

# Technology Assessment



## Catheter Ablation for Treatment of Atrial Fibrillation



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# **Catheter Ablation for Treatment of Atrial Fibrillation**

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## **Pacific Northwest Evidence-based Practice Center**

Andrea Skelly, Ph.D., M.P.H.  
Robin Hashimoto, Ph.D.  
Sana Al-Khatib, M.D., M.H.S.  
Gillian Sanders-Schmidler, Ph.D.  
Rochelle Fu, Ph.D.  
Erika Brodt, B.S.  
Marian McDonagh, Pharm.D.

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## Investigator Affiliations

Andrea Skelly, Ph.D., M.P.H.  
Spectrum Research, Inc.  
Tacoma, WA

Rochelle Fu, Ph.D.  
Oregon Health & Sciences University  
Portland, OR

Robin Hashimoto, Ph.D.  
Spectrum Research, Inc.  
Tacoma, WA

Erika Brodt, B.S.  
Spectrum Research, Inc.  
Tacoma, WA

Sana Al-Khatib, M.D., M.H.S.  
Duke University  
Durham, NC

Marian McDonagh, Pharm.D.  
Oregon Health & Sciences University  
Portland, OR

Gillian Sanders-Schmidler, Ph.D.  
Duke University  
Durham, NC

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## Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

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The list of Key Informants who participated in developing this report follows. Those who also reviewed the draft report are marked with an asterisk.

\*Robin Boineau, M.D., M.A.  
Medical Officer, Division of Cardiovascular  
Diseases  
National Heart, Lung, and Blood Institute  
National Institute of Health  
Bethesda, MD

\*Hugh Calkins, M.D., F.A.C.C., F.H.R.S.,  
F.A.H.A., C.C.D.S.  
Director, Cardiac Arrhythmia Service and  
Electrophysiology Lab  
Johns Hopkins University  
Baltimore, MD

\*Michael LeFevre, M.D., M.S.P.H.,  
A.A.F.P.  
Future of Family Medicine Professor  
Vice Chair, Department of Family and  
Community Medicine  
University of Missouri School of Medicine  
Columbia, MO

Douglas Packer, M.D., F.A.C.C., F.H.R.S.  
Department of Cardiovascular Diseases  
Mayo Clinic  
Rochester, MN

Michael Rich, M.D., A.G.S.F., F.A.C.C.  
Director, Cardiac Rapid Evaluation Unit  
Washington University  
St. Louis, MO

\*Mellanie True Hills  
Patient Advocate  
Founder and CEO, StopAfib.org

Paul Varosy, M.D., F.A.C.C., F.A.H.A.,  
F.H.R.S.  
Director, Electrophysiology  
Denver Veterans Administration Medical  
Center  
Denver, CO

## Technical Expert Panel

In place of a Technical Expert Panel, the Centers for Medicare and Medicaid provided input on the Key Questions and scope of the report.

## Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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The list of Peer Reviewers follows:

Alexandru Costea, M.D.  
Associate Professor of Clinical Medicine  
Cardiac Electrophysiology  
University of Cincinnati  
Cincinnati, OH

Michael Field, M.D., F.A.C.C., F.H.R.S.  
Director of Clinical Electrophysiology and  
Cardiac Arrhythmia Service  
University of Wisconsin  
Madison, WI

Kristen Patton, M.D.  
Division of Cardiology  
University of Washington  
Seattle, WA

Jordan M. Prutkin, M.D., M.H.S.  
Division of Cardiology  
University of Washington  
Seattle, WA

James Reiffel, M.D., F.A.C.C., F.A.H.A.,  
F.H.R.S.  
Faculty Physician, Electrophysiology  
Service  
Co-Director, Electrocardiology Laboratory  
Columbia University Medical Center  
New York, NY

# Catheter Ablation for Treatment of Atrial Fibrillation

## Structured Abstract

**Objectives:** This report evaluates the current state of evidence regarding effectiveness and harms of catheter ablation for atrial fibrillation (AF) with a focus on longer-term outcomes and evidence relevant to the Medicare population.

**Data Sources:** Systematic searches of the following databases: Ovid MEDLINE® (from 2005 to November 2014), Cochrane Central (November 2014), and Cochrane Database of Systematic Reviews (from 2005 to November 2014).

**Review Methods:** Using predefined criteria, randomized trials and observational studies comparing the efficacy, effectiveness, or safety of catheter ablation (radiofrequency or cryoballoon ablation) to medical therapy in patients with AF were included. Analyses were stratified by type of AF and length of followup (>12 months vs. ≤12 months). The quality of included studies was assessed, data were extracted, results were summarized qualitatively and using meta-analysis, and the strength of the evidence was graded for each primary outcome.

**Results:** Of 3,471 citations identified, 46 studies were included. In the Medicare population, evidence was insufficient for all outcomes. Regarding the longer-term effect of radiofrequency ablation (RFA) versus medical therapy in the general population, low-strength of evidence suggested no statistical differences between groups in all-cause mortality for people with paroxysmal AF. Long-term (>12 months) freedom from any atrial arrhythmia recurrence was greater following RFA versus medical therapy (pooled relative risk [RR] 1.24, 95% confidence interval [CI] 1.11 to 1.47) in paroxysmal AF patients (moderate-strength evidence). There was insufficient evidence to draw conclusions for all other long-term primary outcomes including stroke, myocardial infarction, and congestive heart failure. Regarding the short-term (≤12 months) effect of RFA compared with medical therapy, low strength of evidence suggested no significant differences between groups for all-cause mortality regardless of AF type and myocardial infarction in paroxysmal AF patients. Freedom from short-term recurrence was greater following RFA based on moderate strength of evidence (pooled RR 2.62, 95% CI 1.90 to 3.90). Reablation ranged from 0 to 53.8 percent across AF types and time frames. At 6 months, RFA was associated with better health-related quality of life in those with persistent AF and heart failure (low strength of evidence); however, results were inconsistent across measures and heterogeneity precluded pooling of data or drawing firm conclusions. In terms of harms, no statistical differences in 30-day mortality or stroke or 3-month AF recurrence between groups were found, with low strength of evidence. The pooled risk of cardiac tamponade following RFA was 1.7 percent (95% CI 0.8 to 3.6) for people with paroxysmal AF based on low strength evidence, while evidence was insufficient to draw conclusions regarding persistent AF patients. There was insufficient evidence to draw conclusions regarding efficacy or safety for cryoballoon ablation, with the exception of low strength of evidence for greater freedom from protocol-defined failure (which included freedom from AF) following cryoballoon ablation versus medical therapy. There was insufficient evidence to draw conclusions regarding efficacy or safety for cryoballoon ablation versus RFA or medical therapy.

**Conclusions:** There was insufficient evidence to draw conclusions regarding the efficacy, effectiveness, and safety of catheter ablation in the Medicare population. In the general population, there was moderate evidence that RFA is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in both the short and long term regardless of AF type, but reablation was common. RFA does not appear to impact all-cause mortality in the short or long term in those with paroxysmal AF (low strength of evidence); however, there was insufficient evidence to draw conclusions regarding other primary clinical outcomes in the short or long term. Firm conclusions regarding health-related quality of life were not possible given heterogeneity across studies for instruments employed, measurement timing, and clinical characteristics. For harms, no differences between RFA and medical therapy in 30-day mortality, stroke, or 3-month risk of AF were seen, with low strength of evidence. Evidence comparing cryoballoon ablation with medical therapy or with RFA was insufficient to draw conclusions regarding efficacy or safety, with the exception of low strength of evidence for greater freedom from protocol-defined failure following cryoballoon ablation versus medical therapy. To better understand the impact of catheter ablation on key outcomes (stroke, mortality, health-related quality of life, and symptom improvement) compared to other treatment strategies, large methodologically sound studies are needed, particularly on persistent AF patients. Studies with sufficient sample sizes are needed to effectively determine whether catheter ablation versus other treatments will benefit certain patient subgroups more than others, and whether there are subgroups in which catheter ablation might best used as a first- versus second-line treatment.



# Contents

<b>Executive Summary .....</b>	<b>ES-1</b>
<b>Introduction.....</b>	<b>1</b>
Background.....	1
Nature and Burden of Atrial Fibrillation.....	1
Management of Atrial Fibrillation.....	1
Scope and Key Questions.....	3
Key Questions.....	4
Analytic Framework.....	5
<b>Methods.....</b>	<b>7</b>
Topic Refinement and Systematic Review Protocol.....	7
Literature Search Strategy.....	7
Inclusion and Exclusion Criteria.....	8
Study Selection.....	10
Data Extraction.....	11
Quality Assessment of Individual Studies.....	11
Data Synthesis.....	12
Strength of the Body of Evidence.....	14
Applicability.....	15
Peer Review and Public Commentary.....	15
<b>Results.....</b>	<b>16</b>
Results of Literature Searches.....	16
Organization of Results.....	18
Key Question 1a. What is the comparative efficacy and effectiveness of AF catheter ablation versus medical therapy on short-term (6-12 months) and long-term (>12 months) outcomes in the general adult and Medicare populations?.....	18
Key Points.....	18
Radiofrequency Ablation Versus Medical Therapy.....	22
Cryoablation Versus Medical Therapy.....	66
Key Question 1b. What is the comparative efficacy and effectiveness of AF catheter ablation versus different energy sources on short- (6-12 months) and long- (>12 months) term outcomes in the general adult and Medicare populations?.....	70
Key Points.....	70
Description of Included Studies.....	70
Detailed Synthesis.....	77
Key Question 2a. What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation versus medical therapy in the general adult and Medicare populations?.....	81
Key Points.....	81
Radiofrequency Ablation Versus Medical Therapy.....	83
Cryoablation Versus Medical Therapy.....	102
Key Question 2b. What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation versus different energy sources in the general adult and Medicare populations?.....	104
Key Points.....	104
Description of Included Studies.....	105

Detailed Synthesis.....	106
Key Question 3. Are there modifications of efficacy, effectiveness, or harms of catheter ablation versus medical therapy or different energy sources by patient-level characteristics such as age, sex, type of AF, comorbidities, risk for stroke or bleeding events, condition (i.e., patients with significant left ventricular dysfunction/heart failure or patients with significant left atrial enlargement or left ventricular hypertrophy), provider/setting characteristics or technique/approach? .....	113
Key Points.....	113
Detailed Description .....	113
<b>Discussion.....</b>	<b>116</b>
Key Findings and Strength of Evidence .....	116
Findings in Relationship to What is Already Known .....	135
Applicability .....	135
Implications for Clinical and Policy Decisionmaking.....	137
Limitations of the Review Process .....	139
Limitations of the Evidence Base .....	139
Research Gaps.....	140
<b>Conclusions.....</b>	<b>144</b>
<b>Abbreviations and Acronyms .....</b>	<b>146</b>
<b>References .....</b>	<b>148</b>

## Tables

Table A. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF .....	ES-19
Table B. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF .....	ES-21
Table C. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with medical therapy for AF .....	ES-24
Table D. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF .....	ES-25
Table E. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF .....	ES-26
Table F. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with RFA versus medical therapy for AF....	ES-27
Table G. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus medical therapy for AF.....	ES-29
Table H. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus RFA for AF .....	ES-30
Table 1. Summary of inclusion and exclusion criteria .....	9
Table 2. Patient characteristics and overview of study characteristics for RCTs comparing RFA with medical therapy in patients with paroxysmal atrial fibrillation .....	24
Table 3. Patient characteristics and overview of study characteristics for RCTs comparing RFA with medical therapy in patients with persistent atrial fibrillation .....	26

Table 4. Patient characteristics and overview of study characteristics for RCTs comparing RFA with medical therapy in patients with paroxysmal or persistent atrial fibrillation .....	28
Table 5. Patient characteristics and overview of study characteristics for comparative observational studies comparing RFA with medical therapy in patients with paroxysmal atrial fibrillation .....	30
Table 6. Patient characteristics and overview of study characteristics for comparative observational studies comparing RFA with medical therapy in patients with persistent atrial fibrillation .....	31
Table 7. Patient characteristics and overview of study characteristics for comparative observational studies comparing RFA with medical therapy in patients with paroxysmal, persistent or permanent atrial fibrillation.....	31
Table 8. Primary efficacy outcomes for RCTs comparing RFA with medical therapy.....	38
Table 9. Primary effectiveness outcomes for comparative observational studies comparing RFA with medical therapy.....	39
Table 10. SF-36 MCS and PCS scores from RCTs comparing RFA with medical therapy.....	43
Table 11. Meta-analysis results for the SF-36 MCS and PCS at 12-months followup from RCTs comparing RFA with medical therapy in patients with paroxysmal AF .....	45
Table 12. Individual SF-36 domain scores from RCTs comparing RFA with medical therapy ..	46
Table 13. Quality of life outcomes for comparative observational studies comparing RFA with medical therapy.....	47
Table 14. Other health-related quality of life and symptom checklist outcomes from RCTs comparing RFA with medical therapy.....	48
Table 15. Exercise capacity and related outcomes from randomized controlled trials comparing radiofrequency ablation with medical therapy.....	52
Table 16. Intermediate efficacy outcomes for RCTs comparing RFA with medical therapy .....	62
Table 17. Intermediate effectiveness outcomes for comparative observational studies comparing RFA with medical therapy .....	63
Table 18. Cardiac chamber size/function and biomarkers reported by RCTs comparing RFA with medical therapy.....	64
Table 19. Patient characteristics and overview of study characteristics for the STOP AF Pivotal RCT comparing cryoballoon ablation with medical therapy in patients with paroxysmal/early persistent AF .....	67
Table 20. Efficacy outcomes from the STOP AF pivotal RCT comparing cryoballoon ablation with medical therapy in patients with paroxysmal/early persistent AF .....	69
Table 21. Patient characteristics and overview of study characteristics for RCTs comparing cryoballoon ablation with RFA in patients with AF .....	72
Table 22. Patient characteristics and overview of study characteristics for comparative observational studies comparing cryoballoon ablation with RFA in patients with paroxysmal atrial fibrillation .....	74
Table 23. Patient characteristics and overview of study characteristics for comparative observational studies comparing cryoballoon ablation with RFA in patients with paroxysmal, persistent, or permanent atrial fibrillation.....	76
Table 24. Primary and intermediate effectiveness outcomes for comparative observational studies comparing cryoballoon ablation with RFA .....	79
Table 25. Intermediate efficacy outcomes for RCTs comparing cryoballoon ablation with RFA	80
Table 26. Adverse events for RCTs comparing RFA with medical therapy .....	95

Table 27. Adverse events from comparative observational studies comparing RFA with medical therapy.....	100
Table 28. Adverse events for the RCT by Packer et al 2013 comparing cryoballoon ablation with medical therapy.....	104
Table 29. Adverse events for comparative observational studies comparing cryoballoon ablation with RFA.....	109
Table 30. Adverse events for RCTs comparing cryoballoon ablation with RFA.....	112
Table 31. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF .....	123
Table 32. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF .....	125
Table 33. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with medical therapy for AF .....	128
Table 34. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF .....	129
Table 35. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF .....	130
Table 36. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with RFA versus medical therapy for AF .	131
Table 37. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus medical therapy for AF.....	133
Table 38. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus RFA for AF .....	134

