/2011)[11, 12] N = 198 RCT	12 months (2006) (100%) 48 months (2011) (95%)	Treatment-related transient ischemic attack	RF cPVI (n = 99) AADs (n = 99)	1% (1/99) (shortly after procedure, resolved within a few seconds) NR	 n/a
Stabile (2006)[14] N = 137	12 months (97%)	Treatment-related stroke	RF cPVI (n = 68)	1% (1/68) (occurred during left atrium ablation, died of brain hemorrhage 9 months later)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
  RCT			AADs (n = 69)	NR	n/a
Wazni (2005)[15] N = 70 RCT	2 months	Treatment-related stroke	RF PVI (first-line therapy) (n = 33) AADs (first-line therapy) (n = 37)	0% (0/33) 0% (0/37)	 --
Pappone (2003)[18] N = 1171 Prospective cohort study	mean 30 months (98.4%)	Treatment-related stroke	RF cPVI (n = 589) AAD ± cardio-version (n = 582)	0% (0/589) NR	 n/a
Rossillo (2008)[19] N = 170 Retrospective cohort study	15 ± 7 months (% f/u NR)	Treatment-related stroke	RF PVI (n = 85) AAD + cardio-version (n = 85)	1% (1/85) (occurred just after electrical cardioversion, outcome NR) 1% (1/85) (occurred < 30 days after starting treatment, fatal)	 NR
Cryo-PVI versus AADs					
STOP AF Pivotal Trial (2010)[21] N = 245 RCT	12 months (93%)	Procedure-related embolic pneumonia (including stroke)	Cryo cPVI (n = 163) AADs (n = 82)	0% (0/163) n/a	 n/a

AADs: anti-arrhythmic drugs; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

Procedure- or treatment-related congestive heart failure

PVI versus AADs (1 RCT)

In a trial of patients with advanced heart failure, MacDonald et al. found that 15% (3/20) of patients who underwent PVI developed worsening heart failure within the first few days post-procedure (no data reported for the control group)[9]. Patients were followed for six months.

Radiofrequency PVI versus Cox-Maze surgery

No data were reported from this cohort study[22].

Cryo-PVI versus AADs

No data were reported from this trial[21].

PVI

No data were reported from any of the included case series[74-79].

Pericardial effusion or cardiac tamponade (Table 41)

PVI versus AADs (5 RCTs)

Pericardial effusion or cardiac tamponade occurred in a mean of 1.7% patients who received radiofrequency PVI (range, 1% - 9% patients per study, 6/295) as reported by five RCTs[7, 9, 11, 12, 14, 16]. More specifically, there were three cases pericardial effusion. One was described as small and transient, was not caused by cardiac perforation, and did not require pericardiocentesis; the patient was treated conventionally, and there were no long-term sequelae[11, 12]. Another case was ablation-related, did require pericardiocentesis, and long-term outcomes were not reported[14]. No information was provided regarding the treatment and sequelae of the ablation-related pericardial effusion of the third patient[16]. There were three cases of cardiac tamponade, both of which occurred during ablation, were treated with emergency pericardiocentesis, and resolved without long-term complications[7, 9]. In the AAD group, the mean reported incidence of pericardial effusion or cardiac tamponade was 0.8% as reported by two studies (range, 0% - 2%, n = 120)[7, 16], while the three remaining RCTs did not report these data for the control groups.

Radiofrequency PVI versus Cox-Maze surgery (1 cohort study)

Pericardial effusion was reported to occur in 4.6% of radiofrequency PVI patients by one cohort study (9/194). All nine patients were treated with pericardiocentesis. Four of the these patients developed tamponade (overall rate of 2.1% (4/194)), and one required surgical exploration[22].

Cryo-PVI versus AADs (1 RCT)

The RCT that compared cryo-PVI to AADs in patients with AF reported one case of ablation-related cardiac tamponade (0.6%, 1/163). There was also a case of pericardial effusion in the AAD group that was not drug-related. Both patients recovered[21].

PVI (5 case series)

The overall incidence of pericardial effusion or cardiac tamponade following PVI in 11,033 patients was 0.761% (84/11,033, range, 0.2% to 1.54% of patients per study) as reported by five large prospective case series[74-78].

Table 41. Pericardial effusion or cardiac tamponade: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) or Cox-Maze surgery in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Jais (2008)[7] N = 112	12 months (96%)	Cardiac tamponade	RF cPVI (n = 53) AADs (n = 59)	2% (1/53) (required pericardiocentesis, had favorable outcome) 2% (1/59) (required pericardiocentesis, had favorable outcome)	
MacDonald (2011)[9] N = 41 RCT	6 months (93%)	Cardiac tamponade	RF cPVI (n = 22) AADs (n = 19)	9% (2/22) (occurred during ablation procedure, underwent emergency pericardiocentesis and had no long-term complications) NR	
Pappone (2006/2011)[11, 12] N = 198 RCT	12 months (2006) (100%) 48 months (2011) (95%)	Pericardial effusion	RF cPVI (n = 99) AADs (n = 99)	1% (1/99) (not due to cardiac perforation, transient, did not require pericardiocentesis; treated conventionally, no long-term sequelae) NR	
Stabile (2006)*[14] N = 137 RCT	12 months (97%)	Pericardial effusion	RF cPVI (n = 68) AADs (n = 69)	1% (1/68) (ablation-related, required pericardiocentesis, long-term outcome NR) NR	
Wilber (2010)[16] N = 167 RCT	30 days % f/u NR	Pericardial effusion	RF cPVI (n = 106) AADs (n = 61)	1% (1/106) 0% (0/61)	 NR
Cryo-PVI versus AADs					
STOP AF Pivotal Trial (2010)[21] N = 245	12 months (93%)	Pericardial effusion / cardiac tamponade	Cryo cPVI (n = 163)	0.6% (1/163) (cardiac tamponade, procedure related, recovered)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
RCT			AADs (n = 82)	1% (1/82) (pericardial effusion, not drug related, recovered)	NR
Radiofrequency PVI versus Cox-Maze surgery					
Stulak (2011)[22] *N = 289* Retrospective cohort study	RF PVI: 3.1 yrs (median) Cox-Maze: 5.6 yrs (median) (*P* < .001) (92%)	Pericardial effusion	RF PVI (n = 194) Cox-Maze Surgery (n = 97)	4.6% (9/194) (required pericardiocentesis) (acute tamponade developed in 4 patients, 1 required surgical exploration) NR	 NR

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

Pulmonary vein stenosis (Table 42)

PVI versus AADs (3 RCTs, 2 cohort studies)
As reported by three RCTs, the mean incidence of pulmonary vein stenosis in AF patients randomized to receive PVI was 2.8% (3/108), and in those randomized to receive AADs was 0% (0/115)[7, 9, 15].

Two cohort studies reported that pulmonary vein stenosis occurred in a mean of 3.9% of PVI patients (8/205); however no data were reported for the AAD groups[17, 19].

Radiofrequency PVI versus Cox-Maze surgery (1 retrospective cohort study)
Nearly one-tenth of PVI patients developed pulmonary vein stenosis (9.8% (19/194)). Of these 19 patients, 14 required treatment: 18 balloon angioplasties and 11 stenting procedures were performed. No data were reported for the Cox-Maze surgery group[22].

Cryo-PVI versus AADs (1 RCT)
Pulmonary vein stenosis occurred in 3.1% of cryo-PVI patients and in 2% of patients in the AAD group (5/163 versus 2/84, respectively). Both patients in the AAD group who developed pulmonary vein stenosis had crossed over and received cryoablation. The pulmonary vein stenosis in two patients in the cryoablation group (1.2% of cryoablation patients) was considered to be procedure-related due to significant symptoms and disability[21].

PVI (4 case series)

The overall incidence of pulmonary vein stenosis following PVI for AF was 0.17% (8/4579) (range, 0.08% to 0.40% per study) as reported by four case series[74-76, 78].

Table 42. Pulmonary vein stenosis: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) or Cox-Maze surgery in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Jais (2008)[7] N = 112	12 months (96%)	Pulmonary vein stenosis (required dilatation and stent implantation, uneventful course thereafter)	RF cPVI (n = 53) AADs (n = 59)	2% (1/53) 0% (0/59)	 NR
MacDonald (2011)[9] N = 41	6 months (93%)	Pulmonary vein stenosis	RF cPVI (n = 22) AADs (n = 19)	0% (0/22) 0% (0/19)	
Wazni (2005)[15] N = 70	12 months	Pulmonary vein stenosis	RF PVI (first-line therapy) (n = 33) AADs (first-line therapy) (n = 37)	6% (2/33) (mild (n = 1); moderate (n = 1); severe (n = 0) 0% (0/37)	 NR
Lan (2009)[17] N = 240 Prospective	12 months (100%)	Pulmonary vein stenosis	RF circumferential OR segmental PVI (n = 120) AAD (n = 120)	1.7% (2/120) (moderate to severe) NR	
Rossillo (2008)[19] N = 170 Retrospective	15 ± 7 months (% f/u NR)	Pulmonary vein stenosis	RF PVI (n = 85) AAD + cardioversion (n = 85)	7% (6/85) (moderate; asymptomatic) NR	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Cryo-PVI versus AADs					
STOP AF Pivotal Trial (2010)[21] N = 245	12 months (93%)	Pulmonary vein stenosis	Cryo cPVI (n = 163) AADs (n = 82)	Procedure-related: 1.2% (2/163) (classified this way due to significant symptoms and disability) Total: 3.1% (5/163) 2% (2/84) (both patients had crossed over and rec'd cryoablation)	
Radiofrequency PVI versus Cox-Maze surgery					
Stulak (2011)[22] N = 289 Retrospective	RF PVI: 3.1 yrs (median) Cox-Maze: 5.6 yrs (median) (P < .001) (92%)	Pulmonary vein stenosis (≥ 50%)	RF PVI (n = 194) Cox-Maze Surgery (n = 97)	9.8% (19/194) (intervention required in 14 patients, including 18 balloon angioplasties and 11 stenting procedures) NR	

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

Atrioesophageal fistula and esophageal ulcerations

PVI versus AADs

No data on atrioesophageal fistula or esophageal ulcerations were reported in any of the comparative studies[6-12, 14-20].

Radiofrequency PVI versus Cox-Maze surgery

No data on atrioesophageal fistula or esophageal ulcerations were reported[22].

Cryo-PVI versus AADs

No data on atrioesophageal fistula or esophageal ulcerations were reported[21].

PVI (7 case series)

Together, three large prospective case series reported that atrioesophageal fistula occurred in 0.15% of patients (5/3306) (range, 0% to 0.30% of patients per study)[74-76].

In addition, four smaller prospective case series found that esophageal lesions occurred in a total of 6.6% of AF patients who underwent left atrial PVI (48/791) (range, 2.2% to 14.6% of patients per study)[80-83]. Additional study details may be found in Appendix table F9.

Deep vein thrombosis

Cryo-PVI versus AADs (1 RCT)

Deep vein thrombosis developed in 1.2% of patients randomized to receive cryoablation (2/163), neither cases were attributed to the procedure). All patients recovered. No data were reported for the AAD control group[21].

PVI (3 case series)

Taken together, data from three case suggest that pulmonary vascular complications occurred in approximately 0.08% of patients (3/3568) (range, 0.08% to 0.10% of patients per study)[74, 76, 78].

Peripheral vascular complications (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury) (Table 43)

PVI versus AADs (5 RCTs)

Five RCTs reported peripheral vascular complication rates following radiofrequency PVI. Overall, 2.3% (7/308) of PVI patients experienced a peripheral vascular complication, all of which were access-site hematomas[6-8, 11, 12, 16]. For the control AAD group, peripheral vascular complications occurred in 0.8% of patients (1/120) as reported by two RCTs[7, 16].

Radiofrequency PVI versus Cox-Maze surgery (1 cohort study)

Peripheral vascular complications occurred in 3.1% (6/194) of AF patients treated with radiofrequency PVI. Groin hematomas, femoral arterial pseudoaneurysm, and femoral arteriovenous fisula each occurred in two patients. No data were reported for the Cox-Maze surgery group[22].

Cryo-PVI versus AADs (1 RCT)

Peripheral vascular complications developed in 0.6% of patients randomized to receive cryoablation (1/163). One patient developed a procedure-related groin hematoma. No data were reported for the AAD control group[21].

PVI (4 case series)

Taken together, data from four case suggest that peripheral vascular complications occurred in approximately 1.70% of patients (78/4579) (range, 0.99% to 2.392 of patients per study)[74-76, 78].