## Figures

Figure A. Analytic framework for catheter ablation for atrial fibrillation.....	ES-6
Figure 1. Analytic framework for catheter ablation for atrial fibrillation.....	6
Figure 2. Flow chart showing results of literature search.....	17
Figure 3. Profile likelihood model meta-analysis of all-cause mortality and myocardial infarction within 12 months of followup in RCTs comparing RFA with medical therapy.....	34
Figure 4. Profile likelihood model meta-analysis of freedom from any arrhythmia recurrence within 12 months of followup in RCTs comparing RFA with medical therapy.....	55
Figure 5. Profile likelihood model meta-analysis of freedom from any arrhythmia recurrence at followup times greater than 12 months in RCTs comparing RFA with medical therapy in patients with paroxysmal AF.....	56
Figure 6. Reablation for any arrhythmia within 12 months following RFA in patients with paroxysmal and persistent AF.....	57
Figure 7. Reablation for any arrhythmia at long-term followup (>12 months) after RFA from RCTs of patients with paroxysmal AF.....	58
Figure 8. Profile likelihood model meta-analysis of AF recurrence within the first 3 months of followup in RCTs comparing RFA with medical therapy in patients with paroxysmal AF.....	88
Figure 9. Risk of cardiac tamponade following RFA from RCTs in patients with paroxysmal or persistent AF .....	89

Figure 10. Risk of pericardial effusion following RFA from RCTs in patients with paroxysmal AF .....	91
Figure 11. Risk of pulmonary vein stenosis following RFA from RCTs in patients with paroxysmal or persistent AF .....	92

**Appendixes**

Appendix A. Search Strategy	
Appendix B. List of Included Studies	
Appendix C. List of Excluded Studies with Rationale	
Appendix D. Sample Data Extraction Forms	
Appendix E. Evidence Tables (demographics, study characteristics)	
Appendix F. Quality Assessment of Included Studies	
Appendix G. Strength of Evidence Tables	
Appendix H. Description of Outcomes Measures, Devices, and Ongoing Trials, and Additional Results Tables	

# Catheter Ablation for Treatment of Atrial Fibrillation

## Executive Summary

### Background

#### Nature and Burden of Atrial Fibrillation

Atrial fibrillation (AF) is a major public health concern in the United States, affecting an estimated 2.3 million Americans.<sup>1</sup> The prevalence of AF is projected to reach 5.6 to 12.1 million by the year 2050.<sup>2</sup> AF is the most common sustained arrhythmia seen in clinical practice and accounts for approximately one-third of hospitalizations for cardiac dysrhythmias.<sup>3</sup>

Atrial fibrillation is characterized by uncoordinated atrial activation with resulting deterioration of atrial mechanical function.<sup>4,5</sup> While AF can occur in isolation, it may also be associated with other arrhythmias such as atrial flutter or atrial tachycardia. Atrial fibrillation can be paroxysmal, persistent, or permanent. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society AF guidelines<sup>5</sup> defines paroxysmal AF as recurrent AF that terminates spontaneously or with intervention within 7 days of onset, persistent AF as one that is sustained beyond 7 days, and permanent AF as long-standing AF in which restoring and/or maintaining sinus rhythm has failed or has been foregone. Long-standing persistent AF is usually defined as AF that persists for over 1 year. Long-standing persistent and permanent AF is more commonly seen in older patients with structural heart disease.

A number of factors have been associated with increased risk of AF. The prevalence of AF increases with age; it affects 8 to 10 percent of patients 80 years of age and older.<sup>2,6,7</sup> AF is also more common in males: data from the Framingham Heart Study suggest that men are 1.5 times as likely to develop AF than are women after controlling for age and comorbidities.<sup>2</sup> Obesity increases the risk of developing AF. Data from community-based cohorts suggest that obese patients have a 1.5- to 2.3-fold greater risk of developing AF. Furthermore, obesity increases the likelihood that AF will progress from paroxysmal to permanent AF.<sup>7</sup> Additional factors associated with an increased risk of AF include smoking, hypertension, hyperthyroidism, obstructive sleep apnea, diabetes, myocardial infarction, heart failure, and cardiac surgery.<sup>7</sup>

AF is associated with significant mortality, morbidity, and health care costs. Patients with AF have a twofold greater risk of death than do those without this disease. AF is associated with an increased risk of stroke, which affects 5 percent of nonrheumatic AF patients and nearly 7 percent of AF patients with heart failure each year.<sup>8</sup> Furthermore, ischemic stroke that occurs in the setting of AF tends to be either fatal or of moderate to high severity in most patients.<sup>9</sup> AF can also cause a number of cardiac conditions, including myocardial ischemia or infarction, exacerbation of heart failure, and cardiomyopathy if the ventricular rate is insufficiently controlled.<sup>10-13</sup> Although some patients with AF are asymptomatic, other patients experience symptoms like shortness of breath, intractable fatigue, and near-syncope, which can severely affect overall quality of life.<sup>14-17</sup> In total, the management of AF and its complications costs the U.S. health care system approximately \$26 billion each year.<sup>5,18</sup>

## **Management of Atrial Fibrillation**

Treatment of AF involves rate control, rhythm control, prevention of thromboembolic events, and treating the underlying disease (e.g., hypertension) if applicable.<sup>5, 18</sup> Typically, pharmacologic therapy is the primary treatment for rate and rhythm control, while pulmonary vein isolation with catheter ablation is reserved for second-line treatment but may be appropriate as a first-line treatment in select populations when a rhythm control strategy is desired.<sup>5</sup> Discussion of strategies to prevent thromboembolic events or to treat underlying causes of AF are beyond the scope of this report.

While the initial management of AF often includes control of ventricular rate using pharmacological agents (i.e., beta-blockers or nonhydropyridine calcium channel blockers), it is common for the long-term management strategy to focus on restoring and maintaining normal heart rhythm.<sup>5</sup> AF patients who continue to have significant symptoms despite adequate rate control or who desire long-term rhythm control may be considered for treatment using a rhythm control strategy.

### **Pharmacological Rhythm Control**

The primary reason for rhythm control in patients with AF is to improve symptoms. In some patients, adequate rate control is enough to control symptoms, but if patients continue to have symptoms despite good rate control, then rhythm control should be considered. In the absence of symptoms, rhythm control can be used in patients with rapid ventricular response to AF when rate controlling medications are ineffective or cannot be tolerated. Rhythm control should not be used to allow patients to come off anticoagulation as the decision regarding anticoagulation should be based on their risks of thromboembolic events and bleeding.<sup>5</sup> Pharmacologic therapy is typically the first choice. Selection of the first-line antiarrhythmic medication is largely driven by the presence or absence of structural heart disease. For example, the 2014 Guidelines for the Management of Patients with Atrial Fibrillation give a Class I recommendation for treatment with flecainide, dofetilide, propafenone, dronedarone, sotalol and amiodarone; but for amiodarone, the guidelines emphasize that because of its potential toxicities, it should only be used after consideration of risks and when other agents have failed or are contraindicated. In patients with heart failure, the guidelines recommend one of two antiarrhythmic medications as first-line therapy (dofetilide and amiodarone).<sup>5</sup> Side effects can occur with the use of antiarrhythmic medications; some may actually cause more arrhythmias and some may lose effectiveness over time. Patients on these medications therefore need to be monitored to assess the impact of medications on heart rhythm and the potential for side effects and interactions with any concomitant medications such as anticoagulants.

### **Catheter Ablation Rhythm Control**

Catheter ablation for the treatment of AF is increasingly being performed on symptomatic patients as an alternative to medical management, or when medical management has been ineffective or not tolerated.<sup>19-21</sup> AF ablation is typically recommended only for symptomatic patients; asymptomatic patients are usually managed with anticoagulation and/or rate control as needed.<sup>5</sup> The outcomes of this procedure may depend on patient characteristics such as age, AF type, and presence of structural heart disease, as well as on experience of the operator and methods and technologies used during the procedure. Relief of symptoms is a primary reason for considering catheter ablation as a treatment strategy.

In catheter ablation, energy is sent through an electrode at the tip of a catheter into specific areas of the heart to destroy (ablate) or electrically isolate small areas of tissue where abnormal electrical signals that trigger abnormal heart beats originate. The goal of catheter ablation for treatment of AF is to ablate or isolate triggers that mostly originate in the area of the pulmonary veins. Thus, the most commonly used and recommended catheter ablation procedure to treat AF is pulmonary vein isolation (PVI).<sup>19, 22</sup> For the procedure to be successful, complete bi-directional electrical isolation of all pulmonary veins should be achieved. While other approaches may also be used, typically in addition to PVI, there is uncertainty regarding additional benefits or harms of such approaches.<sup>19</sup> Recent systematic reviews attempted to evaluate the efficacy of approaches relative to each other,<sup>23-25</sup> but significant heterogeneity with regard to the approaches compared precluded meaningful conclusions.<sup>23</sup>

Among methods and technologies used during the procedure, energy source is an important factor. Currently, there are two US Food and Drug Administration-approved options for catheter ablation: radiofrequency energy, which heats the target sites, and cryoablation, which cools/freezes the sites. Cryoablation may be performed using either a focal catheter (as in radiofrequency ablation [RFA]) or a balloon catheter. How cryoablation compares with RFA in relation to efficacy and safety is also uncertain and is the subject of ongoing debate.

Imaging may be performed before or during the procedure, including magnetic resonance imaging, computed tomography imaging, and transthoracic, trans-esophageal, and intra-cardiac echocardiography. Electroanatomic mapping, which allows for a real-time three-dimensional view of the heart, is often used during the procedure to look for triggers of AF, confirm successful ablation, and allow characterization of its impact on overall left atrial (LA) function. Mapping techniques vary greatly and continue to evolve. Two examples of mapping systems available for use in clinical practice are CARTO (Biosense Webster Inc., CA, USA) and EnSite NavX (St. Jude Medical Inc., MN, USA). The comparative benefits or harms of these techniques are unclear as to date they have not been evaluated in a randomized controlled trial (RCT). Evaluation of imaging and mapping approach is beyond the scope of this report.

## Scope and Key Questions

In 2009, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review that evaluated efficacy, effectiveness and harms of RFA for AF.<sup>22</sup> Questions remained regarding evidence on health outcomes beyond one year and the potential impact of RFA on the risk of death and stroke. The comparative effectiveness and harms of catheter ablation in the Medicare population ( $\geq 65$  years of age or  $< 65$  years of age and permanently disabled) were not explored. The 2009 report did not compare cryoablation with medical therapy or compare catheter ablation energy sources with one another.

Based on Medicare Provider Analysis and Review (MedPAR) files, use of catheter ablation for the treatment of atrial fibrillation in the Medicare population increased substantially between 2001 and 2006 from an annual total procedural volume of 135 to 1975 cases and an increase in the number of hospitals performing RFA from 100 to 162.<sup>26</sup> Annual complication rates increased from 6.7 to 10.1 percent during the same time period, but increasing age was not associated with a higher rate of complications. Procedural volume was associated with probability of in-hospital death but not with overall risk of complications. An almost two-fold increase in the number of patients treated with catheter ablation was reported between 2003 and 2006 compared with the number treated between 1995 and 2002 based on a world-wide survey of electrophysiology centers.<sup>27</sup> The authors also report that catheter ablation was increasingly being offered to sicker



AF patients. Catheter ablation was reported to be effective in approximately 80 percent of patients. A risk of 4.5 percent for major complications was also reported. Anecdotally, utilization has continued to increase in the Medicare and general populations.

Since the publication of the 2009 AHRQ report, the Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial was initiated to directly compare various methods of catheter ablation with medical therapy in a large, multi-center, multi-national trial that includes older patients (over 60 years old) with paroxysmal and persistent atrial fibrillation. (ClinicalTrials.gov identifier NCT00911508); however, final data collection for the primary outcome measure will not be completed until September 2017.

Because there is increasing use of catheter ablation to treat AF patients in the Medicare population as well as uncertainty regarding the efficacy and harms of this procedure in this population in particular, and given that results from CABANA will not be available until 2018 at the earliest, the Centers for Medicare and Medicaid (CMS) has partnered with AHRQ to commission this independent systematic review to evaluate the current state of comparative evidence to help inform clinical practice and policy and to provide insight into research needs and general approaches for addressing identified evidence gaps.

The objective of this review is to evaluate and synthesize current evidence on the comparative effectiveness and harms of catheter ablation for the treatment of AF. For purposes of this report, efficacy refers to the ability of a treatment to produce a desired effect under optimum controlled conditions, such as during a randomized controlled trial. Effectiveness refers to the effect of treatment in actual clinical practice as evaluated by observational studies or comparative pragmatic trials. Comparative effectiveness review is a general term and in this report refers to the conduct and synthesis of systematic research to compare the interventions of interest, incorporating information on efficacy from RCTs and on effectiveness from comparative observational studies. Comparative effectiveness also includes evaluation of adverse events and harms.

The Key Questions used to guide this report are provided below. The analytic framework (Figure A) shows the target population, interventions and outcomes that were examined.

**Key Question 1.** What is the comparative efficacy and effectiveness of AF catheter ablation on short-term (6 –12 months) and long-term (>12 months) outcomes in the general adult and Medicare populations? Comparisons of interest include:

- a) Catheter ablation compared with medical therapy
- b) Comparing ablation using different energy sources

**Key Question 2.** What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation in the general adult and Medicare populations? Comparisons of interest include:

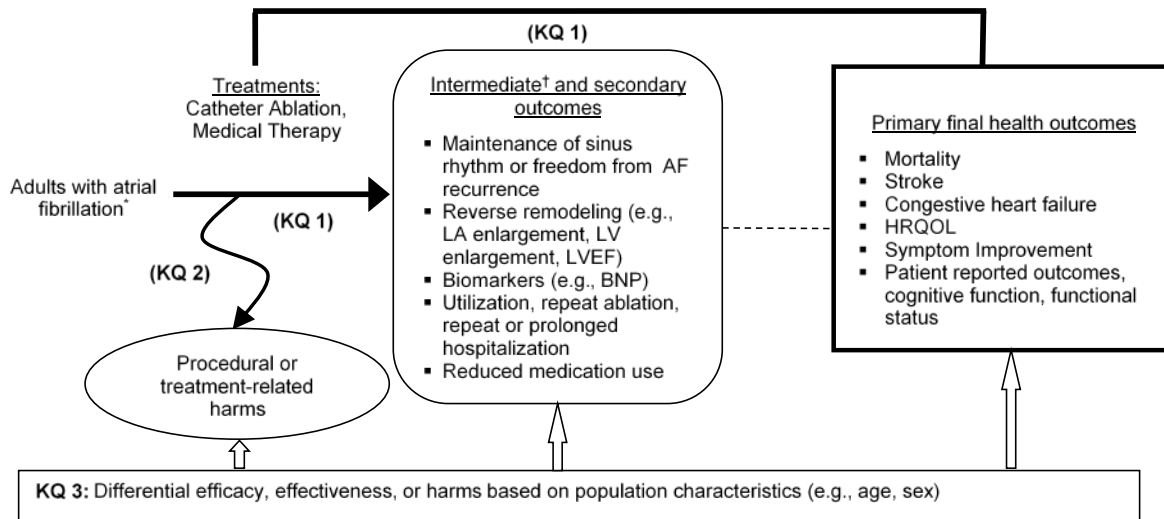
- a) Catheter ablation compared with medical therapy
- b) Comparing ablation using different energy sources

**Key Question 3.** Are there modifications of efficacy, effectiveness, or harms of catheter ablation by patient-level characteristics such as age, sex, type of AF, comorbidities, risk for stroke or bleeding events, condition (i.e., patients with significant left ventricular dysfunction/heart failure

or patients with significant left atrial enlargement or left ventricular hypertrophy), provider/setting characteristics, or technique/approach? Comparisons of interest include:

- a) Catheter ablation compared with medical therapy
- b) Comparing ablation using different energy sources

**Figure A. Analytic framework for catheter ablation for atrial fibrillation**



\*Patients with longstanding persistent atrial fibrillation, persistent atrial fibrillation, or paroxysmal atrial fibrillation (considered

BNP = brain natriuretic peptides; HRQOL = health-related quality of life; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction.