Table 43. Peripheral vascular complications: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) or Cox-Maze surgery in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Forleo (2009)[6] N = 70	12 months (100%)	Access-site hematoma	RF cPVI (n = 35) AADs (n = 35)	3% (1/35) (required prolongation of hospitalization, no transfusion, no sequelae) NR	
Jais (2008)*[7] N = 112	12 months (96%)	Groin hematoma (both had favorable outcome)	RF cPVI (n = 53) AADs (n = 59)	2% (1/53) 2% (1/59)	
Krittayaphong (2003)*[8] N = 30	12 months (93%)	Groin hematoma	RF cPVI (n = 15) AADs ± cardioversion (n = 15)	7% (1/15) (minor) NR	
Pappone (2006/2011)*[11, 12] N = 198	12 months (2006) (100%) 48 months (2011) (95%)	Femoral hematoma	RF cPVI (n = 99) AADs (n = 99)	3% (3/99) (treated conventionally, no long-term sequelae) NR	
Wilber (2010)*[16] N = 167	30 days % f/u NR	Vascular access complication	RF cPVI (n = 106) AADs (n = 61)	1% (1/106) 0% (0/61)	 NR
Cryo-PVI versus AADs					
STOP AF Pivotal Trial (2010)[21] N = 245	12 months (93%)	Peripheral vascular complication	Cryo cPVI (n = 163) AADs (n = 82)	0.6% (1/163) Groin hematoma-0.6% (1/163) (recovered) NR	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus Cox-Maze surgery					
Stulak (2011)[22] N = 289 Retrospective	RF PVI: 3.1 yrs (median) Cox-Maze: 5.6 yrs (median) (P < .001) (92%)	Access complications	RF PVI (n = 194) Cox-Maze Surgery (n = 97)	3.1% (6/194) (groin hematoma (n = 2); femoral arterial pseudoaneurysm (n = 2), femoral arteriovenous fistula (n = 2)) NR	

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

Radiation Exposure

No data were reported by any of the included studies[6-12, 14-22, 74-79].

"AAD-related" adverse events (Table 44)

PVI versus AADs (4 RCTs, 1 cohort study)

Four RCTs reported the incidence "AAD-related side effects". Overall, in those patients randomized to receive PVI, AAD-related side effects occurred in 2.6% patients as reported by three RCTs. Side effects included (but were not limited to) gastrointestinal side effects and sinus node dysfunction[6, 8, 16]. For patients randomized to receive AADs, the overall incidence of AAD-related side effects was 16.2% (34/210) as reported by four RCTs. Reported side effects included (but were not limited to) corneal microdeposit, hypothyroidism, hyperthyroidism, thyrotoxicosis, abnormal liver function test, and sinus node dysfunction[6, 8, 11, 12, 16]. See Table 44 for further details.

One prospective cohort study reported "treatment-related complications" in 5.8% (7/120) of PVI patients compared with 9.2% (11/120) of AAD patients[17]. See Table 44 for further details.

Radiofrequency PVI versus Cox-Maze surgery (1 cohort study)

No relevant data reported.

Cryo-PVI versus AADs (1 RCT)

No relevant data reported.

Table 44. AAD-related adverse events: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) or Cox-Maze surgery in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Forleo (2009)[6] N = 70	12 months (100%)	AAD-related adverse events	RF cPVI (n = 35)	3% (1/35)	
			AADs (n = 35)	17% (6/35)	NS
Krittayaphong (2003)*[8] N = 30	3 months 12 months	AAD-related side effects	RF cPVI (n = 15) AADs ± cardioversion (n = 15)	21% (3/15) (GI side effects (n = 2), sinus node dysfunction (1)) 47% (7/15) (GI side effects (n = 6), corneal microdeposit (n = 2), hypothyroidism (n = 2), abnormal liver function test (n = 2), hyperthyroidism (n = 1), sinus node dysfunction (1))	 NR
Pappone (2006/2011)*[11, 12] N = 198	12 months (2006) (100%) 48 months (2011) (95%)	Thyrotoxicosis	RF cPVI (n = 99) AADs (n = 99)	NR 19% (19/99) (or 19/61 pts taking amiodarone, subclinical) In 7 pts, this "amiodarone-induced thyroid dysfunction was difficult to manage long-term."	
Wilber (2010)*[16] N = 167	30 days % f/u NR	Disabling drug intolerance (considered major adverse event)	RF cPVI (n = 106) AADs (n = 61)	0% (0/106) 5% (2/61)	 NR

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Lan (2009)[17] N = 240 Prospective	12 months (100%)	Treatment-related complications*	RF circumferential OR segmental PVI (n = 120)	5.8% (7/120)	
			AAD (n = 120)	9.2% (11/120)	NS

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

* Details on the majority of treatment-related complications were not provided per treatment group, but included: sinus bradycardia, hypotension, significant QT prolongation, hyperthyroidism, hypothyroidism and heaptic deterioration, pericardial tamponade requiring pericardiocentesis, moderate to severe pulmonary vein stenosis, and cerebral embolism leading to transient retrograde amnesia.

Other adverse events

A variety of other adverse events were reported in the comparative studies that evaluated PVI in AF patients. See Table 45.

Table 45. Other adverse events: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) or Cox-Maze surgery in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus AADs					
Jais (2008)*[7] N = 112	12 months (96%)	Hyperthyroidism	RF cPVI (n = 53) AADs (n = 59)	0% (0/53) 2% (1/59)	 NR
Pappone (2006/2011)*[11, 12] N = 198	12 months (2006) (100%) 48 months (2011) (95%)	Acute pulmonary edema	RF cPVI (n = 99) AADs (n = 99)	NR 4% (4/99) (these patients had all	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
				progressed to permanent AF and had not yet received ablation, all had other comorbidities, treated with rate control medication)	
Stabile (2006)*[14] N = 137	12 months (97%)	Treatment-related transient phrenic paralysis	RF cPVI (n = 68) AADs (n = 69)	1% (1/68) NR	
Wilber (2010)*[16] N = 167	30 days % f/u NR	Pulmonary edema	RF cPVI (n = 106)	1% (1/106)	
			AADs (n = 61)	0% (0/61)	NR
		Pneumonia	RF cPVI (n = 106)	1% (1/106)	
			AADs (n = 61)	0% (0/61)	NR
		Life-threatening arrhythmia	RF cPVI (n = 106)	0% (0/106)	
			AADs (n = 61)	3% (2/61)	NR
Cryo-PVI versus AADs					
STOP AF Pivotal Trial (2010)[21] N = 245	12 months (93%)	Occlusion to left interior pulmonary vein	Cryo cPVI (n = 163) AADs (n = 82)	0.6% (1/163) (sequelae) n/a	
		Pulmonary embolus	Cryo cPVI (n = 163)	0.6% (1/163) (not procedure or device related, recovered)	
			AADs (n = 82)	n/a	
		Phrenic nerve palsy	Cryo cPVI (n = 163)	Procedure-related injury: 0% (0/163) Total: 12/3% (20/163) (first-ablation pts); 10% (3/31) (reablation	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
				pts)	
			AADs (n = 82)	Total: 7% (6/82) (all patients had crossed over and rec'd cryoablation)	
		Systemic embolization (not stroke) (considered major adverse event)	Cryo cPVI (n = 163)	0% (0/163)	
			AADs (n = 82)	0% (0/82)	--
		Hemorrhagic event (not stroke) (considered major adverse event)	Cryo cPVI (n = 163)	1.2% (2/163)	
			AADs (n = 82)	2% (2/82)	.603
		"Serious Adverse Events"*	Cryo cPVI (n = 163)	12.3% (20/163)	
			AADs (n = 82)	15% (12/82)	.688
		Pneumonia	Cryo cPVI (n = 163)	2.5% (4/163)	
			AADs (n = 82)	2% (2/82)	NR
		Acute renal failure	Cryo cPVI (n = 163)	NR	
			AADs (n = 82)	1% (1/82)	NR
		Cardiac arrest	Cryo cPVI (n = 163)	1.2% (2/163) (myocardial infarction)	
			AADs (n = 82)	1% (1/82) (cardiopulmonary arrest)	NR
		Atrial appendage thrombus	Cryo cPVI (n = 163)	NR	
			AADs (n = 82)	1% (1/82)	NR

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency PVI versus Cox-Maze surgery					
Stulak (2011)[22] N = 289 Retrospective	RF PVI: 3.1 yrs (median) Cox-Maze: 5.6 yrs (median) (*P* < .001) (92%)	Myocardial infarction	RF PVI (n = 194)	NR	
			Cox-Maze Surgery (n = 97)	1% (1/97) (< 30 days; nonfatal)	
		Renal failure	RF PVI (n = 194)	NR	
			Cox-Maze Surgery (n = 97)	1% (1/97) (< 30 days; nonfatal)	
		Respiratory failure	RF PVI (n = 194)	NR	
			Cox-Maze Surgery (n = 97)	1% (1/97) (< 30 days; nonfatal)	

AADs: anti-arrhythmic drugs; AF: atrial fibrillation; cPVI: circumferential pulmonary vein isolation; n/a: not applicable; NR: not reported; PVI: pulmonary vein isolation; RCT: randomized controlled trials; RF: radiofrequency

* Serious adverse events included (each event occurred in one patient unless noted):

- Cryo cPVI group: worsening AF (n = 4), recurrent rapid AF, worsening atrial flutter (n = 2), myocardial infarction (n = 2), multiple organ failure, interstitial pneumonitis, pneumonia (n = 4), pericardial effusion (tamponade), acute pyelonephritis secondary to vesical catheter, occlusion to left interior pulmonary vein, hematoma from left groin, cardiopulmonary decompensation, deep vein thrombosis (n = 2), physical deconditioning secondary to procedural complications and immobilization, iletis, focal hemorrhage of ileum secondary to warfarin induced coagulopathy, *E.coli* bacteremia, pulmonary vein stenosis, right lung blebs with persistent air leak, Wegener's granulomatosis, pulmonary embolus, abdominal wall hemorrhage, sepsis-induced hypotensis, subarachnoid hypotension, and acute exacerbation of asthma.
- AAD group: worsening AF (n = 2), worsening atrial flutter (drug-related), pericardial effusion, cardiopulmonary arrest with resuscitation, cardiac tamponade, acute renal failure, gastrointestinal bleeding, AF, appendicitis, right diaphragm paresis (drug-related), non-bacterial meningitis, left atrial appendage thrombus, right wrist heparin lock insertion site infection.

4.4.2 Atrial Flutter

Summary

Studies. We evaluated safety data from all comparative studies included in Key Question 1: data from one RCT[23] that compared radiofrequency ablation was included. In addition, we identified six prospective case series[84-89] that were specifically designed to evaluate adverse events in at least 100 patients who underwent catheter ablation for atrial flutter. Case series data are briefly summarized here; more detailed information can be found in Appendix table F11.

Summary

Procedure- or treatment-related mortality: There is low quality evidence from 1 RCT that there is no difference in procedure- or treatment-related mortality rates following RF PVI compared with AADs in patients with atrial flutter. There were no treatment-related deaths in either group.

Studies

We evaluated safety data from all comparative studies included in Key Question 1: data from one RCT[23] that compared radiofrequency ablation was included. In addition, we identified six prospective case series[84-89] that were specifically designed to evaluate adverse events in at least 100 patients who underwent catheter ablation for atrial flutter. Case series data are briefly summarized here; more detailed information can be found in Appendix table F11.

Device- or procedure-related mortality

Radiofrequency ablation versus AADs (1 RCT)

No patients died as a result of treatments received in either the ablation or the AAD group (0% (0/52) versus 0% (0/51), respectively)[23].

Radiofrequency ablation (5 case series)

Five case series[84, 85, 87-89] reported no procedure-related deaths (0%, 0/1805) following radiofrequency ablation in patients with atrial flutter.

Device- or procedure-related thromboembolic events (including stroke or ischemic attack)

Radiofrequency ablation versus AADs (1 RCT)

No data reported.

Radiofrequency ablation (4 case series)
Overall, the incidence of ablation-related thromboembolic events was 0.3% (8/897) (0% to 1.8% of patients per study) as reported by four case series[84-86, 88].

Cardiac tamponade or pericardial effusion

Radiofrequency ablation versus AADs (1 RCT)
No data reported.

Radiofrequency ablation (3 case series)
The mean incidence of pericardial effusion or cardiac tamponade was 0.20% (2/1044) (0% to 0.7% of patients per study) as reported by three case series[84, 88, 89].

Deep vein thrombosis

Radiofrequency ablation versus AADs (1 RCT)
No data reported.

Radiofrequency ablation (3 case series)
Deep vein thrombosis occurred in a mean of 0.29% (3/1023) patients (0.2% to 0.6% of patients per study) as reported by three case series[84, 85, 88, 89].

Peripheral vascular complications (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury)

Radiofrequency ablation versus AADs (1 RCT)
No data reported.

Radiofrequency ablation (4 case series)
Peripheral vascular complications occurred in a mean of 0.85% (10/1173) patients (0.7% to 1.2% of patients per study) as reported by four case series[84, 85, 88, 89].

Treatment-related adverse events

Radiofrequency ablation versus AADs
The authors reported that significantly fewer treatment-related complications occurred in patients treated with ablation compared with those who underwent conversion to sinus rhythm (0% (0/52) versus 10% (5/51), respectively; $P = .03$). In the control group, these treatment-related complications included hypothyroidism (4% (2/51)), hyperthyroidism (2% (1/51)), and symptomatic sick sinus syndrome (4% (2/51))[23].

The following adverse events of interest were not reported by any of the included studies on atrial flutter:

- Device- or procedure-related congestive heart failure
- Pulmonary vein stenosis
- Atrioesophageal fistula
- Radiation exposure

4.4.3. Supraventricular tachyarrythmias (SVTs)

Summary

Studies. Safety data from all comparative studies included in Key Question 1 were evaluated. For AVNRT, data from three prospective[24, 25, 27] and one retrospective[26] cohort study were included. For AVRT, data from one RCT[29] and one retrospective cohort study[28] were included. For mixed populations of patients with SVT, data from one prospective cohort study[30] were included. In addition, six case series[87-92] that were specifically designed to evaluate adverse events following catheter ablation in at least 500 patients with SVT were also identified for inclusion. Case series data are briefly summarized in the last section on mixed populations; more detailed information can be found in Appendix table F18.

Summary.

Persistent AV block. There is insufficient evidence from one cohort study that ablation results in higher rates of persistent AV block compared with open perinodal surgery in patients with AVNRT (22.7% versus 4%, respectively).

Pacemaker implantation. There is insufficient evidence from one cohort study that there is no difference in the rate of pacemaker implantation in AVNRT patients who were treated with catheter ablation compared with open perinodal surgery (3.1% versus 3%, respectively).

No other comparative safety data were available.

Studies

Safety data from all comparative studies included in Key Question 1 were evaluated. For AVNRT, data from three prospective[24, 25, 27] and one retrospective[26] cohort study were included. For AVRT, data from one RCT[29] and one retrospective cohort study[28] were included. For mixed populations of patients with SVT, data from one prospective cohort study[30] were included. In addition, six case series[87-92] that were specifically designed to evaluate adverse events following catheter ablation in at least 500 patients with SVT were also identified for inclusion. Case series data are briefly summarized in the last section on mixed populations; more detailed information can be found in Appendix table F18.

4.4.3.1 Atrioventricular nodal reciprocating tachycardia (AVNRT)

Data from three prospective[24, 25, 27] and one retrospective[26] cohort study were considered for inclusion.

Device- or procedure-related mortality

No data were reported by any of the four cohort studies[24-27].

Device- or procedure-related embolic complications (including stroke or ischemic attack)

Radiofrequency ablation versus AADs

No data were reported[24].

Radiofrequency ablation versus skeletonization surgery (1 prospective and 1 retrospective cohort study)

The incidence of procedure-related embolic complications following ablation was 0.8% (1/120) as reported by Kimman et al. One patient had an ischemic cerebral infarction two hours after the procedure; the patient fully recovered[25]. No data were provided for the surgery control group. No data were reported by the retrospective cohort study[26].

Radiofrequency ablation versus no treatment

No data were reported[27].

Device- or procedure-related congestive heart failure

No data were reported by any of the four cohort studies[24-27].

Persistent AV block or pacemaker placement

Radiofrequency ablation versus AADs

No data were reported[24].

Radiofrequency ablation versus open perinodal dissection surgery (1 prospective and 1 retrospective cohort study) (Table 46)

Both studies reported atrioventricular (AV) block requiring pacemaker implantation. Kimman et al. reported that 30.0% (36/120) of patients in the radiofrequency AV node modification group had persistent first-degree AV block compared with 8% (2/26) in the open perinodal dissection surgery group. Pacemakers were implanted in 3.3% (4/120) and 8% (2/26) of patients in each treatment group, respectively[25]. Natale et al. reported that 2% of patients in each treatment group had inadvertent complete AV block, and pacemaker implantation was needed in 2% of patients following ablative AV node modification (1/43) and in no patients following surgical AV node medication (0/53)[26].

Radiofrequency ablation versus no treatment

No data were reported[27].

Table 46. Persistent AV block or pacemaker implantation: Cohort studies comparing catheter ablation with open perinodal dissection surgery in patients with AVNRT

Investigator (year)	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Radiofrequency ablation versus AADs					
Kimman (1999)[25] N = 146 Prospective	28 months (mean) (100%)	First-degree persisting AV block	RF ablation (n = 120)	30.0% (36/120)	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	8% (2/26)	NR
	28 months (mean) (100%)	Pacemaker implantation	RF ablation (n = 120)	3.3% (4/120)	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	8% (2/26)	NR
Natale (1993)[26] N = 96 Retrospective	10 months (mean) (100%)	AV block	RF ablation (n = 43)	2% (1/43)	
	38 months (mean) (100%)		Perinodal dissection surgery (n = 53)	2% (1/53)	--
	10 months (mean) (100%)	Pacemaker implantation	RF ablation (n = 43)	2% (1/43)	
	38 months (mean) (100%)		Perinodal dissection surgery (n = 53)	0% (0/53)	--

AV: atrioventricular; AVNRT: atrioventricular nodal reentrant tachycardia; RF: radiofrequency

Pericardial effusion or cardiac tamponade

No data were reported by any of the four cohort studies[24-27].

Pulmonary vein stenosis

No data were reported by any of the four cohort studies[24-27].

Atrioesophageal fistula

No data were reported by any of the four cohort studies[24-27].

Deep vein thrombosis
No data were reported by any of the four cohort studies[24-27].

Peripheral vascular complications (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury)
No data were reported by any of the four cohort studies[24-27].

Radiation exposure
No data were reported by any of the four cohort studies[24-27].

4.4.3.2 AVRT, including Wolff-Parkinson-White (WPW) Syndrome

Data from one RCT[29] and one retrospective cohort study[28] were considered for inclusion.

Device- or procedure-related mortality

Radiofrequency ablation versus AADs or surgery (1 retrospective cohort study)
No data were reported[28].

Radiofrequency ablation versus no treatment (1 RCT)
There were no cases of procedure-related death following radiofrequency ablation (n = 38) as reported by one RCT[29].

Device- or procedure-related embolic complications (including stroke or ischemic attack)
No data were reported by either study[28, 29].

Device- or procedure-related congestive heart failure
No data were reported by either study[28, 29].

Persistent AV block or pacemaker placement
No data were reported by either study[28, 29].

Pericardial effusion or cardiac tamponade
Radiofrequency ablation versus AADs or surgery (1 retrospective cohort study)
While no data were reported for patients treated with ablation (n = 20) or long-term AADs (n = 12), 5% (1/20) of patients who underwent surgery had procedure-related pleural effusion requiring hospitalization[28].

Radiofrequency ablation versus no treatment (1 RCT)
No data were reported[29].

Pulmonary vein stenosis
No data were reported by either study[28, 29].

Atrioesophageal fistula
No data were reported by either study[28, 29].

Deep vein thrombosis
No data were reported by either study[28, 29].

Peripheral vascular complications (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury)

Radiofrequency ablation versus AADs or surgery (1 retrospective cohort study)
No data were reported[28].

Radiofrequency ablation versus no treatment (1 RCT)
One patient developed a femoral hematoma following electrophysiological testing (3% (1/38) as reported by one RCT[29].

Radiation exposure
No data were reported by either study[28, 29].

Other adverse events
Radiofrequency ablation versus AADs or surgery (1 retrospective cohort study)
One case of procedure-related mild mitral regurgitation occurred in the ablation group (5% (1/20)). In the surgery group, two procedure-related adverse events occurred: one patient had a complete heart block (5% (1/20) and another had pericardial effusion (5% (1/20)). No data were reported for the long-term AAD treatment group[29].

Radiofrequency ablation versus no treatment (1 RCT)
The following additional adverse events were reported following ablation: pneumothorax (5% (2/38)) and permanent right bundle branch block (3% (1/38)). In the no treatment group, one patient had a myocardial infarction due to ventricular fibrillation (3% (1/38))[29].

4.4.3.3. Sinus tachycardia, atrial tachycardia, and focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia

No comparative studies met our inclusion criteria.

4.4.3.4. Mixed populations

Studies
Data from one prospective cohort study[30] was considered for inclusion. In addition, six case series[87-92] that were specifically designed to evaluate adverse events following catheter ablation in at least 500 patients with SVT were also identified for inclusion. More detailed information can be found in Appendix table F18.

Device- or procedure-related mortality
Radiofrequency ablation versus AADs (1 prospective cohort study)
No data were reported[30].

Radiofrequency ablation (6 case series)
Six case series[87-92] reported a total of four procedure-related deaths following radiofrequency ablation in 12,604 patients with supraventricular tachyarrhythmia (overall procedure-related mortality: 0.032% of patients (range, 0% to 0.30% of patients per study)). Two patients died periprocedurally: one from a dissected left main coronary artery[91], another from an undetected pacemaker malfunction[89]. One patient died suddenly a week following the procedure, and one patient died two weeks postablation from a presumed pulmonary embolus[91].

Device- or procedure-related embolic complications (including stroke or ischemic attack)

Radiofrequency ablation versus AADs (1 prospective cohort study)
No data were reported[30].

Radiofrequency ablation (4 case series)
Overall, procedure-related embolic complications occurred in a mean of 0.14% of 7798 SVT patients (11/7798) (range, 0% to 0.57% of patients per study) as reported by four case series[88-91].

Device- or procedure-related congestive heart failure
No data were reported by any included study[30, 87-92].

Persistent AV block

Radiofrequency ablation versus AADs (1 prospective cohort study)
No data were reported[30].

Radiofrequency ablation (4 case series)
Persistent AV block was reported in four case series reporting on 10,548 SVT patients: the mean incidence of persistent AV block was 0.379% (40/10,548) (range, 0.16% to 1.00% of patients per study)[88, 89, 91, 92].

Pericardial effusion or cardiac tamponade

Radiofrequency ablation versus AADs or surgery (1 retrospective cohort study)
One ablation patient had pericardial effusion/tamponade (3% (1/39)); emergency pericardiocentesis was performed and there were no permanent sequelae. No data were reported for the AAD group[30].

Radiofrequency ablation versus no treatment (5 case series)
The overall incidence of pericardial effusion or cardiac tamponade in a total of 10,051 SVT patients was 0.567% (57/10,051) (range, 0.2% to 1.1% of patients per study) as reported by five case series[88-92].

Pulmonary vein stenosis
No data were reported by any included study[30, 87-92].

Atrioesophageal fistula
No data were reported by any included study[30, 87-92].

Deep vein thrombosis

Radiofrequency ablation versus AADs (1 prospective cohort study)
No data were reported[30].

Radiofrequency ablation (3 case series)
The overall incidence of deep vein thrombosis in 6094 SVT ablation patients was 0.03% (2/6094) (range, 0 % to 0.08% of patients per study) as reported by three case series[88-90].

Peripheral vascular complications (including pseudoaneurysm, hematoma at catheter insertion site, vascular injury)

Radiofrequency ablation versus AADs (1 prospective cohort study)
No data were reported[30].

Radiofrequency ablation (5 case series)
The overall incidence of peripheral vascular complications in 11,678 SVT ablation patients was 0.839% (98/11,678) (range, 0.4% to 3.23% of patients per study) as reported by five case series[88-92].

Radiation exposure
Radiofrequency ablation versus AADs (1 prospective cohort study)
No data were reported[30].

Radiofrequency ablation (4 case series)
One case series reported on case of radiation injury (0.10% of patients (1/1050))[91]. No details were provided.

4.5 Key Question 4: Does catheter ablation have any differential efficacy or safety compared with other treatment options in subpopulations?

4.5.1 Atrial fibrillation

Catheter Ablation versus Antiarrhythmic Drugs (AADs)

Summary
We found no strong evidence of the differential effectiveness of catheter ablation versus any alternative treatment option in any subpopulation. Although four studies examined outcomes in various subpopulations, none of these studies pre-specified the subgroup analyses, none of the studies performed a test of interaction as the method of subgroup analysis, and some of the studies were inadequately powered to detect differences in treatment effect.

Studies
Four RCTs met our inclusion criteria: three studies investigated predictors for AF recurrence[11, 12, 14, 15] and one study investigated predictors for time to treatment failure[16]. Data from one RCT could not be included: although the authors stated that they evaluated whether a variety of baseline variables were predictors of AF recurrence (and found no significant associations), the specific variables that were examined were not reported[6]. Three cohort studies met our inclusion criteria: one study investigated predictors for AF recurrence[17], one study investigated predictors for all-cause mortality and adverse events[169], and one study investigated predictors for mortality[20].