## Methods

The methods for this Technology Assessment follow the methods suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. All methods were determined *a priori*.<sup>28</sup>

## Topic Refinement and Systematic Review Protocol

This topic was nominated by CMS as an update to a previous report published in 2009,<sup>22</sup> particularly to examine longer-term efficacy of catheter ablation and application to the Medicare population in order to inform CMS policy. The AHRQ Task Order Officer functioned as a liaison between the Evidence-based Practice Center (EPC) and CMS and helped resolve any ambiguities regarding the processes or scope of the project. The EPC drafted the initial Key Questions, analytic framework, and inclusion/exclusion criteria and refined them with input from a panel of Key Informants, all of whom were required to disclose any financial or other conflicts of interest prior to participation. The Key Informant panel included experts in cardiology primarily (with specialties in electrophysiology, heart failure, and cardiovascular aging/cardiovascular disease in older adults) and internal medicine; representatives from relevant specialty societies; government representatives (i.e., Department of Veterans Affairs, National Heart, Lung and Blood Institute); and a patient advocate. After review from AHRQ, the draft questions and framework were posted for public review in December 2013 for 3 weeks. Following review of the public commentary, the EPC drafted a final topic refinement document which was approved by AHRQ and posted to their Web site. In place of a Technical Expert Panel, CMS provided input to the Key Questions and scope of the report. The final topic refinement document served as the basis for the review protocol with minor changes. Both the

final topic refinement document and the systematic review protocol can be found on the AHRQ Web site at <http://www.ahrq.gov/research/findings/ta/>. The protocol was also registered with the PROSPERO international database of prospectively registered systematic reviews.

## Literature Search Strategy

A research librarian conducted searches for primary studies in the following databases: Ovid MEDLINE<sup>®</sup> (from 2005 to November 2014), Cochrane Central (November 2014), and Cochrane Database of Systematic Reviews (from 2005 to November 2014). Searches were limited to a beginning date of January 2005 as there are multiple recent systematic evidence reviews, including good-quality reviews from AHRQ (2013, 2009)<sup>22, 23, 25</sup> and the Washington State Health Technology Assessment Program (2013),<sup>22, 23, 25</sup> that have addressed aspects of the Key Questions for this current review, with searches conducted through late 2013. Key Informant input during topic refinement confirmed that this was a logical approach. The search strategy was developed based on an analysis of the medical subject headings (MeSH), terms, and text words of key articles identified *a priori* (the full search strategy is available in Appendix A). Reference lists of included articles and relevant review articles were inspected for relevant publications. All citations were downloaded and imported into an electronic database (EndNote<sup>®</sup> X7 Thomson Reuters, Philadelphia, PA).

All citations were reviewed independently by two individuals at both the title/abstract and full-text level and differences were resolved by consensus.

## Inclusion Exclusion Criteria

Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Briefly, studies of adult patients with paroxysmal, persistent, or permanent/long-standing AF treated with catheter ablation were sought. For all Key Questions, the focus was on evidence from comparative studies with the least potential for bias. Comparative observational studies were required to have a minimum of 100 patients to be included. Registry and administrative data studies were considered if inclusion criteria were met. Comparators of interest included medical therapy only (i.e., pharmacological agents for rate or rhythm control) and comparisons of different energy sources for catheter ablation (e.g., radiofrequency versus cryoablation). Comparisons of different techniques and/or approaches and mapping were beyond the scope of this report and thus were excluded. For Key Question 2, case series that were specifically designed to evaluate harms and/or adverse events following ablation, had a minimum of 1000 patients and at least 80 percent followup were included because all included comparative studies were relatively small in size. Including these large case series of ablation patients allowed for the calculation of risk estimates of adverse events based on a larger number of patients.

For all Key Questions, both long-term (>12 months) and short-term (≤12 months) outcomes were reported. The primary outcomes (see Rating the Body of Evidence below) were considered to be the most clinically important and were the focus of reporting, decisions for data pooling and determination of overall strength of evidence. Additional outcomes are reported in the detailed evidence synthesis sections of the Key Questions with a focus on outcomes common across studies. Where applicable and where data were available, results from short-term (≤12 months) and long-term (>12 months) followup were described.

Studies published only as conference abstracts, non-English-language articles, and studies of nonhuman subjects were excluded. Studies had to report original data to be included.

## Study Selection

All citations were independently reviewed by two team members to ensure accuracy. All citations found to be potentially appropriate for inclusion by either reviewer underwent full-text review. Each full-text article was independently evaluated for final inclusion by two investigators. For inclusion, both reviewers had to agree that inclusion criteria were met. Differences between reviewers were resolved through consensus and discussion.

## Data Extraction

After studies were selected for inclusion, a total of five experienced staff members trained in using the Systematic Review Data Repository (SRDR) database (AHRQ, Rockville, MD; accessed at <http://srdp.ahrq.gov/>) entered data. After data extraction, at least one other staff member and one study investigator each verified the accuracy and completeness of abstraction for each study included. Discrepancies were resolved by discussion and consensus. SRDR was used to maintain the data and to create detailed evidence tables and summary tables.

## Quality Assessment of Individual Studies

Predefined criteria were used to assess the quality (risk of bias) of included randomized controlled trials and observational studies by using clearly defined templates and criteria as appropriate and following guidance from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>28</sup> Assessment of RCTs followed appropriate criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions*.<sup>29</sup> Comparative observational studies were assessed for study design features and sources of potential bias. These criteria and methods were used in conjunction with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions, in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* where in each study was rated as being “good”, “fair”, or “poor” quality.<sup>30</sup> Two investigators independently assessed the quality of each study, and any discrepancies were resolved through discussion and consensus.

Studies rated “good” are considered to have the least risk of bias and their results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated “fair” are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are least as likely to reflect flaws in the study design as the true difference between the compared interventions. Studies rated as being poor in quality *a priori* were not excluded, but considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Each study evaluated was dual-reviewed for quality by two team members. Any disagreements were resolved by consensus. The final quality assessments are described in detail in Appendix F.

## Data Synthesis

Meta-analysis was conducted in order to provide more precise estimates for outcomes when adequate data were reported. To determine the appropriateness of meta-analysis, clinical and methodological diversity and assessed statistical heterogeneity were considered. A random-effects model was used to combine risk ratios for binary outcomes, mean differences for continuous outcomes (e.g., the Short-Form 36 [SF-36]), and proportions of adverse events that only occurred in the ablation arm, while incorporating variation among studies. For proportions of adverse events, a generalized linear random effects model was used due to sparse data with zero or small number of events. Random effects across studies were assumed, and heterogeneity among the studies was tested based on the random effect variance ( $\tau^2$ ). Otherwise, a profile-likelihood model was used to combine studies<sup>31</sup> and the presence of statistical heterogeneity among the studies was assessed using the standard Cochrane's chi-square tests and the magnitude of heterogeneity by using the  $I^2$  statistic.<sup>32</sup>

To reduce the potential impact of clinical heterogeneity, analyses were stratified by type of AF (paroxysmal, persistent, or mixed population) and length of followup (>12 months versus ≤12 months). Sensitivity analyses were conducted to assess the robustness of results in regards to treatment type (first-line vs. second-line therapy) across all types of atrial fibrillation. For continuous outcomes, results using the mean differences between followup scores were reported as they are slightly more conservative<sup>33</sup> and as results based on mean difference in change score were similar. The number of studies was too small for exploring heterogeneity based on study level characteristics (aggregated patient characteristics, comorbidities, quality indicators, etc.). All analyses were performed using Stata/IC 12.1 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute Inc., Cary, NC).

## Rating the Body of Evidence

The outcomes listed below were considered to be the most relevant and were the focus of reporting, data pooling, and determination of overall strength of evidence. Mortality, stroke and myocardial infarction (MI) occurring after the 30-day peri-procedural period were considered to be efficacy or effectiveness outcomes while such events occurring within the 30-day peri-procedural period were considered adverse events. Primary outcome measures of interest included: mortality (all cause) >30 days postprocedure, stroke (>30 days), MI (>30 days), congestive heart failure (CHF), and health-related quality of life (HRQOL). Intermediate outcome measures of interest included: freedom from recurrence, maintenance of sinus rhythm, and reablation for any arrhythmia (one or more repeat procedures). Primary safety outcomes of interest included: AF (<3 months), mortality (<30 days), stroke (<30 days), cardiac tamponade, pericardial effusion, pulmonary vein stenosis, and adverse drug related events. Outcomes such as pulmonary vein stenosis, cardiac tamponade, and pericardial effusion were considered to be attributable to ablation.

The strength of evidence for each primary efficacy/effectiveness and safety outcome was initially assessed by one researcher using the approach described in the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>28, 30</sup>

In determining the strength of a body of evidence regarding a given outcome, the following domains were considered: study limitations (the extent to which studies reporting on a particular outcome are likely to be protected from bias, graded as low, medium, or high); consistency (the extent to which studies report the same direction of effect for a particular outcome, graded as consistent, inconsistent, or unknown); directness (whether the outcome is directly or indirectly related to health outcomes of interest, graded as direct or indirect); precision (the level of certainty of the estimate of effect for a particular outcome, including consideration of the sample size and number of events, graded as precise or imprecise); and reporting bias (suspected if there was evidence of selective reporting, otherwise considered to be undetected).

A final strength of evidence grade was assigned by evaluating and weighing the combined results of the above domains; final grades are presented in the Discussion, and tables detailing how final grades were arrived at are available in Appendix G. To ensure consistency and validity of the evaluation, the strength of evidence ratings for all key outcomes were reviewed by the entire team of investigators, and discrepancies were resolved by consensus. Briefly, bodies of evidence consisting of RCTs started as high strength of evidence while bodies of comparative observational studies began as low strength of evidence. The strength of the evidence was then downgraded based on the limitations described above. There are also situations in which the observational evidence may be upgraded (e.g., very large size of effect), but we found no instances in which upgrading could be applied to this body of evidence (see the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for details on upgrading). A “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

## **Applicability**

Applicability of the evidence was considered by examining the characteristics of the patient populations included in studies (e.g., demographic characteristics, type of AF, presence of medical comorbidities, stroke risk); the sample size of the studies; and clinical settings (e.g., academic setting, provider experience) in which the studies are performed, as outlined in the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>28, 34</sup> Variability in the studies may limit the ability to generalize the results to other populations and settings, for example studies enrolling relatively younger patients with few comorbidities may be less applicable to older patients (i.e., those in the Medicare population).

## **Peer Review and Public Commentary**

Experts in atrial fibrillation and catheter ablation as well as individuals representing other important stakeholder groups were invited to provide external peer review of this comparative effectiveness review (CER). Comments and editorial review were also provided by the AHRQ Task Order Officer. The draft report was published on the AHRQ Web site for two weeks in order to solicit public comments. At the end of this period, the authors considered both the peer

and public review comments and generated a final report. A disposition of comments report detailing the authors' responses to the peer and public review comments will be made available after AHRQ posts the final report of the review on the public Web site.

## **Results**

### **Results of Literature Searches**

Database searches identified 3,471 potentially relevant citations. After dual review of abstracts and titles, 103 articles were examined at full text, and of these 46 studies (50 publications) were determined by dual review to meet inclusion criteria and were included in this review. The evidence base in this report includes data from randomized controlled trials as well as observational studies. None of the randomized controlled trials was designed as a pragmatic trial.

#### **Key Question 1a. Comparative efficacy and effectiveness of radiofrequency catheter ablation versus medical therapy for treatment of atrial fibrillation**

Thirteen RCTs<sup>35-49</sup> and seven comparative observational studies,<sup>50-56</sup> three prospective and four retrospective, compared RFA with medical therapy. Only one RCT was considered to be good quality; the remaining studies were all considered fair quality. No RCT specifically evaluated the Medicare population while two observational studies were comprised of exclusively Medicare-age populations ( $\geq 65$  years). There was substantial ( $>35\%$ ) crossover from medical therapy to RFA in six trials. Overall, findings from the comparative observational studies were consistent with those reported by the RCTs unless otherwise noted below. See Tables A and B in the Discussion for detailed results.

### **Primary Outcomes**

#### **Short Term ( $\leq 12$ months)**

In patients with paroxysmal AF, all-cause mortality or MI (low strength of evidence), and stroke or CHF (insufficient strength of evidence) occurring beyond 30 days but before 12 months were rare and there were no statistically significant differences between RFA and medical therapy (low strength of evidence). Overall, there were inconsistencies regarding statistical differences between treatments past 3 months across HRQOL measures used in trials of patient with paroxysmal AF. One analysis of the SF-36 Physical Component Score (PCS) in two RCTs and the Symptom Frequency Severity Scale scores in one RCT suggest improved HRQOL at 12 months. There was insufficient evidence, however, to draw conclusions across trials and measures. Similarly, in patients with persistent AF, the frequency of all-cause mortality (low strength of evidence) or stroke (insufficient strength of evidence) was low with no statistical differences between groups. Again, definitive conclusions regarding improvement across measures of HRQOL were not possible due to the variety of measures and inconsistencies in statistical significance across measures. RFA showed greater improvement than medical therapy in SF-36 PCS in one RCT but no difference in the Atrial Fibrillation Quality of Life Questionnaire were seen in another. Three trials in heart failure patients suggested improvement in the Minnesota Living with Heart Failure Questionnaire at 6 months (low strength of evidence) but only one provided information that this may be sustained to 12 months (insufficient strength



of evidence). No studies were identified that reported on short-term outcomes in a Medicare population.

### **Long Term (>12 months)**

In patients with paroxysmal AF, all-cause mortality (low strength of evidence), stroke, MI, or CHF (insufficient strength of evidence) were rare in RCTs with no statistical differences between treatment groups. For persistent AF, no evidence was available in the general adult population; however, one comparative observational study in a Medicare-relevant population (mean age of  $75.6 \pm 5$  years) reported comparable frequency of all-cause mortality, stroke or TIA, MI, or CHF between groups (insufficient strength of evidence). A second observational study in Medicare-age patients (mean age 66.9 years) with both paroxysmal and persistent AF reported greater frequency of all-cause mortality, stroke, and CHF in the medical therapy group compared with RFA but a higher frequency of MI following RFA versus medical therapy (insufficient strength of evidence). In the two RCTs reporting SF-36 PCS and MCS beyond 12 months, there were no statistical differences between treatments in patients with paroxysmal AF. Again, firm conclusions were not possible. One large administrative database study reported lower annualized rates of stroke or TIA following RFA compared with medical therapy at 27 months but no difference in hospitalization for heart failure (insufficient strength of evidence).

## **Intermediate Outcomes**

### **Short Term ( $\leq 12$ months)**

Across nine RCTs, regardless of AF type, RFA was superior to medical therapy at improving freedom from recurrence of any atrial arrhythmia at 12 months (pooled relative risk [RR] 2.62, 95% confidence interval [CI] 1.90 to 3.96) (moderate strength of evidence). RFA was superior to medical therapy at improving maintenance of sinus rhythm in three RCTs (one in patients with paroxysmal AF and two in heart failure patients with persistent AF) but not in a fourth of paroxysmal AF at 12 months (low strength of evidence for both paroxysmal and persistent AF). The frequency of reablation following RFA varied across seven RCTs of paroxysmal or persistent AF (range, 0% to 53.8%) (low strength of evidence).