Data are summarized in Table 47.

Age (4 RCTs, 2 cohort studies)

RCTs: Age was not a significant predictor of AF recurrence as reported by three RCTs[11, 12, 14, 15] or of time to recurrence as reported by one RCT[16].

Cohort studies: Age over 65 years was a significant predictor of all-cause mortality in ablation patients as reported by one cohort study ($P < .001$), but did not significantly predict risk of adverse events in the same study[169]. Another study

found that age was not a significant predictor of AF recurrence (age cutoff not defined)[17].

Left ventricular ejection fraction (LVEF) (2 RCTs, 2 cohort studies)

RCTs: One RCT reported that LVEF was an independent predictor of AF recurrence in patients randomized to AAD therapy, with a hazard ratio of 1.08 (95% CI, 1.03, 1.13; *P* = .003)[11, 12]. However, it was not clear whether higher or lower LVEF was associated with recurrence. The same study found that LVEF was not an independent predictor of recurrence in patients randomized to receive PVI. A second RCT reported that LVEF did not have a statistically significant effect on AF recurrence in either the entire study population or in those patients randomized to receive PVI [14]. An LVEF threshold was not defined in either study.

Cohort studies: A left ventricular ejection fraction (LVEF) < 45% was a significant predictor of all-cause mortality and adverse events in one study (*P* < .001)[169], but was not significantly associated with increased AF recurrence in another study (LVEF threshold not reported)[17].

Left ventricular mass index (1 cohort study)

RCTs: No data reported.

Cohort studies: A left ventricular (LV) mass index greater than 125 g/m^2 was a significant predictor of all-cause mortality and adverse events in one cohort study (*P* < .001)[169].

Hypertension (3 RCTs, 3 cohort studies)

RCTs: Hypertension was a significant predictor of AF recurrence in patients in the AAD group only (hazard ratio, 2.31 (95% CI, 1.34, 3.97; *P* = .003)) as reported by one RCT[11, 12]. In contrast, another RCT found that hypertension was not a significant predictor of AF recurrence[14], while a third reported that hypertension did not predict time to treatment failure[16].

Cohort studies: Hypertension was not a statistically significant predictor of AF recurrence, mortality, or adverse events as reported by three cohort studies[17, 20, 169].

AF duration (3 RCTs, 2 cohort studies)

RCTs: One RCT found that AF duration was a significant predictor of AF in the AAD group only, with a hazard ratio of 1.03 (95% CI, 1.01, 1.11; *P* = .015)[11, 12]. In contrast, a second RCT reported that AF duration had no effect on AF recurrence[14], while a third reported that AF duration was not significantly associated with time to treatment failure[16].

Cohort studies: AF duration was not a statistically significant predictor of AF recurrence, mortality, or adverse events as reported by two cohort studies[17, 169].

History of coronary heart disease (4 RCTs, 2 cohort studies)

RCTs: Coronary heart disease was not a significant predictor of AF recurrence as reported by three RCTs[11, 12, 14, 15] or of time to recurrence as reported by one RCT[16].

Cohort studies: One cohort study reported that history of CAD (coronary artery disease) was a significant predictor of all-cause mortality and adverse events ($P < .001$)[169]. Another study found that CAD was not a significant predictor of mortality[20].

History of stroke or transient ischemic attack (1 cohort study)

RCTs: No RCTs were identified that evaluated this predictor.

Cohort studies: One cohort study found that history of stroke or transient ischemic attack was a significant predictor of adverse events ($P < .001$), but not of all-cause mortality[169].

Other

None of the following were found to be predictors of the specified outcomes:

- Sex:
  - AF recurrence (3 RCTs[11, 12, 14, 15], 2 cohort studies[17, 169])
  - Time to treatment failure (1 RCT[16])
  - Mortality (2 cohort studies[17, 169])
  - Adverse events (2 cohort studies[17, 169])
- Diabetes:
  - AF recurrence (3 RCTs[11, 12, 14, 15], 3 cohort studies[17, 20, 169])
  - Time to treatment failure (1 RCT[16])
  - Mortality (three cohort studies[17, 20, 169])
  - Adverse events (three cohort studies[17, 20, 169])
- Left atrial size/diameter:
  - AF recurrence (3 RCTs[11, 12, 14, 15], 3 cohort studies[17, 20, 169])
  - Time to treatment failure (1 RCT[16])
  - Mortality (three cohort studies[17, 20, 169])
  - Adverse events (three cohort studies[17, 20, 169])
- History of β-blocker use:
  - AF recurrence (2 RCTs[14, 15])
- Paroxysmal versus persistent AF:
  - AF recurrence (1 RCT[14])
  - Mortality (1 cohort study[20])
- Chronic AF:

  - Mortality(1 cohort study[169])
  - Adverse events (1 cohort study[169])
- Medication use (including amiodarone, flecainide, propafenone, ACE-inhibitors or angiotensin receptor blockers, verapamil or diltiazem, statins, oral anticoagulants, oral antiaggregants):
  - AF recurrence (1 RCT[14])
- Number of symptomatic AF episodes:
  - Time to treatment failure (1 RCT[16])
- Frequency of AF episodes:
  - AF recurrence (1 cohort study[17])
- Prior failure of Class II or IV drugs:
  - Time to treatment failure (1 RCT[16])
- Body mass index:
  - AF recurrence (1 cohort study[17])
- Systolic and diastolic blood pressure:
  - AF recurrence (1 cohort study[17])
- History of myocardial infarction:
  - Mortality (1 cohort study[20])
- History of renal disease:
  - Mortality (1 cohort study[20])

Table 47. Differential efficacy or effectiveness: PVI compared with AADs in patients with Atrial Fibrillation

Study	Outcome	Subpopulation	Results*	Interpretation
RCTs				
Pappone (2006/2011)†[11, 12] N = 198 12 months	AF recurrence	Age	ns	Hypertension, longer duration of AF, and LVEF are associated with a higher risk of AF recurrence in AAD patients only. No significant predictors of AF recurrence were found in the ablation treatment group.
		Gender	ns	
		LA size	ns	
		LVEF (threshold NR)	Ablation: ns AAD: HR = 1.08 (1.03 – 1.13, P = .003)	
		Hypertension	Ablation: ns AAD: HR = 2.31 (1.34 – 3.97, P = .003)	
		AF duration (years)	Ablation: ns AAD: HR = 1.03 (1.01 – 1.11, P = .015)	
Stabile (2006) †[14] N = 137 12 months	AF recurrence	Age	ns	The only significant predictor of AF recurrence was the type of treatment (HR for AAD = 3.2, 95% CI = 2.0 – 5.1, P = NR).
		Gender	ns	
		LVEF (threshold NR)	ns	
		Hypertension	ns	
		AF duration (years)	ns	
		Heart disease	ns	
		LA diameter (mm)	ns	

Study	Outcome	Subpopulation	Results*	Interpretation
Wazni (2005)†[15] N = 70 12 months	AF recurrence	Age	ns	There was a significant difference in recurrence of symptomatic AF during follow-up between patients receiving PVI (13%, 4/32) or AAD (63%, 22/35), but no significant differences in subgroups.
		LVEF (threshold NR)	ns	
		Structural heart disease	ns	
		AF duration (months)	ns	
		LA size (cm)	ns	
Wilber (2010) ‡[16] N = 167 9 months	Time to treatment failure	Age	ns	The only significant predictive factor for predicting treatment failure was the type of treatment (HR for ablation = 0.30, 95% CI = 0.19 – 0.47, P < .001).
		Gender	ns	
		Diabetes	ns	
		Hypertension	ns	
		Structural heart disease	ns	
		AF duration (years)	ns	
		LA dimension (mm)	ns	
Cohort studies				
Lan (2009)[17] N = 240 12 months	AF recurrence	Age	ns	The only significant predictor of AF recurrence was the type of treatment: SPVI (RR = 0.35, 95% CI = 0.18 – 0.65, P = .002) and amiodarone + losartan (RR = 0.41, 95% CI = 0.22 – 0.77, P = .006); other treatments included CPVA and amiodarone alone. No difference in AF recurrence-free survival was found between SPVI and amiodarone + losartan treatment groups.
		Gender	ns	
		LA diameter (cutoff NR)	ns	
		LVEF (threshold NR)	ns	
		AF history (years)	ns	
Pappone, Augello (2003)†[169] N = 1171 30 months	Mortality (all causes)	Age (> 65 years)	significant association, data NR	History of CAD, LVEF < 45%, LV mass index > 125 g/m^2, and age > 65 years were significantly associated with higher risk of death. The study authors also added maintenance of SR to their multivariate analysis. There were no substantial changes in the significance of the predictive factors.
		Gender (male)	ns	
		LVEF (< 45%)	significant association, data NR	
		Hypertension	ns	
		AF duration (> 2 years)	ns	
		CAD	significant association, data NR	
		LA diameter (> 45 mm)	ns	
		LV mass index > 125 g/m^2	significant association, data NR	
		Prior stroke or TIA	ns	
	Adverse events	Age (> 65 years)	ns	History of CAD, LVEF < 45%, LV mass index > 125 g/m^2, male gender, CAD, and prior stroke or TIA were
		Gender (male)	significant association, data NR	
		LVEF (< 45%)	significant association, data	

Study	Outcome	Subpopulation	Results*	Interpretation
			NR	significantly associated with higher risk of an adverse event (mainly heart failure and ischemic cerebrovascular events). The study authors also added maintenance of SR to their multivariate analysis. There were no substantial changes in the significance of the predictive factors.
		Hypertension	ns	
		AF duration (> 2 years)	ns	
		CAD	significant association, data NR	
		LA diameter (> 45 mm)	ns	
		LV mass index > 125 g/m^2	significant association, data NR	
		Prior stroke or TIA	significant association, data NR	
Sonne (2009)§[20] N = 351 69 months	Mortality	CAD	ns	The only significant predictive factor for mortality was the type of treatment (HR for ablation = 0.30, 95% CI = 0.19 – 0.47, P < .001).
		Hypertension	ns	
		Diabetes	ns	
		LA diameter (>40 mm)	ns	

AAD: antiarrhythmic drugs; AF: atrial fibrillation; CAD: coronary artery disease; CI: confidence interval; CPVA: circumferential pulmonary vein ablation; HR: hazard ratio; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; NR: not reported; ns: not statistically significant (P ≥ .05); PVI: pulmonary vein isolation; RR: relative risk; SPVI: segmental pulmonary vein isolation; SR: sinus rhythm; TIA: transient ischemic attack

* Study results from univariate[16] or multivariate[11, 12, 14, 17, 20, 169] Cox regression model; details on analysis not reported[15].
† Study included in the 2009 AHRQ HTA[5].
‡ It is unclear which predictive factors were included in the multivariate Cox regression model.[16]
§ Multivariate Cox regression model also included an additional treatment group: atrioventricular junctional ablation[20].

4.5.2 Atrial flutter

Catheter Ablation versus Antiarrhythmic Drugs (AADs)

Summary

We found no strong evidence of the differential effectiveness of catheter ablation versus any alternative treatment option in any subpopulation. Although four studies examined outcomes in various subpopulations, none of these studies pre-specified the subgroup analyses, none of the studies performed a test of interaction as the method of subgroup analysis, and some of the studies were inadequately powered to detect differences in treatment effect.

Studies

One RCT met our inclusion criteria[23]. This study investigated predictors of recurrence of AF after one episode of symptomatic atrial flutter.

History of atrial fibrillation

In patients who had atrial flutter recurrence, there was a trend toward a higher rate of AF in patients with a history of AF compared with patients with no history of AF, however,

the details of the results were not clear. (The authors stated that the "only significant predictor of AF identified after the first episode of atrial flutter was a previous episode of AF (P = .0034)"[23].

4.5.3 Supraventricular tachycardias (SVT)

Summary

We found no strong evidence of the differential effectiveness of catheter ablation versus any alternative treatment option in any subpopulation. Although four studies examined outcomes in various subpopulations, none of these studies pre-specified the subgroup analyses, none of the studies performed a test of interaction as the method of subgroup analysis, and some of the studies were inadequately powered to detect differences in treatment effect.

Studies

One RCT comparing catheter ablation to no treatment in patients with WPW Syndrome met our inclusion criteria[29]: this study investigated predictors for occurrence of arrhythmic events, including supraventricular tachycardia, atrial fibrillation, and ventricular fibrillation. None of the following subgroups were found to be significant predictors of arrhythmic events in this study: age, gender, anterograde refractory period of the accessory pathways before and after isoproterenol treatment, the number of accessory pathways, and the type of inducible arrhythmia[29].

In addition, one cohort study met our inclusion criteria[30]: this study investigated predictors for disease-specific symptoms (including dizziness, palpitations, or syncope) and quality of life. The study reported that ablation was associated with sustained improvement in quality of life and reduction in disease-specific symptoms, especially in women and patients under 50 years of age, but the details of this analysis were not reported[30].

4.6 Key question 5 : What is the evidence of cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term?

4.6.1. Atrial Fibrillation

Summary

Studies. Five cost utility analyses which compared pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) were included[93-97]. All studies were reasonably well-conducted, with QHES scores ranging from 84 to 100 (mean score of 91) after methodological evaluation. Two studies[94, 96] were conducted within the US, while the other three[93, 95, 97] were done from an international perspective (Canada, Sweden, and UK). All studies were published in or after the year 2006.Three of the studies did not include a statement disclosing the source of funding, but authors in four of the studies had consulting relationships with catheter device manufacturers. All of the studies relied on a deterministic Markov decision-analytic model to simulate the evolution of health states over time and estimate associated costs.

Summary

Five-year time horizon: When considering a five-year time horizon, there is moderate evidence that PVI is more cost-effective than AADs depending on how much society is willing to pay per QALY. Three studies evaluated the cost effectiveness of PVI compared with AADs based on a five-year time horizon. The population of interest was hypothetical cohorts of patients with paroxysmal AF and who were refractory to AADs. The patients ranged from 52 to 65 years of age. Only one of the studies was conducted with a US perspective. In two of the studies (including the US study), the incremental cost effectiveness ratio (ICER) ranged from approximately $51,400 to $59,200 per quality-adjusted life year (QALY). In one of the studies, the ICER ranged from $33,201 to $44,221 to QALY, decreasing with increasing stroke risk. All studies concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal AF depending on how much society is willing to pay per QALY.

Lifetime horizon. When considering a lifetime horizon, there is moderate evidence that PVI is more cost-effective than AADs depending on how much society is willing to pay per QALY. Three studies evaluated the cost effectiveness of PVI compared with AADs based on a lifetime horizon. The population of interest was hypothetical cohorts of patients with paroxysmal or persistent AF with low to moderate stroke risks. Two of the studies specified that patients were considered to be refractory to AADs and that patients ranged from 52 to 65 years of age. Only one of the studies was conducted with a US perspective. One study reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation was more cost-effective than AADs. The two other studies reported ICERs ranging from approximately $12,400 to $29,100 per QALY, and concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal or persistent AF depending on how much society is willing to pay per QALY. In general,

ablation is more cost-effective in the lifetime horizon compared with the five-year horizon models due to long-term costs associated with AAD therapy.

Results

Assasi et al. 2010

Overview:

Assasi et al.[93] evaluated the cost-effectiveness of minimally invasive ablation and antiarrhythmic drug therapy (AAD) as practical treatments for atrial fibrillation (AF). The economic analysis consisted of a review of previous studies as well as primary evaluation; both were sections of a larger Health Technology Assessment investigating the clinical effectiveness of ablation. The objective of the economic analysis was to estimate the expected costs and the number of quality adjusted life years (QALY) corresponding to each treatment arm and then evaluate the two using the incremental cost-effectiveness ratio (ICER).

The study was designed to describe resource costs and clinical practices specific to health care in Canada. The publicly funded Canadian health care system was the perspective assumed by the study. A discount rate of 5% was applied to all relevant costs and quality of life measures with the base year being 2004.

A deterministic Markov decision-analytic model was constructed to simulate the evolution of health states over time. The model was chosen to have a similar structure to Rodgers[97]. The model incorporated both a short-term and long-term component. A short-term decision-tree was designed to reflect the observed clinical outcomes associated with each treatment. The estimates from the short-term model were then used as the starting health states for the long-term model. Beyond twelve months, the patients entered into the long-term model that simulates probable health states every three months for five years.

Assumptions:

A hypothetical cohort was designed to reflect a target population of patients suffering from paroxysmal AF who had been unsuccessfully treated with an AAD. The target demographic was selected to be 65-year-old males with a $CHADS_2$ risk of stroke score of 2. The AAD intervention was assumed to be 200 mg/day of amiodarone.

In addition to estimates found previously within the HTA, the authors also performed a literature review to populate the model and describe the effectiveness of the treatment arms. Normal sinus rhythm after twelve months was assumed to be 76% for ablation patients and 26% for AADs. The rate of reversion back to atrial fibrillation from normal sinus rhythm was estimated to be 3.6% for radiofrequency ablation and 22% for AADs. The risk of ischemic stroke was 4% based on the assumed $CHADS_2$ score of 2. Radiofrequency ablation complications included cardiac tamponade, stroke, pulmonary vein stenosis and operative death with respective risks of 0.8%, 0.3%, 0.2% and 0.5%. Complications associated with AADs were minor and major bleeds on warfarin with respective risks of 0.5%, and 1.2%.

Costs were similarly derived from several sources. Procedural costs per ablation were assumed to be $12,179. The cost of amiodarone was estimated to be $433 per year. The cost of complications and side effects was taken from the literature. The authors expected the cost of gastrointestinal bleed to be $6,023, the cost of ischemic stroke to be $53,576 and the cost of hemorrhagic stroke to be $56,573.

Utility values for patients in normal sinus rhythm were taken from estimates of population utilities for the age and gender of the patient. Time spent in the AF health state was decremented by 0.05. Utility measure decrements for events considered by the study varied with the health state the patient was in when the event occurred. Pulmonary toxicity was assigned a weight of 0.6 while ischemic and hemorrhagic strokes resulted in utility weights of 0.46 and 0.28 respectively.

Results:
The base-case results showed ablation to be more expensive and yielded more QALYs. The expected costs were $21,150 and $12,611 for ablation and AAD therapy, respectively. The model predicted a QALY of 3.42 for ablation and 3.27 for AADs. These values result in an ICER or $59,194.

To test how robust the results were, the authors explored several possible variations in their sensitivity analysis. First, the nature of the risk of stroke was examined while allowing age and gender to vary. With a constant risk of ischemic stroke the ICER across genders was similar, but decreased to $57,088 for 55-year-old patients and increased to $65,129 for 75-year-old patients. Assuming increasing risk of ischemic stroke the ICER for 55-year-olds was $67,918 for females and $65,672 for males, while for 75-year-olds it dropped to $49,363 for females and $55,275 for males. A $CHADS_2$ score of 0 caused the ICER to increase to $68,822 and a score of 4 reduced it to $44,652. Extending the time horizon to ten years produced an ICER or $14,273. The disutility of being in the AF health state proved to be an influential parameter. Varying it from 0 to 0.02 to 0.08 resulted in ICER of $221,831, $101,083 and $38,390 respectively.

Conclusions and limitations:
With the estimated ICER of $59,194/QALY, Assasi et al. conclude that minimally invasive ablation was a cost-effective alternative to AAD therapy for 65 year old male patients suffering from paroxysmal AF if society was willing to pay that amount or greater for each quality adjusted year of life.

There are several potential limitations to consider with this study. The indirect costs were not incorporated into the analysis. The clinical data estimating the efficacy of the interventions was derived from only short-term data. The authors found limited published sources detailing the disutility of not being in the normal sinus rhythm health state, which in the sensitivity analysis was shown to be highly significant. Lastly, the economic analysis was designed specifically for the Canadian health care system and consideration should be taken when generalizing the results outside of that context.

Notes:

- No direct funding was disclosed.
- Several authors have had consulting relationships with AF ablation device manufacturer and have helped to develop AF ablation techniques.
- This was a reasonably-well conducted economic study, with a QHES of 90/100.

Chan et al. 2006

Overview:
Chan et al.[94] performed a cost-utility analysis assessing the cost-effectiveness of PVI +left linear lesions. Antiarrhythmic drug therapy (amiodarone) and rate control therapy were used as the comparative interventions. The analysis addressed different risk levels of stroke when computing expected costs and evaluating the effectiveness of each intervention. The ICER is presented as the primary outcome.

The study was conducted in the United States and a direct cost perspective is assumed. All costs and quality of life measures were discounted at 3% per year and values given in 2004 units.

The methodology included a Markov decision-analytic model that simulated changes in health states over time. The model followed patients until death at three-month intervals incorporating both short- and long-term potential outcomes.

Assumptions:
The target population was stratified into three hypothetical cohorts. There were two 65-year-old cohorts; one with low and one with moderate risk of stroke. There was also a 55-year-old cohort that was assumed to have a moderate risk of stroke. Patients with moderate risk of stroke were defined as having a single risk factor (hypertension, diabetes mellitus, coronary artery disease, or congestive heart failure), while patients at low risk of stroke had zero risk factors.

Effectiveness measures were derived from a literature review. It was assumed that ablation efficacy was 80% with a redo rate of 30% and a relapse rate back to AF after restoration of normal sinus rhythm of 2%. Ablation complications included cardiac tamponade, stroke, atrio-esophageal fistula and operative death with respective risks of 0.7%, 0.8%, 0.2% and 0.1%. AAD therapy had a cardioversion success rate of 85% with reversion to AF of 30% in the first six months and 5% each year after. Complications associated with AADs were pulmonary toxicity, stroke within first month and mortality with respective risks of 0.5%, 0.3%, and 0.01%.

Costs were inferred from various sources. Medicare reimbursement, hospital accounting, Red Book for wholesale drug cost, and literature review were all used. The cost per ablation was estimated to be $16,500 and the cost of amiodarone was assumed to be $1,200 per year.

To account for patient utility levels the authors referred to estimates made by published literature. Normal sinus rhythm was given a utility level of 1, amiodarone was weighted by 0.98, mild stroke with intracranial bleeding was weighted by 0.76, and moderate stroke with intracranial bleeding was weighted by 0.39. Pulmonary toxicity decreased utility by a factor of 0.6 and all short-term events deducted a factor of 0.5.

Results:
The base-case results were presented for each of the three cohorts. For 65-year-old patients with moderate risk of stroke the expected costs for ablation, AAD and rate control were $52,369, $43,358, and $39,391 respectively. Their QALY estimates were 11.06, 10.75 and 10.81. These values in turn yield an ICER with ablation of $29,068 for AAD and $51,800 for rate control therapy. In the cohort of 65-year-old patients with low risk of stroke the expected costs for ablation, AAD and rate control were $43,036, $38,425, and $24,540 respectively. Their QALY estimates were 11.40, 11.02 and 11.21. The resulting ICER with ablation was $12,134 for AAD and $98,900 for rate control therapy. For 55-year-old patients with moderate risk of stroke the expected costs for ablation, AAD and rate control were $59,380, $55,795, and $50,509 respectively. Their QALY estimates were 14.26, 13.81 and 13.95. These values in turn give an ICER with ablation of $7,966 for AAD and $28,700for rate control therapy.

The study conducted a one-way sensitivity analysis comparing PVI to rate control therapy. The rate of stroke, discount factor, PVI reversion rate, PVI cost, utility of warfarin therapy, rate of hemorrhage, and the efficacy of the rate control. The ICER range did not exceed $95,000 per QALY for any of the variables examined in one-way analysis, which considered only patients at moderate risk of stroke included in analysis. A multivariate sensitivity analysis was also performed for ablation and rate control. Running Monte Carlo simulations suggested that for 65-year-olds with moderate risk of stroke there was a 22% chance greater that the ICER could be more than $100,000/QALY and 40% chance less than $50,000/QALY. For 55-year-olds with moderate risk of stroke there was only a 4% chance greater that the ICER could be more than $100,000/QALY and 82% chance less than $50,000/QALY.

Conclusions and limitations:
Chan et al. found the cost-effectiveness of ICER of PVI + left linear lesions to be closely tied to the risk of stroke associated with individual AF patients. Younger patients with a lower likelihood of stroke had an ICER as low as approximately $8,000 when comparing ablation to AAD therapy. The cost-effectiveness decreased with age and as risk of stoke increased. 65-year-old patients with a moderate risk of stroke had an ICER nearly four times greater than the younger cohort at $29,068/QALY. The authors concluded that in moderate-risk patients, ablation a feasible, cost-effective alternative; especially if the efficacy rates in restoring sinus rhythm is capable of reducing morbidity.

The study mentions a potential limitation could be that the model focuses on 55 and 65 year old cohorts and that the finding may not generalize to patients of different ages. It also suggests that alternative AADs could have been compared with different results.

Notes:

- No direct funding was disclosed.
- Two authors have financial relationships with AF ablation device manufacturer and have helped to develop AF ablation techniques.
- This was a reasonably-well conducted economic study, with a QHES of 88/100.

Eckard et al. 2009

Overview:
Eckard et al.[95] assessed the cost-effectiveness of radiofrequency ablation and antiarrhythmic drug therapy (amiodarone) for patients suffering from atrial fibrillation. The primary outcome under consideration was measured in terms of ICER.