### **Long Term (>12 months)**

In patients with paroxysmal AF, catheter ablation was superior to medical therapy at improving freedom from recurrence of any atrial arrhythmia based on data from three RCTs (pooled RR 1.24, 95% CI 1.11 to 1.47) (moderate strength of evidence). The frequency of reablation following RFA for paroxysmal AF varied across four RCTs (pooled risk 24.2%, 95% CI 12.6 to 41.5) (low strength of evidence). There were no data for persistent AF patients in the general population for any of the intermediate outcomes. In one comparative observational study of a Medicare-relevant population with persistent AF, sinus rhythm was maintained in 58 percent of the RFA group versus 43 percent of the medical therapy group and 18.3 percent of RFA patients required reablation (insufficient strength of evidence for both).

## **Key Question 1a. Comparative efficacy and effectiveness of cryoablation versus medical therapy for treatment of AF**

One fair-quality, multi-center RCT compared cryoballoon ablation with medical therapy in a general adult population with paroxysmal or persistent AF (mixed population).<sup>57</sup> This study had

substantial crossover from medical therapy to cryoballoon ablation. No observational studies were identified for this comparison. Freedom from protocol-defined treatment failure was significantly greater in the cryoballoon ablation group compared with the group treated medically (low strength of evidence). See Table C in the Discussion for detailed results.

### **Key Question 1b. Comparative efficacy and effectiveness of cryoablation versus radiofrequency ablation for treatment of atrial fibrillation**

Two small RCTs, one fair quality<sup>58</sup> and the other poor quality,<sup>59</sup> compared cryoballoon ablation with RFA in general adult populations at 12 months. Neither trial reported on the primary outcomes of interest (insufficient strength of evidence). Freedom from AF recurrence was less common following cryoballoon ablation, but the difference wasn't statistically significant in either the trial in paroxysmal AF patients<sup>58</sup> or the trial in a mixed population.<sup>59</sup> The need for reablation was more common following cryoballoon ablation in both trials, with the trial in paroxysmal AF patients reporting this as statistically significant (insufficient strength of evidence). Six observational studies (2 fair quality, 4 poor quality) compared cryoballoon ablation to RFA.<sup>60-65</sup> No differences between treatments were reported for any of the primary outcomes at 24 months. No differences between treatments for freedom from recurrence were reported across these studies but one poor-quality study in a mixed population reported a higher proportion of patients in the RFA group requiring reablation. Findings from these observational studies did not alter overall strength of evidence. See Tables D and E in the Discussion for detailed results.

### **Key Question 2a. Complications and harms associated with radiofrequency catheter ablation versus medical therapy for treatment of atrial fibrillation**

All 13 RCTs and six of the comparative observational studies<sup>50, 51, 53-56</sup> comparing RFA with medical therapy that were included in Key Question 1a reported adverse events. One observational study was conducted in a Medicare-relevant population (elderly patients, mean age 75.6 years). See Table F in the Discussion for detailed results.

#### **Mortality (all-cause) (within 30 days)**

The 30-day mortality risk was low and similar for RFA versus medical therapy based on data from five RCTs (low strength of evidence), with similar results in studies of paroxysmal AF patients (3 RCTs) and persistent AF patients (2 RCTs). One prospective comparative observational study of a Medicare-relevant population (age 65 years and older) with persistent AF reported low risk in both treatment groups (insufficient strength of evidence).

#### **Stroke (any type) (within 30 days)**

Regardless of AF type, the 30-day stroke risk was low following RFA and medical therapy based on data from eight RCTs (low strength of evidence), and no statistical differences between groups were reported. One comparative observational study of a Medicare-relevant population (age 65 years and older) with persistent AF reported higher risk following RFA versus medical therapy (insufficient strength of evidence).

#### **AF (within 3 months)**

No difference in 3-month AF risk between groups was reported in two RCTs of paroxysmal AF (pooled RR 0.67; 95% CI 0.40 to 1.10) (low strength of evidence), whereas data from two

trials of persistent AF patients found a lower 2-month risk of AF following RFA versus medical therapy (pooled RR 0.18; 95% CI 0.11 to 0.30) (low strength of evidence).

### **Cardiac Tamponade**

In patients with paroxysmal AF, the pooled risk of cardiac tamponade following RFA was 1.7 percent (95% CI 0.8 to 3.6) based on data from four RCTs (low strength of evidence) while the pooled risk in patients with persistent AF was higher as reported by three small RCTs (5.5%, 95% CI 2.1 to 13.7) (insufficient strength of evidence). One comparative observational study of a Medicare-relevant population (age 65 years and older) with persistent AF reported no events (insufficient strength of evidence).

### **Pericardial Effusion**

Regardless of AF type, the risk of pericardial effusion following RFA was low based on data from five RCTs (three RCTs in paroxysmal AF, one in persistent AF, and one in a mixed population): range, 0.5 to 0.9 percent (low strength of evidence for all). One comparative observational study of a Medicare-relevant population (age 65 years and older) with persistent AF reported a risk of 1.9 percent (insufficient strength of evidence).

### **Pulmonary Vein Stenosis**

The risk of pulmonary vein stenosis following RFA for treatment of paroxysmal AF ranged from 0 to 3.1 percent across five RCTs; for persistent AF, risk ranged from 0 to 0.9 percent across two RCTs; and for a mixed population in one RCT, no cases were identified (low strength of evidence for all). One comparative observational study of a Medicare-relevant population (age 65 years and older) with persistent AF reported no cases (insufficient strength of evidence).

### **Drug Intolerance Leading to Discontinuation**

Overall, 5 to 23 percent of patients with paroxysmal AF randomized to medical therapy discontinued antiarrhythmic drugs due to adverse events or intolerance (2 RCTs) (low strength of evidence). In one RCT of a mixed population, a similar risk was reported between groups (insufficient strength of evidence). One comparative observational study of Medicare-aged patients reported this event in fewer patients in the RFA (2.6%) versus the medical therapy group (12.7%) (insufficient strength of evidence).

## **Key Question 2a. Complications and harms associated with cryoablation versus medical therapy for treatment of atrial fibrillation**

The RCT comparing cryoballoon ablation with medical therapy in a mixed population (i.e., patients with paroxysmal and persistent AF) included in Key Question 1a reported adverse events. No observational studies were identified for this comparison. There was insufficient evidence from this single study to draw conclusions. Within 30 days of initiation of treatment no deaths were reported for either group and stroke occurred in 0.6 percent in the cryoballoon ablation group, compared with 1.2 percent in the medical treatment group. Over half (51.5%) of cryoablation patients experienced AF recurrence within 3 months of treatment, but no data were reported for the medical therapy group. Following cryoballoon ablation, risk of cardiac tamponade was 0.9 percent and pulmonary vein stenosis was 3.1 percent. See Table G in the Discussion for detailed results.

## Key Question 2b. Complications and harms associated with cryoablation versus radiofrequency catheter ablation for treatment of AF

Two RCTs (one fair quality and one poor quality) plus five nonrandomized comparative studies (one fair-quality and four poor-quality observational studies) comparing cryoballoon ablation with RFA that were included in Key Question 1b reported adverse events. Due largely to lack of RCT data and poor-quality nonrandomized studies, the strength of evidence was insufficient for all outcomes. See Table H in the Discussion for detailed results.

## Key Question 3. Differential efficacy, effectiveness, or harms of catheter ablation versus medical therapy or different energy sources

All studies described in this Key Question were included in Key Question 1a. Evidence was insufficient to draw conclusions on the potential impact of patient or provider characteristics on the efficacy, effectiveness, or harms of catheter ablation as compared with medical therapy or comparing ablation using different energy sources (insufficient strength of evidence). Studies conducted in specific subgroups of the population found the following: rates of 30-day cerebral thromboembolism and pericardial effusion were higher, but not significantly, with RFA in patients 70 years or older; no differences were seen at 60 days in freedom from recurrence or adverse events. In patients who were receiving RFA as either first- or second-line treatment for AF, both long- and short-term freedom from recurrence rates favored RFA over medical therapy. In patients with heart failure, RFA was associated with improved HRQOL measured via the Minnesota Living with Heart Failure Questionnaire across three studies (low strength of evidence). Two trials reported improved maintenance of sinus rhythm following RFA (50.0%–88.0%) compared with medical therapy (0%–7.7%) at 6 to 12 months. Across the three studies, repeat ablation occurred in 34 percent (95% CI 19.3 to 52.6) of patients. In these studies the rate of major complications following RFA were 4 percent and 15 percent. In patients with Type 2 diabetes, RFA patients had greater improvements in quality of life at 12 months and more patients were free from AF recurrence versus those treated with medical therapy.

## Discussion

### Key Findings and Strength of Evidence

The key findings of this review and strength of evidence for the outcomes identified as being most clinically important are summarized in Tables A–H and factors used to determine the overall strength of evidence are summarized in Appendix G.

Only one RCT was considered to be high quality,<sup>42</sup> the remaining RCTs had various methodological limitations. For most Key Questions and outcomes, the strength of evidence was rated no higher than low due to small study sizes and methodological shortcomings. For the comparison of RFA with medical therapy, for the primary clinical outcomes (mortality, stroke, MI, CHF, and HRQOL), all ratings were low or insufficient. Strength of evidence was low or insufficient for most intermediate outcomes as well. Exceptions were freedom from recurrence of any atrial arrhythmia in patients with paroxysmal AF in both the short term ( $\leq 12$  months) and longer term ( $>12$  months) and for the pooled estimate across all studies regardless of AF type for which the strength of evidence was rated as moderate for the comparison of radiofrequency ablation with medical therapy. For many outcomes for a specific AF type, only single studies were available and conclusions were not possible because of study limitations (i.e.,

methodology), small sample sizes resulting in imprecise estimates, and/or limited data from these single studies leading to a strength of evidence rating of insufficient. Overall, findings from observational studies did not alter conclusions or impact the strength of evidence for any of the specified outcomes.

Evidence was most robust for the comparison of RFA with medical therapy. Overall, data were sparse for primary clinical outcomes such as mortality and stroke for both the short term and long term. The differences in results for long versus short term, particular with respect to freedom from recurrence and reablation, may be due to a variety of factors including fewer studies reporting longer-term outcome and the short-term followup being too short to capture later relapses, thus longer-term benefit appears lower. There were insufficient data to evaluate the extent to which difference in technique or population characteristics may have impacted outcomes.

In the Medicare-age population, there were no RCTs to provide evidence for efficacy and included trials did not provide subanalysis by age. Definitive conclusions regarding effectiveness could not be drawn from the two comparative observational studies identified that reported on patients aged 65 years and older with followup beyond 12 months.<sup>54, 55</sup> Evidence was insufficient for all outcomes. Across these studies comparing RFA with medical therapy, all-cause mortality and hospitalization for CHF after 30 days were greater in the study in a mixed population following RFA but comparable with medical therapy in the study of those with persistent AF. Similar to long-term outcomes in the general population, maintenance of sinus rhythm was more common following RFA (58% vs. 43%) in one study of persistent AF. Reablation was required in 18 percent of patients. In one study of Medicare age patients with persistent AF, there was higher 30-day stroke risk following RFA versus medical therapy (2.6% vs. 0.4%) as well as lower risk of antiarrhythmic drug intolerance requiring discontinuation following RFA (2.6% vs. 12.7%). The inconsistency of these findings and insufficient strength of evidence may make it challenging to weigh overall benefits and risks of RFA compared with medical therapy in this population from an evidence-based perspective.

In the general population, the bulk of evidence was in those with paroxysmal AF, and there were limited data on primary short- and long-term clinical outcomes. In this group, no statistical differences between treatments in all-cause mortality were seen in either the short or long term, but the strength of evidence was low. No differences between treatments for stroke, MI and CHF development were found in the long term but the evidence was from single studies and considered insufficient. Conclusions regarding the impact of RFA on HRQOL in both the long and short term were not possible. This is not to say that there was not improvement in HRQOL or symptoms following ablation, but there are challenges in confirming this with the currently available evidence from comparative studies that met the inclusion criteria. While individual studies reported statistically significant results favoring RFA over medical therapy for specific measures or isolated domains of measures, others did not. The variety of measures used, along with varied measurement timing and extensive cross-over made it difficult to draw firm conclusions regarding the impact of catheter ablation on HRQOL compared with use of anti-arrhythmic drugs as it is difficult to effectively evaluate consistency across measures and effect sizes. This was the basis for the rating of insufficient evidence. Although SF-36 was employed most frequently, measurements occurred at a variety of time points across studies and data were presented in different ways. These factors, combined with possible differences in patients receiving catheter ablation as a first line treatment versus a second line treatment precluded meaningful pooling of data. Where data were pooled, for the SF-36 PCS, different analysis

methods yielded differing results, calling the stability of the estimate into question. Across four clinically heterogeneous trials with discrepant time frames (6–48 months), the SF-36 bodily pain domain was significantly more improved in the RFA (vs. medical therapy) groups in three<sup>35, 43, 48</sup> of the four trials that provided data, however given the differences in clinical populations and time frames, definitive conclusions are not advisable. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was reported in three small trials in patients with persistent AF and concomitant heart failure. Two of three studies reported improvement favoring RFA at 6 months; the third didn't reach significance but tended to favor RFA (low strength of evidence). One of the trials reported that the difference was also evident at 12 months (insufficient strength of evidence). For all measures, there was likely insufficient sample size in many studies to detect differences between treatments. Clinically, a primary indication for performing RFA is to improve symptoms. While it may be that patients experience relief of symptoms following RFA, the majority of the HRQOL measures reported may not capture the type and range of symptoms experienced by those with AF or the potential impact of RFA on patient symptoms. There were inadequate data to evaluate the influence of use of RFA as a first versus second-line treatment on HRQOL.

Regarding intermediate outcomes, while moderate evidence indicated that RFA was superior to medical therapy at improving freedom from recurrence, reablation was commonly required and strength of evidence was low for this outcome. Information on utilization was sparse; however, overall rehospitalization for cardiac causes was more common in the medical treatment group.

There were no RCT data on primary outcomes for patients with persistent AF over the long term and a paucity of data over the short term for weighing risks and benefits in this population.

For the comparison of cryoballoon ablation with medical therapy, freedom from protocol-defined treatment failure was significantly more common in the cryoballoon ablation group compared with the group treated medically, but the strength of evidence for this outcome was low. Across the two trials comparing cryoballoon ablation with RFA, freedom from AF was less common and the need for reablation more common following cryoballoon ablation compared with RFA. Failure to demonstrate statistical differences between these energy sources may be partially a function of small sample size and strength of evidence for these outcomes was insufficient.

With regard to harms, in general, no differences between RFA and medical therapy were seen in RCTs for periprocedural harms (those within 30 days), but strength of evidence ranged from low for paroxysmal AF to insufficient for persistent AF, limiting the conclusions that could be drawn. Overall in the general population, risk of any major adverse event within 30 days (all-cause mortality, stroke, myocardial infarction, major bleeding/hemorrhage, need for transfusion and heart failure) from RCTs ranged from 0 to 14.8 percent in those receiving RFA and from 0 to 5.7 percent for those receiving medical therapy. However sample sizes were small and the study that reported that 14.3 percent of RFA procedures had worsening heart failure was based on only 21 patients (3 cases) in advanced heart failure patients. Cardiac tamponade risk ranged from 0 to 4.5 percent following RFA. In studies of patients with heart failure and persistent AF, risks were higher; overall risk of any major complication was 14.8 percent of all procedures in one RCT and risk of cardiac tamponade ranged from 3.8 to 9.5 percent across two RCTs. These overall ranges are from controlled studies conducted in tertiary referral centers with procedures performed by experienced personnel and may not reflect broader clinical practice outside of such centers.