The study was carried out in Sweden. All relevant costs and measures effectiveness were presented from a Swedish direct cost perspective. Results were discounted at a rate of 3% using 2006 as the base year.

A multi-state Markov decision model was implemented. Hypothetical patients moved from mutually exclusive health states on an assumed annual basis allowing estimates of associated costs and treatment effectiveness to be determined.

Assumptions:
Symptomatic AF patients not previously responding to AADs were used as the target population. Twelve-month rates of efficacy were available from published randomized clinical trials. Further literature search yielded numerous data sources including register data and published papers. Both paroxysmal and persistent AF was considered.

Treatment effectiveness estimates were used to predict transition between health states and assign quality of life approximations. Overall efficacy, measured in terms of being AF free after 12 months was assumed to 78% for radiofrequency ablation and 9% for AADs. An average of 1.47 radiofrequency ablation procedures were needed per patient with a complication rate of 3%. The risk of stroke was assumed to be constant at 1.5% in all health conditions.

The cost of a single radiofrequency ablation procedure was $9,860, while the annual cost of AAD treatment was $1,640. The expected cost of a procedural complication was $2,190. Anticoagulation medication (warfarin) cost $770 per year. The cost of a stroke was assumed to be $19,180 in the first year, after which a cost of $4,380 per annum was used.

The expected QALY weights were derived from a review of published literature. For males under the age of 69 a value of 0.83 was applied. For those between the age of 70 and 79 a value of 0.8 was used. Anyone over the age of 80 was assigned a QALY weight of 0.74. Patients suffering from AF received a QALY penalty of 0.1 and the occurrence of a stroke incurred a decrement of 0.25.

Results:
The base-case analysis presented the expected costs along with an estimate of the number of QALYs. The projected costs were $25,460 and $30,440 for radiofrequency ablation and AADs respectively. Radiofrequency ablation yielded 9.46 QALYs while AAD was only 8.86. AAD was dominated with respect to both cost and effectiveness by radiofrequency ablation.

A one-way sensitivity analysis was performed to measure the impact the annual probability of reversion back to AF. The treatment alternatives were compared using their ICER. At an annual reversion rate of 5%, 10%, and 15% the respective ICERs were increased from $8,290 to $26,460 to $48,310.

Conclusions and limitations:
With the modeling technique used and the assumed input parameters Eckard et al. concluded that that radiofrequency ablation is a cost-effective alternative to AADs. Ablation procedures were both cost saving and more effective than the use of AAD therapy. As the rates of reversion increases, the ICER of the two interventions still falls below common thresholds.

There are potential limitations in the applicability of these results to the US healthcare system. Given that the study was conducted in Sweden costs and effectiveness measure may differ. Also worth noting is a considerable discrepancy between assumed success rates of both radiofrequency ablation and AAD compared to other credible studies.

Notes:
- The authors disclosed no direct funding.
- All costs were converted to US dollars using purchase power parities.[170]

Reynolds et al. 2009

Overview:
Reynolds et al.[96] compared the cost-effectiveness of radiofrequency ablation combined with AAD therapy against the use of AAD therapy alone as treatment options for AF. The study produced estimates of the ICER to compare the two intervention methods.

The objective of the study was to model the cost-effectiveness of radiofrequency ablation from a U.S. health care system perspective. All costs and utility measures were discounted rate of 3%. No base year was specified.

A disease simulating Markov model was implemented to forecast probable costs. The model had a 5-year time horizon with health state transitions occurring every month. A short-term decision tree designed to capture the immediate outcomes of radiofrequency ablation. In the short-term phase of the model, outcomes measured included the risk of operative death and other operative complications (cardiac tamponade, PV stenosis, and stroke). Long-term outcomes were also predicted. In the long-term phase, patients were at risk of a recurrence of AF and drug toxicity.

Assumptions:
A hypothetical cohort represented a target population of patients suffering from paroxysmal AF refractory to at least one AAD. 60-year-old males without severe structural heart disease were the assumed demographic.

Model input parameters for costs and effectiveness were found from clinical trials, a patient registry, Medicare claims data, and the primary data from the authors' institution. Ablation efficacy was assumed to be 60% with a redo rate of 25%. AAD was successful 30% of the time after the first ablation and 35% of the time after the second. Radiofrequency ablation complications included cardiac tamponade, stroke, pneumothorax, vascular access and operative death with respective risks of 0.8%, 0.3%, 1.2% and 0.05%. The reoccurrence of AF while on AAD therapy was 65% and there was a 10% risk of pulmonary toxicity. It was assumed that the risk of non-procedural stroke was the same in both cohorts and that those on AAD would not crossover to radiofrequency ablation.

Procedural costs per ablation were assumed to be $15,000. The cost while well of taking amiodarone was estimated to be $3,500. The cost of complications and side effects was also taken into consideration. The authors expected the cost of a stroke in the first year to be $8,200, the cost of vascular access to be $8,000 and telemetry admission was $5,000.

To account for changes in quality of life, utility levels were assigned to chronic health states. In the absence of previously published data, responses to SF-36 and SF-12 health surveys were used to approximate utility levels. Patients who were well, whether post ablation or AAD, were assigned a QALY weight of 0.79. The patient's quality of life was estimated to be 0.76 after a procedural related minor stroke and 0.39 for a major stroke.

The disutility for short term events was also considered and non-fatal drug toxicity, telemetry admission and ablations complication were assumed to impact the patient's quality of life for 7, 3 and 4 days respectively.

Results:
The base-case analysis found ablation to be more expensive and result in more QALYs. The expected costs were $26,584 and $19,898 for ablation and AAD therapy respectively. The model estimated the number of QALYs of 3.51 for ablation and 3.38 for AADs. These values result in an ICER or $51,431.

The study included an analysis of the models sensitivity to the input parameters. One-way sensitivity analyses was conducted for all model inputs and two-way sensitivity analysis was performed on the utility of successful sinus rhythm maintenance after ablation and the utility of the rate control health state in an attempt to measure the combined impact of these key variables on the model's behavior. Varying the time horizon to only 3 years resulted in an ICER of $157,000 while extending it to 10 years cause the ICER to drop below $1,000. Letting the cost of ablation increase to $20,000 predicted an ICER or approximately $100,000. Assuming the difference between utility levels was greater than 0.04 resulted in an ICER that was under $100,000.

Conclusions and limitations:
Reynolds et al. found ablation to be a cost-effective alternative to AAD therapy alone provided society is willing to pay approximately $51,500 for each quality adjusted life year. The sensitivity analysis demonstrated that reasonable fluctuations in input parameters did not change this conclusion.

The authors address many of the potential limitations of their study. First, they caution that the results are not readily applicable to other subsets of the AF population including newly detected and persistent AF. Second, not all possible treatment alternatives were considered, some of which may have been reasonable alternatives. Lastly, many of the input parameters were difficult to estimate, resulting in some model parameters being defined to mimic previously published results.

Notes:
- The publication states that the lead author was supported by a grant from the National Institutes of Health.
- Two co-authors are reported to have consulted with an AF ablation device manufacturer.
- This was a reasonably-well conducted economic study, with a QHES of 84/100.

Rodgers et al. 2008

Overview:
Rodgers et al.[97] investigated the cost-effectiveness of radiofrequency ablation and antiarrhythmic drug therapy (AAD) as a curative treatment for atrial fibrillation (AF). Expected costs and the number of quality adjusted life years (QALY) corresponding to each treatment arm were estimated and the incremental cost-effectiveness ratio (ICER) was then calculated to make a comparison is between the two.

The study was designed to account for costs specific to health care in the United Kingdom. The perspective assumed by the study was the UK National Health Service and Personal Social Services. All costs and quality of life measures were discounted at 3.5% per year and were given in 2006 units.

The analysis consisted of a deterministic Markov decision-analytic model that was used to simulate changes in health states over time. Long-term costs and patient utility levels were then inferred by monitoring these estimated health states. The model incorporated both a short-term and long-term component. A short-term decision-tree was designed to reflect the observed clinical outcomes associated with each treatment. The estimates from the short-term model were then used as the starting health states for the long-term model. Beyond twelve months, the patients entered into the long-term model that simulates probable health states each year until death.

Assumptions:
The study considered patients with paroxysmal AF who were refractory to at least one AAD. A hypothetical cohort was constructed using data from a systematic review in addition to a synthesis of clinical effectiveness found in the same health technology assessment. Patients were assumed to 52 years old and 80% male.

Meta-analytic techniques were used to generate treatment effectiveness estimates appropriate for the UK's health care system. An approximation for the restoration of normal sinus rhythm after twelve months was assumed to 84% for radiofrequency ablation patients and 37% for those taking AADs. The rate of reversion back to atrial fibrillation from normal sinus rhythm was estimated to be 3.3% for radiofrequency ablation and 28.8% for AADs. The results were categorized by the risk of stroke given by the $CHADS_2$ index score. An annual risk of 1.9%, 2.8%, 4%, and 5.3% were assigned to $CHADS_2$ scores of 0, 1, 2, 3, and 4 respectively. The authors made a distinction between the risk of stroke for patients with normal sinus rhythm and patients with AF by consulting published literature, which suggested the presence of AF to be significantly associated with a 60% increase in the risk of stroke. The likelihood of mortality caused by stroke was assumed to have a relative of risk of 7.4 compared the general population and 2.3 for each subsequent year. Potential radiofrequency ablation complications included cardiac tamponade, stroke, PV stenosis and operative death with respective risks of 1.2%, 0.28%, 0.74% and 0.05%. Side effects associated with AADs were pulmonary

complication, minor bleed on warfarin and major bleed on warfarin with respective risks of 15%, 2.4%, and 15%.

Costs were derived from several sources. Procedural costs were estimated using an expert opinion, which figured the cost per ablation to be $15,635. The *British National* Formulary was used to obtain an estimate for the cost of drugs to be $51 per year. Literature was reviewed in order to determine the cost of complications and side effects. The authors estimated the cost of tamponade to be $1,298, the cost of PV stenosis to be $5,127, the cost of toxicity to be $2,385, and lastly, the cost of stroke was assumed to $15,002.

Utility measure decrements considered by the study depended on the health state the patient was in when the event occurred. While experiencing AF, a decrement of 0.003 utils was applied for ablation and 0.09 for AADs. From normal sinus rhythm no decrement was assumed for ablation and 0.02 for AAD therapy. Patients who had a mild stroke were assumed to have a quality of life of 0.74 while moderate strokes implied a quality of life of 0.38.

Results:
Two alternatives were presented in the base-case analysis which were further subdivided according to $CHADS_2$ scores. First, results were provided under the assumption that the quality of life benefits lasted for the patient's lifetime. In this case, the ICER was found to be $12,372/QALY for patients with a CHADS score = 0, $12,400/QALY ($CHADS_2$ = 1) and $12,600/QALY ($CHADS_2$ = 3). A second analysis was presented that assumed that the quality of life benefits only lasted for five years. Under this assumption, the ICER was much higher and was calculated to be $44,221/QALY for patients with a CHADS score = 0, $40,658/QALY ($CHADS_2$ = 1) and $33,201/QALY ($CHADS_2$ = 3).

A sensitivity analysis was carried out using a constant $CHADS_2$ index score of 1. Varying the duration of the quality of life measure from 10 to 20 years resulted in ICERs of $23,542 and $15,128. If the starting age was assumed to be 65 the ICER was $46,849 and $17,887 for the five-year quality of life measure and lifetime measure respectively. Assuming a reversion back to AF post-radiofrequency ablation of 15% caused the ICER to increase to $51,058 and $13,871 for time horizon of five-years and lifetime respectively. No significant influence was seen when varying gender or the source of data.

Conclusions and limitations:
When determining the cost-effectiveness of radiofrequency ablation compared to AAD Rodger et al. showed the time horizon of health benefits to be essential. If the quality of life benefits are maintained over the patient's remaining lifetime radiofrequency ablation's ICER falls well below conventional thresholds for a broad range of underlying baseline assumptions. This suggests radiofrequency ablation to be a cost-effective alternative to AAD if society is willing to pay approximately $12,500 for each quality

adjusted life year. When the quality of life benefits are assumed to only last for five years, the ICER of radiofrequency ablation increases dramatically, and given the uncertainty of many of the model's parameters the cost-effectiveness less conclusive.

There are however a number of potential limitations. First, the quality of life estimates were found to be difficult to quantify and suspect to a high degree of uncertainty. Together with the difficulties of measuring, determining the appropriate time horizon for the quality of life estimates proved to be a significant factor when interpreting the results. A thorough sensitivity analysis was conducted to explore the breadth of these potential limitations. Also important to note when generalizing the results of this study, is the cost-effectiveness outcomes presented were specifically designed with the UK's National Health Service in mind.