With regard to individual harms, the risk for cardiac tamponade following RFA in patients with paroxysmal AF was imprecise (pooled estimate 1.7%, 95% CI 0.8 to 3.6) and strength of evidence was low, while evidence in patients with persistent AF evidence was insufficient. Overall, 5 to 23 percent of patients with paroxysmal AF who were randomized to medical therapy discontinued antiarrhythmic drugs due to adverse events or intolerance (low strength of evidence). For the comparison of cryoballoon ablation with RFA, there were insufficient quality data to draw firm conclusions.

Conclusions regarding the extent to which catheter ablation may be more efficacious or harmful for specific population subgroups were not possible based on the available evidence. None of the RCTs provided sufficient data to stratify by subgroups. Two studies in patients with concomitant heart failure and persistent AF reported that maintenance of sinus rhythm<sup>37,38</sup> was improved within the ablation patients in the short term and a third trial reported similar results concerning freedom from arrhythmia recurrence;<sup>48</sup> however, reablation was common. RFA was associated with improved HRQOL (i.e., MLHFQ) across all three studies<sup>37,38,48</sup> and with improved functional outcomes in two studies.<sup>37,48</sup> However, given that these studies did not directly compare treatment effect in those who did not have heart failure, modification of treatment effect by presence of heart failure could not be confirmed. Similarly, one study of people who had diabetes as well as either paroxysmal or persistent AF reported a significant benefit in quality of life and freedom from recurrent in ablation patients.<sup>35</sup> Again, modification of treatment effect in those with diabetes could not be verified. In the one small study (N=65) in which RFA was used as first-line treatment<sup>43</sup> and in the seven trials in which it was used following failure of antiarrhythmic medications,<sup>35,36,39-42</sup> it appeared that the relative risk point estimates were in the same direction (favoring RFA) for freedom from recurrence to 12 months and that there was substantial overlap in the confidence intervals.<sup>35,36,39,40,42,47</sup> Similarly, at followup >12 months, the point estimates for the two studies where RFA was used as the first-line treatment were similar to the one study where RFA was used as a second-line treatment, and there was substantial overlap in the confidence intervals.

**Table A. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF**

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality (All Cause) &gt;30 Days</b>	Paroxysmal AF	2 RCTs (N=408)	Low	At 24 months, one RCT reported no deaths in either group; the other, two (1.4%) in RFA and four (2.8%) in the medical treatment group.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable mortality in both groups at 60 months: 1.3% RFA, 1.9% medical therapy. Definitive conclusions are not possible.*
	Mixed	1 comparative observational (N=170)	Insufficient*	Comparable mortality in both groups at 16 months: 0% RFA, 1.2% medical therapy. Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	Greater mortality in the medical therapy arm at 69 months (2.1% RFA, 16.5% medical therapy); Definitive conclusions are not possible.*
<b>Stroke &gt;30 Days</b>	Paroxysmal AF	1 RCT (N=127)	Insufficient*	No strokes reported at 24 months. Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable frequency in both groups for stroke or TIA at 60 months (1.3% RFA, 1.9% medical therapy). Definitive conclusions are not possible.*
	Mixed	2 comparative observational (N=1772 )	Insufficient*	Increased stroke risk in medical therapy group (0% RFA vs. 4.7% medical therapy at 16 months in one study; annualized rate 3.4% RFA vs. 5.5% medical therapy in an administrative database study with a mean followup of 27 months). Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	At 69 months, risk 0% RFA versus 1.5% medical therapy group. Definitive conclusions are not possible.*
<b>Myocardial Infarction &gt;30 Days</b>	Paroxysmal AF	1 RCT (N=294)	Insufficient*	One (0.7%) fatal MI in the medical treatment group by 24 months. Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable MI events in both groups at 60 months (0% RFA, 0.4 % medical). Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	Greater MI events in ablation group at 69 months (1.4% RFA, 0% medical therapy). Definitive conclusions are not possible.*
<b>Congestive Heart Failure</b>	Paroxysmal AF	1 RCT (N=294)	Insufficient*	By 24 months, no one in the RFA group and two people (1.4%) in medical therapy group developed CHF. Definitive conclusions are not possible.*



Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable CHF development in both groups at 60 months (0% RFA, 1.2% medical therapy). Definitive conclusions are not possible.*
	Mixed	1 comparative observational (N=1602)	Insufficient*	Comparable annualized rates of hospitalization for heart failure: 1.5% RFA, 2.2% medical therapy in one administrative data study with a mean followup of 27 months. Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	Greater CHF in medical therapy group at 69 months (0.7% RFA, 9.8% medical therapy). Definitive conclusions are not possible.*
<b>Health-Related Quality Of Life: SF-36</b>	Mental Component Score and Physical Component Score: Paroxysmal AF	1 RCT (N=294) at 24 months; 1 RCT (N=198) at 48 months	Insufficient*	Mean MCS was similar between groups at 24 months (RFA: 51.1 ± 9.2; Medical therapy: 50.9 ± 8.0) (1 RCT) and at 48 months (RFA: 52.9 ± 9; Medical therapy: 51.9 ± 9) (1 RCT); Mean PCS was similar between groups at 24 months (RFA: 50.0 ± 8.8; Medical therapy: 47.9 ± 8.9) (1 RCT) and at 48 months (RFA: 52.3 ± 9; Medical therapy: 52.6 ± 8) (1 RCT). Definitive conclusions are not possible.*
<b>Freedom From Recurrence (Any Arrhythmia)</b>	Paroxysmal AF	3 RCTs (N=619)	Moderate	At 24–48 months, RFA was associated with greater freedom from recurrence compared with medical therapy (pooled RR 1.24; 95% CI 1.11 to 1.47).
	Mixed	1 comparative observational (N=85 in RFA arm)	Insufficient*	Rate was 74% at 15 months for RFA group; not reported for medical therapy. Definitive conclusions are not possible.*
<b>Maintenance Of Sinus Rhythm</b>	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	At 60 months, rate was 58% in the RFA group versus 43% in the medical therapy group. Definitive conclusions are not possible.*
	Mixed	1 comparative observational (N=170)	Insufficient*	At 15 months, rate was 82% in the RFA group versus 40% in the medical therapy group. Definitive conclusions are not possible.*
<b>Reablation (Any Arrhythmia)</b>	Paroxysmal AF	4 RCTs (N=337)	Low	Over followup periods ranging from longer than 12 months to 48 months, frequency of reablation varied across trials (range, 12.5%–49.2%) with a pooled risk of 24.2% (95% CI 12.6 to 41.5).
	Persistent AF: Medicare population	1 comparative observational (N=153 ablation group only)	Insufficient*	Rate was 18.3% at 60 months for RFA group; not reported for medical therapy. Definitive conclusions are not possible.*

AF = atrial fibrillation; CHF = congestive heart failure; KQ = Key Question; MCS = Mental Component Score; MI = myocardial infarction; PCS = Physical Component Score; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations (i.e. methodology), small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table B. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF**

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality (All Cause) &gt;30 Days</b>	All RCTs (regardless of AF type)	7 (N=814)	Low	Low frequency of mortality with risk similar between groups (0%–3.8% for RFA and 0%–2.9% for medical therapy).
	Paroxysmal AF	3 RCTs (N=333)	Low	One death was reported in the RFA group, two in the medical treatment group.
	Persistent AF	3 RCTs (N=344)	Low	Two deaths were reported in the RFA group with none reported for medical treatment.
	Mixed	1 RCT (N=137)	Low	One death was reported in the RFA group and two in the medical therapy group.
<b>Stroke &gt;30 Days</b>	Paroxysmal AF	1 RCT (N=67)	Insufficient*	No strokes were reported for either treatment. Definitive conclusions are not possible.*
	Persistent AF	1 RCT (N=146)	Insufficient*	No strokes were reported for either treatment. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=70) (Diabetic patients)	Insufficient*	No strokes were reported for either treatment. Definitive conclusions are not possible.*
<b>Myocardial Infarction &gt;30 Days</b>	Paroxysmal AF	2 RCTs (N=270)	Insufficient*	Two fatal MIs occurred, one in each treatment group. Definitive conclusions are not possible.*
<b>Congestive Heart Failure</b>	None for any AF type	None	Insufficient	No data available
<b>Health-Related Quality Of Life: SF- 36</b>	Mental Component Score: Paroxysmal AF	2 RCTs (N=406); 1 comparative observational (N=166)	Insufficient*	No statistical difference between treatment: pooled estimates for difference in change scores (1.88; 95% CI -0.47 to 4.50) and difference in mean scores (2.26; 95% CI -2.12 to 7.40) based on RCTs.
	Mental Component Score: Persistent AF (Patients with heart failure)	1 RCT (N=41) at 6 months	Insufficient*	No difference in mean change from baseline between groups (RFA: +0.4 ± 9.5; Medical Therapy: +5.9 ± 8.5). Definitive conclusions are not possible.*
	Physical Component Score: Paroxysmal AF	2 RCTs (N=406); 1 comparative observational (N=166)	Insufficient*	No statistical difference between treatments based on the pooled estimate from RCTs for difference in change scores (2.88; 95% CI -0.18 to 5.25); however, RFA was favored based on the pooled estimate using difference in mean scores (2.85; 95% CI 0.93 to 4.82). Definitive conclusions are not possible.*
	Physical Component Score: Persistent AF (Patients with heart failure)	1 RCT (N=41) at 6 months	Insufficient*	Greater change from baseline for RFA group reached statistical significance (+4.0 ± 9.5 vs. -1.0 ± 4.4 for medical therapy). Definitive conclusions are not possible.*

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Other Health-Related Quality Of Life Measures</b>	<i>Minnesota Living with Heart Failure Questionnaire</i> : Persistent AF in heart failure patients	3 RCTs (N=141) (heart failure)	Low (6 months) Insufficient* (12 months)	Two studies reported statistically significant differences favoring RFA at 6 months; means were different in one study (23.7 versus 47.0, p=0.001) and the other provided no data, (p=0.02). No statistical difference between groups (change from baseline $-5.7 \pm 19.7$ for RFA vs. $-2.8 \pm 17.9$ ) were seen in the third trial but tended to favor RFA. One trial reporting a difference favoring RFA at 6 months which persisted to 12 months. Definitive conclusions beyond 6 months are not possible.*
	<i>EuroQOL -5D and Symptom Check List</i> : Paroxysmal AF	1 RCT (N=127) EQ5D; 1 RCT (N=112) Symptom Check List	Insufficient*	Small, single RCTs each reported different measures. No differences between treatments for EQ5D (one trial). Another reported no differences in the Symptom Checklist Frequency Scale but a difference favoring RFA in the Severity Scale. Definitive conclusions are not possible.*
	<i>AFQOL, KCCQ, and NYHA score</i> : Persistent AF	1 RCT (N=146) AF-QOL; 1 RCT (N=127) KCCQ; 1 RCT (N=48) NYHA score	Insufficient*	No differences between treatments for AFQOL and KCCQ; RFA favored at 6 months based on NYHA score. Definitive conclusions are not possible.*
	<i>Zung Self-Rating Anxiety Scale and Depression Scale</i> : Paroxysmal AF	2 comparative observational (N=365)	Insufficient*	Mean SAS and SDS scores were significantly decreased compared with baseline scores in ablation group but not in the medical group. Magnitude not reported in one study. Definitive conclusions are not possible.*
<b>Freedom From Recurrence (Any Arrhythmia)</b>	All RCTs (regardless of AF type)	9 (N=1089)	Moderate	Freedom from recurrence of any arrhythmia was greater for RFA versus medical therapy (pooled RR 2.62; 95% CI 1.90 to 3.96).
	Paroxysmal AF	4 RCTs (N=538); 2 comparative observational (N=322)	Moderate	Freedom from recurrence of any arrhythmia was greater for RFA versus medical therapy (pooled RR 3.06; 95% CI 2.35 to 3.90).
	Persistent AF	3 RCTs (N=344)	Low	Rate is 58%–74% in the RFA group versus 4%–58% in the medical therapy group. Studies are too heterogeneous to combine. Findings are suggestive of benefit, but more data are needed.
	Mixed	2 RCTs (N=207)	Low	Rate is 56%–80% in the RFA group versus 9%–43% in the medical therapy group. Studies are too heterogeneous to combine. Findings are suggestive of benefit, but more data are needed.
<b>Maintenance Of Sinus Rhythm</b>	Paroxysmal AF	2 RCTs (N=310); 2 comparative observational (N=385)	Low	Rate is 88%–92.9% for RFA group versus 35.4%–87% for medical therapy arm across RCTs; Rate is 71.1%–72% in the RFA arm vs. 20.2%–47.1% in the medical therapy arm in comparative observational studies.

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Persistent AF (patients with heart failure)	2 RCTs (N=93)	Low	Rate 50.0%–88.0% for RFA group versus. 0%–7.7% for medical therapy group.
<b>Reablation (Any Arrhythmia)</b>	All RCTs (regardless of AF type)	8 (N=430) (ablation group only)	Low	The frequency of reablation following RFA varied across eight RCTs (range, 0%–53.8%).
	Paroxysmal AF	3 RCTs (N=184); 1 comparative observational (N=82) (ablation groups only)	Low	Rates varied widely (0%–43.3%) and consequently were not pooled.
	Persistent AF	5 RCTs (N=246) (ablation group only)	Low	Rates ranged from 8.1%–53.8% with a pooled estimate of 25.5% (95% CI 13.6% to 42.6%).
	Persistent AF (patients with heart failure)	3 RCTs (N=71) (ablation group only)	Low	Pooled estimate: 34% (95% CI 19.3% to 52.6%).

AF = atrial fibrillation; AFQOL = Atrial Fibrillation Quality of Life Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; KQ = Key Question; MCS = Mental Component Score; MI = myocardial infarction; PCS = Physical Component Score; RCT = randomized controlled trial; RFA = radiofrequency ablation; SAS = Zung Self-Rating Anxiety Scale; SDS = Zung Self-Rating Depression Scale.

\*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table C. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with medical therapy for AF**

<b>Outcomes*</b>	<b>Number of Studies (N)</b>	<b>Strength of Evidence Grade</b>	<b>Conclusions, Effect Size</b>
<b>Mortality (All Cause) &gt;30 Days</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	One unrelated fatal MI at 10 months reported in the cryoballoon ablation group. Definitive conclusions are not possible. <sup>†</sup>
<b>Stroke &gt;30 Days</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	Three strokes occurred >30 days from randomization (with one being 5 days after repeat RFA for atrial flutter). Definitive conclusions are not possible. <sup>†</sup>
<b>Myocardial Infarction &gt;30 Days</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	One unrelated fatal MI at 10 months reported in the cryoballoon ablation group. Definitive conclusions are not possible. <sup>†</sup>
<b>Congestive Heart Failure</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	One cryoballoon ablation patient was hospitalized with AF-related congestive heart failure. Definitive conclusions are not possible. <sup>†</sup>
<b>Health-Related Quality Of Life</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	Reported that SF-36 symptoms improved in cryoballoon ablation population but did not publish data or include comparison with medically treated patients. Definitive conclusions are not possible. <sup>†</sup>
<b>Freedom From Protocol-Defined Treatment Failure</b>	1 RCT (N=245)	Low	Cryoballoon ablation was associated with greater freedom from protocol-defined treatment failure compared with medical therapy: 69.9% versus 7.3%.