Notes:

- The study was commissioned by a grant from the National Institute for Health Research Technology Assessment Programme. The authors claim to have no competing interests.
- All costs were converted from British pounds to US dollars using purchase power parities.
- This was a well conducted economic study, with a QHES of 100/100.

4.6.2. Atrial flutter

No studies were identified that met our inclusion criteria.

4.6.3 Supraventricular Tachycardias (SVTs)

Summary

Studies. Two cost utility analyses which radiofrequency ablation with anti-arrhythmic drugs (AADs) were included[98, 99]. Both studies were reasonably well-conducted, with QHES scores of 88 and 73 after methodological evaluation. Both studies were conducted within the US and were published the years 1993 and 2000, making them older studies. Neither study was funded from nor did authors disclose relationships with device manufacturers. Both studies relied on a deterministic Markov decision-analytic model to simulate the evolution of health states over time and estimate associated costs.

Summary

Lifetime horizon. Considering a lifetime horizon, there is low quality evidence from two cost utility studies that radiofrequency ablation is more cost effective than AADs to treat patients with SVT. Both studies evaluated the cost effectiveness of ablation compared with AADs based on a lifetime horizon. The population of interest was a hypothethical

cohort of patients 40 years of age with either highly symptomatic SVT (60% considered to have AVNRT)[99] or with WPW Syndrome[98]. Both studies reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation treatment was more cost-effective than AADs alone.

Cheng et al. 2000

Overview:
Cheng et al.[99] evaluated the cost-effectiveness of radiofrequency ablation with that of medical management of supraventricular tachycardia. The objective of the economic analysis was to calculate the expected costs and the number of QALYs associated with each treatment arm and then compares the two through their ICERs.

The study was carried out in the United States and assumes a societal perspective. A discount rate of 3% was applied to convert all relevant costs and quality of life measures into 1999 units.

A state-transition Markov model was used to simulate the evolution of health states over time. Patients were followed over the course of their remaining lifetime at 1-month intervals.

Assumptions:
A hypothetical cohort was designed to reflect a target population of symptomatic patients suffering from supraventricular tachycardia. It was assumed that patients had 4.6 unscheduled visits per year to emergency room or physician's office while receiving drug therapy and had been suffering from symptoms for a median of 3 years. Demographically, 70% of patients were female and it were assumed to be 40-years-old. Additionally, 30% have a bypass tract and 60% have atrioventricular nodal reentrant tachycardia.

Probabilities of clinical outcomes were estimated from the literature and treatment efficacy was estimated from reports from clinical studies at major medical centers. Ablation success rate was 93% and the reoccurrence of AF after ablation was 8%. The risk of major complication from radiofrequency ablation was 1.5%. The efficacy of AAD therapy was assumed to be 60%.

Costs were projected from a major academic hospital and published literature. It was assumed that radiofrequency ablation cost $8,190 per procedure. The annual drug prescription was estimated to $120.

Quality of life was reduced to 0.833 for patients undergoing long-term drug therapy and 0.828 for those receiving episodic drug treatment. Patients cured by radiofrequency ablation experienced a quality of life of 0.983. Those having an atrioventricular block

were assumed to have a quality of life of .776. Procedural complications and unscheduled visits to a physician incurred a disutility penalty measured in days of perfect health lost, which were 1 and 0.25 days respectively.

Results:
The base-case analysis found AAD therapy to be dominated by radiofrequency ablation. The expected costs were $61,880 and $89,820 for ablation and AAD respectively. The expected number of QALYs was 21.66 for ablation and 18.56 for AAD therapy.

Cheng et al. included one-way, multivariate, and best vs. worse case sensitivity analysis. Varying key variables did not change the outcome of the results. Simultaneously changing all variables within their 95% confidence range resulted in radiofrequency ablation dominating AAD in 93.7% of the simulations. Comparing changes in annual cost of drug therapy and increases in QoL after radiofrequency ablation, authors again found radiofrequency ablation to dominated AAD with for all cost greater than $250/year and changes in QoL from 0.01 to 0.15.

Conclusions and limitations:
The authors found that radiofrequency ablation significantly improve the quality of life and reduces costs associated with treating supraventricular tachycardia. Eliminating the need for long-term drug therapy and frequent unscheduled visits to an emergency department or a physician's office ultimately offset the higher upfront expense of radiofrequency ablation.

The model measured the lifetime costs of care for patients who have supraventricular tachycardia. Radiofrequency ablation was cost saving over this time horizon; however, the authors recognize that the time required to recover the initial cost of radiofrequency ablation may be 10 years or more. The influence of time horizon assumptions could be explored further.

Notes:
- Grant support from Agency for Healthcare Research and Quality and from Veterans Affairs Health Services Research and Development Services.
- No conflicting interests were stated.
- This was a reasonably-well conducted economic study, with a QHES of 88/100.

Hogenhuis et al. 1993

Overview:
Hogenhuis et al.[98] performed a cost utility analysis of alternative treatments for patients suffering from Wolf-Parkinson-White Syndrome. Five interventions were considered in all including observation alone, observation until cardiac arrest and then drug therapy,

non-invasively guided drug therapy, surgical ablation and radiofrequency ablation. The treatment arms were evaluated in terms of their ICER.

The study was conducted in the United States. All costs and measures of clinical effectiveness were argued from a U.S. societal perspective. Results were discounted at a rate of 5% using 1992 as the base year.

A Markov simulation model was implemented. Hypothetical patients transition from mutually exclusive health states on an assumed annual basis. The model follows patients for the remainder of their lifetime.

Assumptions:
Hogenhuis et al. focused specifically on patients with Wolf-Parkinson-White Syndrome (WPW). The target population was defined to consist of 40-year-old patients suffering from WPW Syndrome.

Treatment effectiveness estimates were acquired from published literature. Radiofrequency ablation success was estimated to be 85% while AAD therapy had an efficacy of 90%. Possible complications from radiofrequency ablation include mortality, inguinal hematoma, and cardiac tamponade, which had respective risks of 0.01%, 5%, and 1%. Annual mortality associated with AAD was assumed to be 0.02%.

Cost data was estimated by Clinical Cost Manager and by hospital specific costs using a relatively small sampling of only 13 consecutive patients. Hospital, physician and vascular surgery cost were assumed to be $3,000, $1,700 and $5,000 respectively. The occurrence of cardiac tamponade was estimated to cost $600.

Adjustments to utility levels were assigned using authors judgment. AF episodes led to a quality of life of 0.9. Drug side effects gave patients a quality of life of 0.95 and cardiac arrest episodes were weighted by 0.85. A heart block (permanent pacemaker) caused the quality of life of a patient to drop to 0.99 for the remainder of their life.

Results:
The base-case analysis presented the expected costs along with an estimate of QALYs. The projected costs were $6,250 and $20,250 for radiofrequency ablation and AADs respectively. Radiofrequency ablation yielded 17.21 QALYs while AAD therapy resulted in 11.18 QALYs. AAD therapy was dominated by radiofrequency ablation.

A one-way sensitivity analysis was performed to measure the impact of certain variables. The analysis showed the cost of radiofrequency ablation and rate of incidence of AF in asymptomatic patients to be most sensitive variables.

Conclusions and limitations:
The model constructed by the authors found that radiofrequency ablation was under most circumstances, a cost-effective treatment alternative for patients with WPW.

A potential limitation of the Hogenhuis et al. study is that the utility scores for each health state were assigned by the authors with the use of a validated instrument. The year of publication should also be taken into consideration.

Notes:
- Supported by grants from the National Library of Medicine and from the John A. Hartford Foundation.
- No conflicting interests were stated.
- This was a reasonably-well conducted economic study, with a QHES of 73/100.

Term/ Abbreviation	Definition
ICER	Incremental Cost Effectiveness Ratio defined to be the difference in cost divided by the difference in QALY. A generalized measure of cost per unit of improvement.
NSR	Normal sinus rhythm
QALY	Quality Adjusted Life Years. A utility weighted measure of patients' duration and quality of life.
QHES	Quality of Health Economics Score

5. Summary by Key Question – Strength of Evidence

Summary of the overall quality of evidence for primary findings have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report.

Table 48. Quality of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes in persons with atrial fibrillation compared with other treatment options?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
PVI versus AADs: Freedom from Recurrence (PRIMARY OUTCOME)											
RF PVI vs. AADs	6-12 mos. 714 (7 RCTs) 6-12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	50% (95% CI, 43%, 58%; *P* < .00001) NNT: 2 (95% CI, 2, 2)	PVI	74.6% (303/406) (56 – 89%)	23.6% (87/369) (9 – 43%)
	48 mos. 198 (1 RCT) 48 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	61% (95%, CI, 48%, 70%) NNT: 2 (95% CI, 1, 2)	PVI	73% (72/99)	12% (12/99)
Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low	63% (95% CI, 52%, 70%) NNT: 2 (95% CI, 1, 2)	PVI	69.9% (114/163)	7% (6/82)

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
PVI versus AADs: Mortality (not procedure-related) (PRIMARY OUTCOME)											
RF PVI vs. AADs	137 (1 RCT**) 12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	1% (1/68) **	3% (2/69) **
Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0.6% (1/163)	0% (0/82)
PVI versus AADs: Stroke (not procedure-related) (PRIMARY OUTCOME)											
RF PVI vs. AADs	140 (2 RCTs†† 12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0% (both studies) (0/68) ††	0% (both studies) (0/72) ††
Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0.6% (1/163)	0% (0/82)
PVI versus AADs: Congestive heart failure (PRIMARY OUTCOME)											
RF PVI vs. AADs	198 (1 RCT) 48 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0% (0/99)	0% (0/99)
Cryo-PVI vs. AADs	245 (1 RCT) 12 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0.6% (1/163)	0% (0/82)
PVI versus Cox-Maze Surgery: Freedom from recurrence (PRIMARY OUTCOME)											
RF PVI vs Cox Maze	289 (1 cohort	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious imprecision§	Undetected	Insufficient	NS	NS	74% (144/194)	84% (81/97)

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
	study) 54 mos.										
PVI versus Cox-Maze Surgery: Freedom from recurrence <u>in the absence of AADs</u> (PRIMARY OUTCOME)											
RF PVI vs Cox Maze	289 (1 cohort study) 54 mos.	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Insufficient	26%	Surgery	56% (109/194)	82% (80/97)
PVI versus Cox-Maze Surgery: Stroke (not procedure-related) (PRIMARY OUTCOME)											
RF PVI vs Cox Maze	289 (1 cohort study) 54 mos.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious imprecision‡	Undetected	Insufficient	NS	NS	1.7% (3/194)	2% (2/97)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

<u>Reasons for downgrading quality of evidence:</u>
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

** Only 1 RCT reported data for both treatment groups. Mortality rates were similar as reported for the PVI group only by 2 additional RCTs and for the AAD group only by 1 additional RCT.
†† 2 RCTs reported data for both treatment groups. Stroke rates were similar as reported for the AAD group only by 1 additional RCT.

Table 49. Quality of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes in persons with atrial flutter compared with other treatment options?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
PVI versus AADs: Freedom from recurrence (PRIMARY OUTCOME)											
RF ablation vs. AADs	104 (1 RCT) 13 ± 6 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate	26% (95% CI, 13%, 41%) NNT: 4 (95% CI, 2, 8)	Ablation	96% (50/52)	70% (36/52)
PVI versus AADs: Mortality (not procedure-related) (PRIMARY OUTCOME)											
RF ablation vs. AADs	104 (1 RCT) 13 ± 6 mos.	Serious risk of bias*	No serious inconsistency	No serious indirectness	Serious imprecision§	Undetected	Low	NS	NS	11% (6/52)	16% (8/52)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 50. Quality of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes in persons with AVNRT compared with other treatment options?