AF = atrial fibrillation; KQ = Key Question; MI = myocardial infarction; RCT = randomized controlled trial; RFA = radiofrequency ablation; SF-36 = Short-Form 36 questionnaire.

\*All outcomes are for the same RCT in a mixed population (no other studies were identified for this comparison).

<sup>†</sup>Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table D. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF**

<b>Outcomes, Population</b>	<b>Number of Studies (N)</b>	<b>Strength of Evidence Grade</b>	<b>Conclusions, Effect Size</b>
<b>Mortality (all cause) &gt;30 days</b> (Paroxysmal AF)	1 comparative observational (N=396)	Insufficient*	At 23 months, mortality occurred in 1.2% (3/260) in the RFA arm versus none (0/136) in the cryoballoon ablation arm. Definitive conclusions are not possible.*
<b>Freedom from recurrence (any arrhythmia)</b> (Paroxysmal AF)	2 comparative observational (N=498)	Insufficient*	No statistical differences at 23–28 months with 55%–63% experiencing freedom from recurrence following cryoballoon ablation versus 55%–57% following RFA. Definitive conclusions are not possible.*
<b>Reablation (AF only)</b> (Mixed)	1 comparative observational (N=177)	Insufficient*	By 14 months, reablation for AF was performed in 14% of cryoballoon recipients versus 23% of those receiving RFA. Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table E. Key findings and strength of evidence for Key Question 1: Short-term ( $\leq 12$  months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF**

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Freedom From Recurrence (AF only)</b>	Paroxysmal AF	1 RCT (N=50); 1 comparative observational (N=143)	Insufficient*	Freedom from AF recurrence was less common in the cryoballoon ablation group (48%) versus RFA (68%) in one RCT, however results failed to reach statistical significance. Rates were 77% and 72%, respectively, in one comparative observational study. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=60)	Insufficient*	Freedom from AF recurrence was less common in the cryoballoon ablation group (66.7%) versus RFA (86.7%) however results failed to reach statistical significance. Definitive conclusions are not possible.*
<b>Reablation (AF only)</b>	Paroxysmal AF	1 RCT (N=50)	Insufficient*	Reablation for AF only was more common following cryoballoon ablation (24%) versus none for RFA (0%); RR 0.22 (95% CI 0.07 to 0.37), p=0.0122. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=60)	Insufficient*	Reablation for AF only was more common following cryoballoon ablation (30%) versus RFA (13.3%), but statistical significance was not reached. Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table F. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with RFA versus medical therapy for AF**

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality &lt;30 Days</b>	All RCTs (regardless of AF type)	5 RCTs (N=761)	Low	Low frequency of 30-day mortality with similar risk between groups: RFA 0%–0.7%; medical therapy 0%–4.2% (1/24).
	Paroxysmal AF	3 RCT (N=570)	Low	Low frequency of 30-day mortality with similar risk between groups: RFA 0%–0.7%; medical therapy 0%. One death occurred following a procedure-related cerebral stroke.
	Persistent AF	2 RCTs (N=191)	Low	Low frequency of 30-day mortality with similar risk between groups: RFA 0%; medical therapy 0%–4.2%. One sudden cardiac death occurred in a heart failure patient.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Low 30-day mortality risk in both groups: RFA 0%; Medical therapy 0.4%. Definitive conclusions are not possible.*
<b>Stroke &lt;30 Days</b>	All RCTs (regardless of AF type)	8 RCTs (N=919)	Low	30-day stroke risk following both treatments: RFA 0%–4.8%; medical therapy 0%.
	Paroxysmal AF	3 RCTs (N=481)	Low	Low frequency of 30-day stroke with similar risk between groups: RFA 0%–0.7%; medical therapy 0%. One procedure-related cerebral stroke occurred (and resulted in death).
	Persistent AF	3 RCTs (N=231)	Low	Low 30-day stroke risk following both treatments: RFA 0%–4.8%; medical therapy 0%. Both strokes occurred in patients with heart failure: one during the procedure and the other 6 days post-ablation.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Higher 30-day stroke risk following RFA (2.6%) versus medical therapy (0.4%) (p=0.046). Definitive conclusions are not possible.*
	Mixed	2 RCTs (N=207); 1 comparative observational (N=166)	Low	Low 30-day stroke risk following both treatments: RFA 0%–1.5%; medical therapy 0%. One procedural stroke occurred. In the comparative observational study, 30-day stroke risk between groups: RFA 1.2%; medical therapy 1.2%.
<b>AF &lt;3 Months</b>	Paroxysmal AF	2 RCTs (N=183)	Low	No difference in 3-month AF risk between groups (pooled RR 0.67 [95% CI 0.40 to 1.10]).
	Persistent AF	2 RCTs (N=196)	Low	2- to 3-month risk of AF lower following RFA versus medical therapy (pooled RR 0.18 [95% CI 0.11 to 0.30]).
<b>Cardiac Tamponade<sup>†</sup></b>	Paroxysmal AF	4 RCTs (N=512); 1 comparative observational (N=85)	Low	The pooled cardiac tamponade risk following RFA was 1.7% (95% CI 0.8 to 3.6) based on data from four RCTs. The comparative observational study reported no cases of cardiac tamponade.



Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Persistent AF	3 RCTs (N=73)	Insufficient*	The pooled cardiac tamponade risk following RFA was 5.5% (95% CI 2.1 to 13.7). Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=158)	Insufficient*	Cardiac tamponade occurred in 0% of patients. Definitive conclusions are not possible.*
<b>Pericardial Effusion</b> <sup>†</sup>	All RCTs (regardless of AF type)	5 RCTs (N=772)	Low	Low pericardial effusion risk following RFA (range, 0.5%–0.9%).
	Paroxysmal AF	3 RCTs (N=519)	Low	Low pericardial effusion risk following RFA (pooled risk 0.6% (95% CI 0.2 to 1.8).
	Persistent AF	1 RCT (N=116)	Insufficient*	Low pericardial effusion risk following RFA (0.9%). Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=158)	Insufficient*	Pericardial effusion occurred in 1.9% of patients. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=137)	Low	Low pericardial effusion risk following RFA (0.7%).
<b>Pulmonary Vein Stenosis</b> <sup>†</sup>	Paroxysmal AF	5 RCTs (N=433) 1 comparative observational (N=85)	Low	Low pulmonary vein stenosis risk following RFA from five RCTs with followup ranging from 1–24 months (range, 0%–3.1%). Pooled risk based on two trials with 12-month followup: 1.6% (95% CI 0.4 to 6.3). Pooled risk based on two trials with 24-month followup: 0.7% (95% CI 0.2 to 2.8). No cases reported in the comparative observational study with 12 months followup.
	Persistent AF	2 RCTs (N=137)	Low	Low pulmonary vein stenosis risk following RFA (range, 0%–0.9%). Pooled risk: 0.7% (95% CI 0.1 to 5.0).
	Persistent AF: Medicare population	1 comparative observational (N=158)	Insufficient*	There were no cases of pulmonary vein stenosis. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=137); 1 comparative observational (N=85)	Low	No cases of pulmonary vein stenosis following RFA based on the RCT. In the comparative observational study, stenosis occurred in 7.1% of patients. Definitive conclusions are not possible from this study.*
<b>Drug Intolerance Requiring Discontinuation</b>	Paroxysmal AF	2 RCTs (N=155 medical therapy patients)	Low	Overall, 5% to 23% of patients randomized to medical therapy discontinued anti-arrhythmic drugs due to adverse events or intolerance; by 1 month in one trial, timing not reported in the second trial Due to limited duration and/or usage of medical therapy in the RFA group it is difficult to make comparative conclusions.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Lower risk of antiarrhythmic drug intolerance requiring discontinuation following RFA (2.6%) versus medical therapy (12.7%) (p=0.0005). Definitive conclusions are not possible.*

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Mixed	1 RCT (N=70)	Insufficient*	Low risk of antiarrhythmic drug intolerance requiring discontinuation following RFA and medical therapy (2.9% vs. 0%); timing not reported Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

†Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

**Table G. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus medical therapy for AF**

Harms/ Complications*	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality &lt;30 days</b>	1 RCT (N=245)	Insufficient†	The 30-day all-cause mortality risk was 0% in both treatment groups. Definitive conclusions are not possible.†
<b>Stroke &lt;30 days</b>	1 RCT (N=245)	Insufficient†	The 30-day stroke risk was low in both groups: cryoballoon ablation 0.6%; medical therapy 1.2%. Definitive conclusions are not possible.†
<b>AF &lt;3 months</b>	1 RCT (N=163)	Insufficient†	Over half of cryoablation patients experienced AF recurrence within 3 months of treatment (51.5%); data was not reported for the medical therapy group. Definitive conclusions are not possible.†
<b>Cardiac tamponade‡</b>	1 RCT (N=228)	Insufficient†	The incidence of cardiac tamponade following cryoballoon ablation was low (0.9%). Definitive conclusions are not possible.†
<b>Pericardial effusion‡</b>	Not reported	Insufficient	No data available
<b>Pulmonary vein stenosis‡</b>	1 RCT (N=228)	Insufficient†	The incidence of pulmonary vein stenosis following cryoballoon ablation was low (3.1%). Definitive conclusions are not possible.†
<b>Drug intolerance requiring discontinuation</b>	Not reported	Insufficient	No data available

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial.

\*All harms/complications are for the same RCT in a mixed population (no other studies were identified for this comparison).

†Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

‡Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

**Table H. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus RFA for AF**

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality &lt;30 Days</b>	Paroxysmal AF	2 comparative observational (N=4171)	Insufficient*	There were no cases reported in either group during the periprocedural period in two nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>Stroke &lt;30 Days</b>	Paroxysmal AF	1 comparative observational (N=133)	Insufficient*	There were no cases reported in either group in one nonrandomized comparative study. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>AF &lt;3 Months</b>	Paroxysmal AF	1 comparative observational (N=3775)	Insufficient*	One nonrandomized comparative study reported similar AF recurrence rates in both groups during the hospitalization period. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>Cardiac Tamponade†</b>	Paroxysmal AF	3 comparative observational (N=4304)	Insufficient*	Periprocedural cardiac tamponade rates ranged from 0.7%–2.2% during cryoablation and from 1.1%–1.5% during RFA based on data from three nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>Pericardial Effusion†</b>	Paroxysmal AF	2 comparative observational (N=529)	Insufficient*	Pericardial effusion occurred in 7.3%–8.7% of cryoablation patients and in 10.0%–13.8% of RFA patients based on data from two nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF	Not reported	Insufficient	No data available
	Mixed	2 comparative observational (N=267)	Insufficient*	Pericardial effusion occurred in 0%–1.1% of cryoablation patients and in 1.6%–3.8% of RFA patients based on data from two nonrandomized comparative studies. Definitive conclusions are not possible.*
<b>Pulmonary Vein Stenosis†</b>	Paroxysmal AF	2 comparative observational (N=4171)	Insufficient*	There were no cases reported in either group during the periprocedural period in two nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF	Not reported	Insufficient	No data available
	Mixed	1 comparative observational (N=124)	Insufficient*	There were no cases reported in either group during the periprocedural period in one nonrandomized comparative study. Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

†Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

## **Findings in Relationship to What is Already Known**

Findings in this review were generally consistent with prior systematic reviews that included evaluation of catheter ablation versus medical therapy for AF.<sup>23, 25</sup>

This review expands information available from previous reviews in a number of ways. First, more recent publications comparing RFA with medical therapy with information on longer-term outcomes (>12 months) were included, as were studies comparing different energy sources. An attempt to specifically identify and summarize studies focused on the Medicare population was made. Based on input from Key Informants during Topic Refinement, analyses were stratified based on AF type (paroxysmal and persistent) when possible, as these are clinically different populations. Analyses to evaluate differential efficacy and harms for use of catheter ablation as a first-line treatment versus a second-line treatment, age, patient characteristics and comorbidities, provider characteristics and other factors were considered; however, data were too sparse to draw conclusions. This report also expands analyses of ablation-specific adverse events and includes a broader spectrum of outcomes such as reablation, echocardiographic parameters and biomarkers.

The two previous reviews yielded similar findings to the current review with respect to the benefit of RFA over medical therapy in improving freedom from recurrence of AF and/or maintenance of sinus rhythm.<sup>23, 25</sup> The current review, however, extends the findings of both reviews report to include longer-term outcome data and a broader spectrum of endpoints, stratifying them by AF type. Similar to this current report, the Washington State Health Technology Assessment (HTA) in 2013 found low frequency of mortality or stroke not attributed to the procedure, with no differences between the ablation and medical therapy groups and there was low quality of evidence that there was no difference between RFA (or cryoablation) and medical therapy for the primary harms of interest.<sup>25</sup> Both previous reports focused on the general population and reported a paucity of data in Medicare populations and for important clinical endpoints such as all-cause mortality, stroke, and heart failure, particularly in the long term.

Comparison of catheter ablation approaches/techniques to each other is an important question of interest to CMS but was beyond the scope of this review. There was substantial heterogeneity across included studies with respect to ablation techniques and sites that precluded their assessment in this review. Previous reviews provide some insight into this question. In the 2013 AHRQ review,<sup>22, 23, 25</sup> information on the following aspects of the procedure was captured: type of ablation catheter used, whether cavotricuspid isthmus (CTI) ablation was performed in conjunction with the PVI, whether ablation of complex fractionated atrial electrograms (CFAEs) was done, and whether sites other than CTI and CFAEs were ablated. However, the data could not be pooled due to the insurmountable heterogeneity observed in different aspects of the procedure. RCTs that compared different approaches (i.e., PVI, wide area circumferential ablation [WACA], addition of right or left lines, CFAE) were included in the Washington State HTA.<sup>25</sup> In terms of freedom from recurrence, there was low-quality evidence that WACA was favored over PVI, moderate-quality evidence that PVI plus CFE favored PVI alone, and moderate-quality evidence that there was no difference in recurrence following PVI versus PVI plus left lines or plus right lines. The HTA did not compare different ablation techniques.

## **Applicability**

The applicability of the findings from this review is described below.

## Patients

The bulk of the available trial data were in populations predominantly male (59%–88%), with mean ages ranging from 51 to 64 years, and two observational studies provided only limited information in people  $\geq 65$  years of age. Based on information from Key Informants during the topic refinement process, primary clinical decisionmaking regarding use of ablation and ablation approach was based on type and characteristics of AF, presence and type of other cardiac disease, and patient presentation, rather than on any specific age consideration or characteristics specific to the Medicare population. Patients with AF may have had a number of comorbid conditions and other underlying cardiovascular problems. Three RCTs investigated outcomes in populations with comorbidities often seen in conjunction with AF: two were conducted specifically in patients with heart failure (all with persistent AF)<sup>37, 38</sup> and one in patients with type 2 diabetes mellitus.<sup>35</sup> Mean left ventricular ejection fractions across studies that did not focus on heart failure were greater than 50 percent. Comorbidities were variably reported across the other RCTs. Hypertension was the most commonly reported comorbidity, with proportions ranging from 11 to 56 percent across studies. A number of subgroups of potential interest were identified by the Key Informants. However, there were insufficient data from included studies to evaluate the benefits and harms of catheter ablation in any subgroup. The evidence presented in this review may not apply to older people or to those with a greater number of comorbidities or more severe comorbidities (e.g., heart failure).