								Effect		Treatment groups		
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**	
Catheter ablation versus AADs: Improvement of symptoms – patient-reported freedom from symptoms (SECONDARY OUTCOME)												
RF ablation vs. AADs	93 (1 cohort study) 1-8 years	Serious risk of bias†	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Insufficient	39% (versus chronic AADs) 55% (versus short-term AADs)	Ablation	100% (18/18)	Chronic AADs 61% (15/24)	Short-Term AADs 45% (17/38)
Catheter ablation versus Open Perinodal Dissection Surgery: Freedom from recurrence (PRIMARY OUTCOME)												
RF ablation vs. Surgery	242 (2 cohort studies) 14 yrs. (1 study, NR in other)	Serious risk of bias†	No serious inconsistency.	No serious indirectness.	Serious imprecision§	Undetected.	Insufficient	NS	NS	87.8% (143/163) (85 – 95%)	93% (63/69) (88 – 94%)	
Catheter ablation versus no treatment: Freedom from recurrence (PRIMARY OUTCOME)												
RF ablation vs. no treatment	27 (1 cohort study) 13 – 23 mos.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious imprecision§	Undetected	Insufficient	64%	Ablation	100% pts (16/16)	36% pts (4/11)	

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:

* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)

† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)

‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 51. Quality of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes in persons with AVRT compared with other treatment options?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Catheter ablation versus AADs: Improvement of symptoms – patient-reported freedom from symptoms (SECONDARY OUTCOME)											
RF ablation vs. AADs	32 (1 cohort study) 8 – 58 mos.	Serious risk of bias†	No serious inconsistency.	No serious indirectness.	Serious imprecision§	Undetected	Insufficient	82%	Ablation	90% (18/20)	8% (1/12)
Catheter ablation versus surgery: Improvement of symptoms – patient-reported freedom from symptoms (SECONDARY OUTCOME)											
RF ablation vs. surgery	40 (1 cohort study) 8 – 58 mos.	Serious risk of bias†	No serious inconsistency.	No serious indirectness.	No serious imprecision	Undetected	Insufficient	NS	NS	90% (18/20)	100% (20/20)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 52. Strength of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes in persons with WPW Syndrome compared with other treatment options?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Catheter ablation versus no treatment: Freedom from recurrence (PRIMARY OUTCOME)											
RF ablation vs. no treatment	24 mos. 76 (1 RCT) 24 mos. (median)	Serious risk of bias*	No serious inconsistency.	No serious indirectness.	No serious imprecision	Undetected	Moderate	55% (95% CI, 35%, 70%) NNT: 2 (95% CI, 1, 3)	Ablation	95% (36/38)	40% (15/38)
	48 mos. 72 (1 RCT) 5 years	Serious risk of bias*	No serious inconsistency.	No serious indirectness.	No serious imprecision	Undetected	Moderate	55% (95% CI, 34%, 70%) NNT: 2 (95% CI, 1, 3)	Ablation	93% (35/37)	23% (14/35)
Catheter ablation versus no treatment: Mortality (PRIMARY OUTCOME)											
RF ablation vs. no treatment	24 mos. 76 (1 RCT) 24 mos. (median)	Serious risk of bias*	No serious inconsistency.	No serious indirectness.	Serious imprecision‡	Undetected	Low	NS	NS	0% (0/38)	0% (0/38)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 53. Strength of evidence summary for Key Question 1: Does catheter ablation improve patient outcomes in persons with mixed SVT diagnoses compared with other treatment options?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Catheter ablation versus AADs: Improvement of symptoms – patient-reported freedom from symptoms (SECONDARY OUTCOME)											
RF ablation vs. AADs	95 (1 cohort study) 12 mos.	Serious risk of bias†	No serious inconsistency	No serious indirectness	Serious imprecision§	Undetected	Low	30%	Ablation	85% (33/39)	55% (24/44)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 54. Quality of evidence summary for Key Question 1a: If catheter ablation is efficacious compared with other treatment options for atrial flutter, is there differential efficacy between radiofrequency ablation versus cryoablation?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**RF Ablation (% pts)**	**Cryoablation (% pts)**
Radiofrequency ablation versus Cryoablation: Freedom from recurrence (PRIMARY OUTCOME)											
RF ablation vs. Cryoablation	134 (3 RCTs) 5-15 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness.	Serious imprecision§	Undetected.	Low	NS	NS	63% (43/65) (33 – 93%)	57% (37/65) (31 – 85%)
Radiofrequency ablation versus Cryoablation: Persistent bidirectional conduction block (PRIMARY OUTCOME)											
RF ablation vs. Cryoablation	191 (1 RCT) 3 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness.	Serious imprecision§	Undetected	Low	19% (95% CI, 4%, 33%) NNT: 5 (95% CI, 3, 24)	RF Ablation	85% (51/60)	62% (42/64)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (RF ablation – cryoablation) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT); RF: radiofrequency

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 55. Quality of evidence summary for Key Question 1a: If catheter ablation is efficacious compared with other treatment options for AVNRT, is there differential efficacy between radiofrequency ablation versus cryoablation?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**RF Ablation (% pts)**	**Cryoablation (% pts)**
Radiofrequency ablation versus Cryoablation: Freedom from recurrence (PRIMARY OUTCOME)											
RF ablation vs. Cryoablation	739 (3 RCTs) 6 - 12 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness.	No serious imprecision	Undetected.	Moderate	5% (95% CI, 1%, 9%) NNT: 21 (95% CI, 11, 92)	RF Ablation	95.4% (349/366) (71–99%)	90.5% (325/359) (77–92%)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (RF ablation – cryoablation) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT); RF: radiofrequency

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 56. Quality of evidence summary for Key Question 2: What is the evidence regarding the comparative efficacy of various approaches to radiofrequency catheter ablation for patients with atrial fibrillation?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Approach 1 (% pts)**	**Approach 2 (% pts)**
PVI versus WACA: Freedom from recurrence (PRIMARY OUTCOME)											
PVI vs. WACA	500 (5 RCTs) 3-15 mos.	Serious risk of bias*	Serious inconsistency **	No serious indirectness	No serious imprecision	Undetected	Low	10% (95% CI, 1%, 18%) NNT: 10 (95% CI, 5, 73)	WACA	PVI 55.5% (141/254) (56 – 89%)	WACA 65.4% (161/246) (9 – 43%)
PVI versus PVI + additional left-sided ablation lines: Freedom from recurrence (PRIMARY OUTCOME)											
PVI vs. PVI + left lines	1243 (8 RCTs) 7-36 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	No serious imprecision	Undetected	Moderate	NS	NS	PVI 65.5% (366/559) (12 – 87%)	PVI + left lines 70.3% (444/631) (21 – 88%)
PVI versus PVI + additional right-sided ablation lines: Freedom from recurrence (PRIMARY OUTCOME)											
PVI vs. PVI + right lines	683 (4 RCTs) 8-12 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	No serious imprecision	Undetected	Moderate	NS	NS	PVI 68.2% (236/346) (32 – 100%)	PVI + right lines 70.8% (218/308) (34 – 100%)
PVI versus PVI + CFE: Freedom from recurrence (PRIMARY OUTCOME)											
PVI vs. PVI + CFE	587 (6 RCTs) 12-23 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	No serious imprecision	Undetected	Moderate	17% (95% CI, 9%, 25%)	PVI+ CFE	PVI 50.5% (159/315) (11 – 89%)	PVI + CFE 67.6% (184/272) (39 – 91%)

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Approach 1 (% pts)**	**Approach 2 (% pts)**
								NNT: 6 (95% CI, 4, 11)			

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)
** Serious risk of inconsistency: 3/5 studies favored WACA, 1/5 studies favored PVI

Table 57. Quality of evidence summary for Key Question 3: What is the evidence regarding the safety of catheter ablation for patients with atrial fibrillation?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**PVI (% pts)**	**Control (% pts)**
Procedure- or treatment-related mortality											
RF PVI vs. AADs	112 (1 RCT**) 12 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0% (0/53) **	0% (0/59) **
Procedure- or treatment-related thromboembolic events											
RF PVI vs. AADs	310 (3 RCTs††) 2-15 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0.7% (1/153) (0 – 1%) ††	0.6% (1/157) (0 – 1%) ††
Pericardial effusion or cardiac tamponade											
RF PVI vs. AADs	279 (2 RCTs‡‡) 1-12 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	1.3% (2/159) (1 – 2%) ‡‡	0.8% (1/120) (0 – 2%) ‡‡
Cryo PVI vs. AADs	245 (1 RCT) 0-1 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0.6% (1/163)	1% (1/82)
Pulmonary vein stenosis											
RF PVI vs. AADs	223 (3 RCTs§§) 6-12 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	2.8% (3/108) (0 – 6%)	0 % (0/115) (0%)

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**PVI (% pts)**	**Control (% pts)**
										§§	§§
Cryo PVI vs. AADs	245 (1 RCT) 0-1 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	1.2% (2/163)	2% (2/84)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

** 1 RCT reported data for both treatment groups. Treatment-related mortality rates were similar as reported for the PVI group only by 1 additional RCT.
†† 3 RCTs reported data for both treatment groups. Treatment-related thromboembolic rates were also reported for the PVI group only by 4 additional RCTs, and occurred in 0% to 7% of patients of these studies.
‡‡ 2 RCTs reported data for both treatment groups. Pericardial effusion or cardiac tamponade were also reported for the PVI group only by 3 additional RCTs, and occurred in 1% to 9% of patients of these studies.
§§3 RCTs reported data for both treatment groups. Pulmonary vein stenosis was also reported for the PVI group only by 2 additional RCTs, and occurred in 1.7% to 7% of patients of these studies.

Table 58. Quality of evidence summary for Key Question 3: What is the evidence regarding the safety of catheter ablation for patients with atrial flutter?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Procedure- or treatment-related mortality											
RF ablation vs. AADs	104 (1 RCT) 13 ± 6 mos.	Serious risk of bias*	No serious inconsistency.	No serious indirectness	Serious imprecision‡	Undetected	Low	NS	NS	0% (0/52)	0% (0/51)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 59. Quality of evidence summary for Key Question 3: What is the evidence regarding the safety of catheter ablation for patients with SVTs?

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Persistent AV block											
RF ablation vs. open perinodal dissection surgery (AVNRT)	Ablation: 120 (1 cohort study) 1 mos.	Serious risk of bias†	No serious inconsistency.	No serious indirectness	No serious imprecision	Undetected	Insufficient	19%	Surgery	22.7% (37/163)	4% (3/79)
Pacemaker implantation											
RF ablation vs. open perinodal dissection surgery (AVNRT)	Ablation: 120 (1 cohort study) 1 mos.	Serious risk of bias†	No serious inconsistency.	No serious indirectness	No serious imprecision	Undetected	Insufficient	NS	NS	3.1% (5/163)	3% (2/79)

n/a: not applicable; NR: not reported; NS: not statistically significant; RD: risk difference (ablation – control) (for statistically significant results from RCTs or meta-analyses of well-measured primary outcomes, the absolute value of the risk difference is reported and used to determine NNT)

Reasons for downgrading quality of evidence:
* Serious risk of bias: the majority of studies did not meet one or more criteria of a good quality RCT (see Appendices D and E for details)
† Serious risk of bias: the majority of studies did not meet two or more criteria of a good quality cohort (see Appendices D and E for details)
‡ Serious risk of imprecision: confidence in the estimate is low (rare event, relatively small sample size)
§ Serious risk of imprecision: confidence in the estimate is low (wide confidence intervals)

Table 60. Quality of evidence summary for Key Question 4: Does catheter ablation have any differential efficacy or safety compared with other treatment options in subpopulations.

								Effect		Treatment groups	
Interventions	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**RD & NNT or RD Range**	**Favors**	**Ablation (% pts)**	**Control (% pts)**
Catheter ablation versus Other treatment	0 studies reporting	-	-	-	-	-	Insufficient	-	-		

Table 61. Quality of evidence summary for Key Question 5: What is the evidence of the cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term in patients with atrial fibrillation?

Note that GRADE has not been developed to evaluate the quality of cost-effectiveness evidence.

Interventions	Studies Time horizon	Countries	QHES Range	Overall quality of evidence	Conclusions
PVI versus AADs	3 cost-utility analyses 5- year time horizon	USA Canada UK	90-100	Moderate	In two of the studies (including the US study), the incremental cost effectiveness ratio (ICER) ranged from approximately $51,400 to $59,200 per quality-adjusted life year (QALY). In one of the studies, the ICER ranged from $33,201 to $44,221 to QALY, decreasing with increasing stroke risk. All studies concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal AF depending on how much society is willing to pay per QALY.
	3 cost-utility analyses Lifetime horizon	USA Sweden UK	84-100	Moderate	One study reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation was more cost-effective than AADs. The two other studies reported ICERs ranging from approximately $12,400 to $29,100 per QALY, and concluded that catheter ablation may be a cost-effective alternative to AADs in patients with paroxysmal or persistent AF depending on how much society is willing to pay per QALY. In general, ablation is more cost-effective in the lifetime horizon compared with the five-year horizon models due to long-term costs associated with AAD therapy.

Table 62. Quality of evidence summary for Key Question 5: What is the evidence of the cost-effectiveness of catheter ablation compared with alternative treatment options in the short- and long-term in patients with SVT?

Note that GRADE has not been developed to evaluate the quality of cost-effectiveness evidence.

Interventions	Studies Time horizon	Countries	QHES Range	Overall quality of evidence	Conclusions
Catheter ablation versus AADs	2 cost-utility analyses Lifetime horizon	USA	73-88	Low	Both studies reported that ablation dominated AADs (that is, ablation was associated with less cost and more QALYs compared with AADs), and concluded that ablation treatment was more cost-effective than AADs alone.

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