## Interventions

A wide variety of ablation strategies were used across studies. Based on input from Key Informants there is substantial variability in techniques and approaches used in clinical practice as well. Heterogeneity across studies with respect to techniques used precluded evaluation or comparison of specific techniques (and such evaluation was beyond the scope of this report). Findings from one small study comparing cryoballoon ablation to medical therapy may not be applicable to the broader population of AF patients eligible for catheter ablation. This is also true for the studies comparing energy sources.

## Comparators

The primary antiarrhythmic medications used in studies included amiodarone, sotalol, flecainide, and propafenone. Amiodarone is the most commonly used antiarrhythmic in clinical practice, but the others are also used. Antiarrhythmic agents used in the included studies were considered to be reflective of clinical practice and applicable to broad clinical populations with AF.

## Outcomes

Findings related to rare outcomes may not be fully applicable to broader clinical populations in part due to small study sizes and inability to fully characterize such outcomes. The nature of the comorbidities and study settings of the study populations may have also influenced findings and may differ from broader clinical populations. “Freedom from recurrence” is a complex concept and there is no clear consensus in the medical community on how best to measure it and no standard of care for monitoring it. Definitions varied across trials with some counting any atrial arrhythmia, whether symptomatic or asymptomatic, as recurrence, while others specified symptomology, duration, and characteristics. The heterogeneity in definition and measurement

of recurrence makes it challenging to fully evaluate freedom from recurrence as a benefit of catheter ablation.

## **Settings**

RCTs were primarily conducted in academically-oriented centers. Input from Key Informants suggested that there is great variability in practice in the clinical community. Findings from studies based in high volume centers with highly experienced providers may not be applicable to smaller centers and/or less experienced providers. Observational studies may be more reflective of the range of experience across settings. Both effectiveness and adverse events may differ by setting; however, there were insufficient data to evaluate this.

## **Implications for Clinical and Policy Decisionmaking**

RFA is increasingly being used to treat AF. The bulk of the available evidence compared RFA with medical therapy and in patients with paroxysmal AF. Evidence in this report provided insights that may be useful for clinical and policy decisionmaking on use of RFA compared with medical therapy to treat patients with paroxysmal AF and persistent AF as distinct clinical populations and on use of RFA as a first or second-line treatment. Evidence for shorter-term and longer-term efficacy, effectiveness, and safety is also valuable to decisionmaking. For clinical outcomes, there was insufficient evidence for the use of cryoballoon ablation compared with either medical therapy or RFA to support evidence-based decisionmaking in the general population and no evidence for these comparisons in the Medicare population.

## **Medicare Population**

Neither of the included comparative observational studies provided data for patients with paroxysmal AF for either short- or long-term effectiveness precluding evidence-based conclusions for this AF type in the Medicare population. One study was in patients with persistent AF<sup>55</sup> and the other in patients with various AF types,<sup>54</sup> although approximately 70 percent were classified by the authors as having “nonparoxysmal” without further description. No data on short-term outcomes were available and for all long-term outcomes, evidence was considered insufficient. RFA was used as second-line treatment in both studies, thus no evidence on the benefits or harms of RFA as a first-line therapy in the Medicare population was available to support evidence-based decisionmaking. Conflicting findings across the two studies with regard to long-term mortality and development of CHF may be attributable to difference in comorbidities, study execution, and confounding control. Only the study in those with persistent AF provided data that long-term maintenance of sinus rhythm occurred more frequently following RFA (58%) compared with those remaining on medical therapy (43%).<sup>55</sup> Definitive conclusions regarding effectiveness are not possible based on the evidence available. Similarly, insufficient evidence on harms of RFA compared with medical therapy precluded drawing evidence-based conclusions in the Medicare population.

## **General Population**

In the general population, evidence on the long-term efficacy of RFA compared with medical therapy for reducing mortality was low for paroxysmal AF. Data on the other primary outcomes of stroke, MI, and heart failure were sparse for patients with paroxysmal AF, and no long-term RCT data for any of these outcomes were found for those with persistent AF. Data on quality of life were not conclusive as results could not be pooled from studies due to substantial

heterogeneity. In patients with persistent AF and concomitant heart failure, three small studies suggested better HRQOL following RFA compared with medical therapy at 6 months. For intermediate outcomes, moderate-strength evidence indicated that for patients with either paroxysmal AF or persistent AF, radiofrequency ablation is effective in the short term ( $\leq 12$  months) for preventing recurrence of atrial arrhythmias compared with medical therapy. While this appeared to be sustained over a longer term in patients with paroxysmal AF, there is insufficient evidence for this in patients with persistent AF. Thus, evidence-based decisionmaking regarding the long-term efficacy for those with persistent AF is limited.

Overall, hospitalization was more frequent in those who received medical therapy versus RFA, however studies did not provide detail regarding reasons for hospitalization and the extent to which hospitalization for reablation procedures or crossover from medical therapy to ablation were included.

This review found very limited evidence from one study that compared cryoballoon ablation with medical therapy and included patients with different AF types. Two small RCTs comparing cryoballoon ablation with RFA provided no data on primary outcomes of interest and neither reported on adverse events. Freedom from recurrence was less common following cryoballoon ablation and reablation was more common, but sample sizes may have precluded observation of statistical differences between treatments. There was limited evidence comparing cryoballoon ablation with other treatment options (including RFA) to inform policy or decisionmaking regarding the balance of benefits and risks based on current evidence.

In general, guidelines and consensus statements from professional societies such as the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) recommend catheter ablation for symptomatic AF that is refractory or intolerant to antiarrhythmic medication(s), however the specifics and strength of the recommendations vary by guideline.<sup>18, 19, 66, 67 68</sup> Current ACC/AHA/HRS guidelines recommend that AF catheter ablation: is useful for symptomatic paroxysmal AF refractory or intolerant to at least one antiarrhythmic medication (Class I); is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least one antiarrhythmic medication (Class IIa); is reasonable as an initial rhythm-control strategy before drug therapy in patients with recurrent symptomatic paroxysmal AF (Class IIa); may be considered for symptomatic long-standing persistent AF refractory or intolerant to at least one antiarrhythmic medication (Class IIb); and may be considered in patients with symptomatic persistent AF (Class IIb). They further recommend that AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy with the sole intent of obviating the need for anticoagulation (Class III).<sup>5</sup> Evidence in our report suggested that effect sizes for freedom from recurrence are not different when RFA is used as a first-line treatment or as a second-line treatment, but there was insufficient evidence to draw conclusions regarding how RFA as a first-line treatment versus a second-line treatment may influence a broader range of outcomes or for the longer term, and no evidence on this in the Medicare population.

## **Limitations of the Review Process**

The findings presented have limitations related to the approach and scope of this review. First, comparative evaluation of ablation techniques and approaches was beyond the scope of this review. There was substantial heterogeneity across included studies with regard to techniques and approaches that precluded comparative evaluation of studies. Though evaluation of mapping

modalities and strategies was also beyond the scope of this review, we found insufficient information from included studies to assess mapping.

Stratification by AF type was felt to be clinically important and stratification to assess data at followup at >12 months was important to answering Key Questions. This resulted in fewer studies available for pooling within followup strata. Profile likelihood methods were used to provide more conservative estimates and confidence intervals given the small number of studies. This, combined with sparse data for many outcomes, may have limited the ability to explore statistical heterogeneity and precluded ability for further subgroup analyses.

Non-English studies were excluded and searches for studies published only as abstracts were not conducted. Formal assessment of publication bias was not conducted as there were fewer than 10 studies available for outcomes based on AF type, and research indicates that such methods can be misleading with smaller numbers of studies.<sup>69</sup>

Every attempt was made to assure that variables and outcomes were assessed and abstracted accurately, however wide variability across studies (in the quality of reporting of study methods, in how outcomes were defined, and in which patients were included) has the potential for introducing inaccuracies.

## Limitations of the Evidence Base

Important limitations of the evidence base include the sample size of the available trials, limited data available on primary clinical outcomes particularly at followup times >12 months, and the substantial crossover from medical therapy to catheter ablation in most trials. These factors made it difficult to draw strong conclusions regarding the effects and benefits of catheter ablation. Only one RCT comparing cryoballoon ablation with medical therapy was identified, and two small trials comparing cryoballoon ablation with RFA were identified but didn't provide data on primary outcomes of interest. This precludes drawing conclusions regarding the comparative effectiveness of various energy sources.

The evidence base was constrained by the methodological limitations of the included studies. Common methodological shortcomings included unclear allocation concealment (only one trial documented concealed allocation) and lack of assessor blinding for primary outcomes. Four studies did not report information on random sequence generation.<sup>36, 39, 41, 47</sup>

Although not a factor for determination of individual study quality or overall strength of evidence, the high frequency of crossover from medical therapy to ablation in most included studies may have hindered drawing definitive conclusions regarding the full benefits and harms of catheter ablation compared with medical therapy.

Study sizes were likely insufficient to effectively determine risk of the primary clinical outcomes (e.g., mortality) for either group or to detect statistical differences between treatment groups. Two recent large observational studies that reported on the primary outcomes of interest in this report were identified but were excluded as there was insufficient information on use of anti-arrhythmic drugs versus rate control medications or no treatment in the control groups.<sup>70, 71</sup> Both studies suggest that risk of stroke was significantly lower in patients receiving catheter ablation for AF compared with those who did not receive ablation in followup to 3.5 years. One study, based on administrative data from a large regional registry, stratified stroke risk by CHADS2 score and age reported that reduced stroke risk was present in all age groups and across all CHADS2 risk profiles.<sup>70</sup> The other study based on Taiwan's National Health Insurance claims database, reported that there was no association between RFA and lower mortality or hospitalization for heart failure.<sup>71</sup> Although both studies attempted to control for confounding,



the possibility of residual confounding from unmeasured factors should be considered as should the limitations of administrative data (such as misclassification) when interpreting these findings.<sup>72</sup> Findings should be confirmed in additional high-quality studies that provide specifics regarding treatments received.

A variety of HRQOL measures were used at varied time frames across trials; this, along with small sample sizes, limited the ability to pool data or draw firm conclusions regarding the impact of catheter ablation on HRQOL, as discussed previously.

For the freedom from recurrence outcome, the definitions used by each study were accepted. This outcome was variably defined across studies, with variations in the type of arrhythmia (i.e., AF, AF or atrial flutter, or any atrial arrhythmia) and whether study reports were limited to symptomatic or asymptomatic AF or not. Maintenance of sinus rhythm appeared to be used interchangeably with freedom from recurrence in many studies, although these two outcomes are not the same.

Most studies focused on the intermediate outcome related to freedom from recurrence. This was variably defined and adjudicated across studies; there was heterogeneity across studies regarding whether recurrence included any atrial arrhythmia or AF only, whether symptomatic and asymptomatic recurrences were included, and whether characteristics related to duration were considered. In addition, blanking periods ranged from 1 to 3 months across 11 RCTs. This variability in study protocols likely introduces variation in the cross-study calculations of the proportion of those free from AF after the blanking period.

There was less evidence on the effectiveness of catheter ablation in patients with persistent AF and limited evidence on use of catheter ablation as a first-line treatment, limiting the conclusions that can be drawn in these instances. No data were available to assess the differential efficacy and harms of catheter ablation by patient or provider characteristics.

## Research Gaps

Gaps in evidence were identified for each Key Question.

Key Question 1: RFA or cryoablation versus medical therapy and comparison of cryoablation versus RFA

- There was limited data on the impact of RFA compared with medical therapy on final clinical outcomes such as mortality, particularly in the long term. Long-term data was particularly sparse for those with persistent AF.
- Data was sparse for the comparison of cryoballoon ablation versus medical therapy and for the comparison of cryoballoon ablation with RFA for all clinically-relevant outcomes.
- No data from high-quality comparative studies on Medicare-relevant populations were identified.
- Across studies, there was lack of a standardized, consistent method of measuring, monitoring, and reporting “freedom from recurrence” or maintenance is sinus rhythm.
- Conclusions related to HRQOL and symptom relief were not possible from the included studies due the variety of HRQOL measures reported across different time frames and inconsistency in statistical significance.
- Ideally future studies would conceptualize strategies for treatment of AF, such as catheter ablation and medical therapy, and evaluate the impact of such strategies on hard clinical outcome such as death and stroke.

### Key Question 2: Harms

- Comparative data on rare harms were limited by study sample sizes particularly in those with persistent AF. This was true for the comparisons of RFA versus medical therapy as well as for the comparisons of cryoballoon ablation with medical therapy or RFA.

### Key Question 3: Differential efficacy, effectiveness, harms

- Available RCTs did not have sufficient power to evaluate differential efficacy or harm of catheter ablation (RFA or cryoballoon ablation) versus medical therapy or for comparison of cryoballoon ablation with RFA for specific patient subgroups or provider settings. No conclusions are possible regarding which patients may benefit most or regarding which patients may not benefit from catheter ablation with current evidence.
- Limited data on use of RFA as the first treatment of choice (first-line therapy) versus a second-line therapy following failure of antiarrhythmic medications were available. No data for cryoballoon ablation were available to evaluate its use as first versus second-line therapy.

Some of these gaps may be addressed via the CABANA Trial (<https://www.cabanatrial.org/>), which is scheduled for completion in March 2018. This RCT conceptualizes ablation and medical therapy as strategies for treatment of AF and compares first-line ablation with pharmacologic therapy for reducing the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest in patients with atrial fibrillation. The target sample size is 2200 and current enrollment is about 1650 patients across 126 study sites in 10 countries. The trial will likely have good representation of Medicare patients, as to be eligible for the trial, patients must be either 65 years of age or older or have at least one risk factor for stroke. In addition, inclusion of patients with specific risk factors for stroke (e.g. hypertension, diabetes) may facilitate better understanding of the impact of catheter ablation in subpopulations with specific risk factors. One potential limitation of the trial includes the use of a composite outcome as the primary outcome measure, which may preclude adequate characterization and representation of important individual outcomes. This may limit conclusions which can be drawn regarding the efficacy of catheter ablation versus medical therapy to affect clinical outcomes such as mortality, stroke, and development of CHF if there is insufficient power to evaluate these as separate outcomes although they are listed as intermediate outcomes for this study. Another limitation is its span over a very long period of time (started in 2009) during which technology is evolving quickly. Thus, equipment and techniques that were used earlier in the trial may not be relevant to clinical practice when the trial ends. It is not clear if there will be sufficient data to evaluate efficacy separately by AF type or to compare ablation techniques. The planned followup of approximately 5 years will provide additional evidence on the longer-term impact of catheter ablation on clinical outcomes. Results from CABANA will enhance the current evidence base and provide much needed information on efficacy and safety particularly in those >65 years of age. In addition to CABANA, several other trials are currently evaluating aspects of catheter ablation for the treatment of AF, including a total of 14 relevant ongoing clinical trials were identified using the United States National Institute of Health clinical registry ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) (Appendix, Table H8).

In addition to the evidence the CABANA trial and other currently open trials may yield, there is a need to evaluate effectiveness across clinical settings and provider skill levels outside of randomized trials. There are several key elements that might augment the productivity of future

research. For example, high-quality clinical registries, designed *a priori* to address specific clinical questions, could provide an important source for addressing some research gaps. Such registries could be designed to extend the observations from randomized trials; this approach might differ from currently available study results by allowing for evaluation of the durability of the effects seen with longer followup, including a larger sample size to examine rare events, and including a broader range of patients to facilitate evaluation of how well patient groups are represented in clinical trials. Specific components that could be considered for capture include: more detailed information on patient and provider characteristics; AF details (duration, prior treatments, and episode severity); procedural details (e.g., mapping, catheter use, and technique/approach); management of patients before, during, and after procedure; and acute procedural outcomes as well as longer-term outcomes and complications. Such a registry could be used to address important issues such as how outcomes in clinical practice compare with outcomes observed in clinical trials and how outcomes are associated with characteristics of patients and providers. Registries could help determine performance measures and assist with quality improvement, post-marketing safety public reporting as well. There are, however, a number of limitations and factors to consider for registries. A challenge of creating and maintaining a registry is the potential difficulty of balancing the burden of high-quality data collection with acceptable registry size. Designing a large registry can be more costly but not necessarily more valuable than a registry of smaller size or other study types. Registries designed to test specific medical devices face logistical problems including variability in insurance coverage for specific devices, influence of operator characteristics while using the same device, and difficulty in differentially identifying unique devices in use. An additional challenge of maintaining a registry is that research questions may change after data collection begins which causes a shift in the importance of some of the data elements collected.<sup>73</sup> Registry studies would not replace the need for high-quality comparative studies. Pragmatic trials and comparative observational studies that are designed to reduce bias may facilitate evaluation of effectiveness and safety in the “real world” and over the long term in particular. Such studies could provide a foundation for registry development. Methodologically rigorous prospective cohort studies comparing treatments based on standardized protocols can potentially provide high-quality data. Such studies might be complemented with data from registries.

There may be some value in performing meta-analysis on individual patient data from relevant clinical trials to more effectively stratify outcomes by patient characteristics, comorbidities, and factors such as use of catheter ablation as an initial first-line treatment versus a second-line treatment. The small sample sizes of individual trials may, however, limit such exploration.

In order to evaluate the extent to which there is differential efficacy or harm for specific subpopulations, clinical trials need to have sufficient statistical power to stratify by important groups and to test for statistical interaction. Future studies, regardless of design, would benefit from the use of standardized definitions and methods of measuring salient outcomes (e.g., freedom from recurrence) and detailed reporting of cointerventions that may influence outcomes (e.g., use of antiarrhythmic medications in ablation groups and use of anticoagulation).

The technologies and strategies related to catheter ablation (and mapping) continues to evolve. Information on newer technologies including phased radiofrequency ablation (phased RFA), laser balloon ablation, contact force-guided radiofrequency (CF-guided RFA), and mesh ablation is emerging in the peer-reviewed literature. Present literature indicates they may be

effective alternatives to currently available technologies, however additional evidence is needed to verify early findings.<sup>74-79</sup>

Future systematic reviews will need to include technologies as they are approved and become widely available as well as updated studies of newer technologies such as cryoballoon ablation that are already approved but have a limited evidence base. Given the rapid evolution of catheter ablation, it will be important to update reviews such as this in the near future.

## Conclusions

Evidence was insufficient to draw conclusions on the efficacy, effectiveness, and harms of catheter ablation for AF specific to the Medicare population. In the general population, conclusions regarding the long-term efficacy of catheter ablation to impact primary clinical outcomes were limited; in those with paroxysmal AF, strength of evidence is low that there is no difference between RFA and medical therapy in all-cause-mortality. Low strength of evidence means that there is limited confidence that the effect estimate is close to the true effect. Evidence from RCTs was insufficient for no differences in stroke, MI and CHF after 12 months. Although observational studies may suggest lower stroke and heart failure risk following RFA versus medical therapy, the evidence was insufficient. In the short term, strength of evidence was low that there were no differences between treatments for all-cause mortality and MI and insufficient for stroke and CHF, regardless of AF type. No overall conclusions could be drawn regarding the impact of RFA on HRQOL across studies. In patients with heart failure and persistent AF, low strength of evidence suggested quality of life may be improved following RFA up to 6 months. No long-term RCT data in those with persistent AF for the primary outcomes of mortality, stroke, MI, or development of CHF were identified. For intermediate outcomes, moderate strength of evidence indicated that RFA is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in the short term in those with paroxysmal AF and appears to be sustained for the longer term. Strength of evidence was low for freedom from recurrence in those with persistent AF in the short term and insufficient in the longer term. Regarding harms, there was low strength of evidence for no difference between RFA and medical therapy in 30-day mortality or 30-day stroke. There was low strength of evidence that there was no difference between RFA and medical therapy in 3-month risk of AF in paroxysmal AF patients, but data from two trials of persistent AF patients suggested significantly lower risk of 2- to 3-month AF recurrence following RFA versus medical therapy (low strength of evidence). Risk estimates for cardiac tamponade following RFA were imprecise; the strength of evidence was low regardless of AF type. There is insufficient evidence comparing cryoballoon ablation with medical therapy for outcomes other than freedom from protocol defined treatment failure which favored cryoballoon ablation. There was insufficient evidence comparing cryoballoon ablation versus RFA to draw conclusions regarding efficacy or safety.

In summary, there was insufficient evidence to draw conclusions regarding the efficacy, effectiveness and safety of catheter ablation in the Medicare population. In the general population, there was moderate evidence that RFA is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in both the short- and long- term regardless of AF type, but reablation is common. RFA does not appear to impact all-cause mortality in the short or long term in those with paroxysmal AF (low strength of evidence), however there was insufficient evidence to draw conclusions regarding other primary clinical outcomes in the short or long term. Firm conclusions regarding HRQOL are not possible given heterogeneity across studies for instruments employed, measurement timing, and clinical characteristics. For harms,

no differences between RFA and medical therapy in 30-day mortality, stroke, or 3-month risk of AF were seen (low strength of evidence). Evidence comparing cryoballoon ablation with medical therapy or with RFA was insufficient to draw conclusions regarding efficacy or safety, with the exception of low strength of evidence for greater freedom from protocol-defined failure following cryoballoon ablation versus medical therapy. To better understand the impact of catheter ablation on key outcomes (stroke, mortality, quality of life, and symptom improvement) compared to other treatment strategies, large methodologically sound studies are needed, particularly on persistent AF patients. Studies with sufficient sample sizes are needed to effectively determine whether catheter ablation versus other treatments will benefit certain patient subgroups more than others, and whether there are subgroups in which catheter ablation might best used as a first- versus second-line treatment.

## References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001 May 9;285(18):2370-5. PMID: 11343485.
2. Magnani JW, Rienstra M, Lin H, et al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. *Circulation*. 2011 Nov 1;124(18):1982-93. PMID: 22042927.
3. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *The Medical clinics of North America*. 2008 Jan;92(1):17-40, ix. PMID: 18060995.
4. Sause A, Tutdibi O, Pomsel K, et al. Limiting esophageal temperature in radiofrequency ablation of left atrial tachyarrhythmias results in low incidence of thermal esophageal lesions. *BMC cardiovascular disorders*. 2010;10:52. PMID: 20977747.
5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014 Dec 2;64(21):2246-80. PMID: 24685668.
6. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *American Journal of Cardiology*. 1994 Aug 1;74(3):236-41. PMID: 8037127.
7. Schotten U, Verheule S, Kirchhof P, et al. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiological reviews*. 2011 Jan;91(1):265-325. PMID: 21248168.
8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991 Aug;22(8):983-8. PMID: 1866765.
9. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. *The Framingham Study*. *Stroke*. 1996 Oct;27(10):1760-4. PMID: 8841325.
10. Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *American Journal of Medicine*. 1995 May;98(5):476-84. PMID: 7733127.
11. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003 Jul 5;362(9377):7-13. PMID: 12853193.

12. Maggioni AP, Latini R, Carson PE, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). *American Heart Journal*. 2005 Mar;149(3):548-57. PMID: 15864246.
13. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003 Jun 17;107(23):2920-5. PMID: 12771006.
14. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *Journal of the American College of Cardiology*. 2006 Aug 15;48(4):721-30. PMID: 16904540.
15. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *Journal of the American College of Cardiology*. 2000 Oct;36(4):1303-9. PMID: 11028487.
16. Chung MK, Shemanski L, Sherman DG, et al. Functional status in rate- versus rhythm-control strategies for atrial fibrillation: results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Functional Status Substudy. *Journal of the American College of Cardiology*. 2005 Nov 15;46(10):1891-9. PMID: 16286177.
17. Hagens VE, Ranchor AV, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *Journal of the American College of Cardiology*. 2004 Jan 21;43(2):241-7. PMID: 14736444.
18. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011 Mar 15;123(10):e269-367. PMID: 21382897.
19. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS 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: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm*. 2012 Apr;9(4):632-96 e21. PMID: 22386883.
20. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace*. 2006 Sep;8(9):651-745. PMID: 16987906.

21. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011 Jan 4;123(1):104-23. PMID: 21173346.
22. Ip S, Terasawa T, Balk EM, et al. Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation. AHRQ Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009.
23. Al-Khatib SM, Allen Lapointe N, Chatterjee R, et al. Treatment of Atrial Fibrillation. AHRQ Comparative Effectiveness Reviews, No. 119. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
24. Chen HS, Wen JM, Wu SN, et al. Catheter ablation for paroxysmal and persistent atrial fibrillation. *Cochrane Database Syst Rev*. 2012;4:CD007101. PMID: 22513945.
25. Hashimoto RE, Raich AL, Junge M, et al. Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation. Olympia, WA: Washington State Health Care Authority, Health Technology Assessment Program. [www.hta.hca.wa.gov/svta.html](http://www.hta.hca.wa.gov/svta.html).: 2103.
26. Ellis ER, Culler SD, Simon AW, et al. Trends in utilization and complications of catheter ablation for atrial fibrillation in Medicare beneficiaries. *Heart Rhythm*. 2009 Sep;6(9):1267-73. PMID: 19716081.
27. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010 Feb;3(1):32-8. PMID: 19995881.
28. Agency for Healthcare Research and Quality. Methods guide for Effectiveness and Comparative Effectiveness Reviews. . AHRQ Publication No. 10(14)-EHC063-EF. Rockville MD: Agency for Healthcare Research and Quality; January 2014. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov). Accessed July 30, 2014.
29. Higgins JPT GS, ed *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. ed; 2011.
30. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. *J Clin Epidemiol*. 2010 May;63(5):513-23. PMID: 19595577.
31. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. *Statistics in medicine*. 1996 Mar 30;15(6):619-29. PMID: 8731004.
32. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed.)*. 2003 Sep 6;327(7414):557-60. PMID: 12958120.
33. Fu R, Vandermeer BW, Shamliyan TA, et al. AHRQ Methods for Effective Health Care Handling Continuous Outcomes in Quantitative Synthesis. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
34. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. PMID: 21463926.
35. Forleo GB, Mantica M, De Luca L, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *Journal of Cardiovascular Electrophysiology*. 2009 Jan;20(1):22-8. PMID: 18775050.

36. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study.[Erratum appears in *Circulation*. 2009 Sep 8;120(10):e83]. *Circulation*. 2008 Dec 9;118(24):2498-505. PMID: 19029470.
37. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *Journal of the American College of Cardiology*. 2013;61(18):1894-903. PMID: CN-00907192 NEW.
38. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart*. 2011 May;97(9):740-7. PMID: 21051458.
39. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *European heart journal*. 2013 Oct 17PMID: 24135832.
40. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006 Mar 2;354(9):934-41. PMID: 16510747.
41. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *Journal of the American College of Cardiology*. 2006 Dec 5;48(11):2340-7. PMID: 17161267.
42. Stabile G, Bertaglia E, Senatore G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *European heart journal*. 2006 Jan;27(2):216-21. PMID: 16214831.
43. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA*. 2005 Jun 1;293(21):2634-40. PMID: 15928285.
44. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010 Jan 27;303(4):333-40. PMID: 20103757.
45. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012 Oct 25;367(17):1587-95. PMID: 23094720.
46. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA*. 2014 Feb 19;311(7):692-700. PMID: 24549549.
47. Pappone C, Vicedomini G, Augello G, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. *Circ*. 2011 Dec;4(6):808-14. PMID: 21946315.
48. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol*. 2014 Feb;7(1):31-8. PMID: 24382410.
49. Reynolds MR, Walczak J, White SA, et al. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes*. 2010 Nov;3(6):615-23. PMID: 20940250.
50. Lan X, Su L, Ling Z, et al. Catheter ablation vs. amiodarone plus losartan for prevention of atrial fibrillation recurrence in patients with paroxysmal atrial fibrillation. *Eur J Clin Invest*. 2009 Aug;39(8):657-63. PMID: 19490069.



51. Sang C-H, Chen K, Pang X-F, et al. Depression, anxiety, and quality of life after catheter ablation in patients with paroxysmal atrial fibrillation. *Clin Cardiol*. 2013 Jan;36(1):40-5. PMID: 22777577.
52. Yu S, Zhao Q, Wu P, et al. Effect of anxiety and depression on the recurrence of paroxysmal atrial fibrillation after circumferential pulmonary vein ablation. *Journal of Cardiovascular Electrophysiology*. 2012 Nov;23 Suppl 1:S17-23. PMID: 22998234.
53. Rossillo A, Bonso A, Themistoclakis S, et al. Role of anticoagulation therapy after pulmonary vein antrum isolation for atrial fibrillation treatment. *J Cardiovasc Med (Hagerstown)*. 2008 Jan;9(1):51-5. PMID: 18268419.
54. Sonne K, Patel D, Mohanty P, et al. Pulmonary vein antrum isolation, atrioventricular junction ablation, and antiarrhythmic drugs combined with direct current cardioversion: survival rates at 7 years follow-up. *J Interv Card Electrophysiol*. 2009 Nov;26(2):121-6. PMID: 19789970.
55. Blandino A, Toso E, Scaglione M, et al. Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation. *Journal of Cardiovascular Electrophysiology*. 2013 Jul;24(7):731-8. PMID: 23551460.
56. Reynolds MR, Gunnarsson CL, Hunter TD, et al. Health outcomes with catheter ablation or antiarrhythmic drug therapy in atrial fibrillation: results of a propensity-matched analysis. *Circ Cardiovasc Qual Outcomes*. 2012 Mar 1;5(2):171-81. PMID: 22373904.
57. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *Journal of the American College of Cardiology*. 2013 Apr 23;61(16):1713-23. PMID: 23500312.
58. Perez-Castellano N, Fernandez-Cavazos R, Moreno J, et al. The COR trial: a randomized study with continuous rhythm monitoring to compare the efficacy of cryoenergy and radiofrequency for pulmonary vein isolation. *Heart Rhythm*. 2014 Jan;11(1):8-14. PMID: 24103221.
59. Herrera Siklody C, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. *Journal of the American College of Cardiology*. 2011 Aug 9;58(7):681-8. PMID: 21664090.
60. Chierchia GB, Capulzini L, Droogmans S, et al. Pericardial effusion in atrial fibrillation ablation: a comparison between cryoballoon and radiofrequency pulmonary vein isolation. *Europace*. 2010 Mar;12(3):337-41. PMID: 20056597.
61. Knecht S, Sticherling C, von Felten S, et al. Long-term comparison of cryoballoon and radiofrequency ablation of paroxysmal atrial fibrillation: a propensity score matched analysis. *Int J Cardiol*. 2014 Oct 20;176(3):645-50. PMID: 25149399.
62. Kojodjojo P, O'Neill MD, Lim PB, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. *Heart*. 2010 Sep;96(17):1379-84. PMID: 20801856.
63. Mandell J, Amico F, Parekh S, et al. Early experience with the cryoablation balloon procedure for the treatment of atrial fibrillation by an experienced radiofrequency catheter ablation center. *J Invasive Cardiol*. 2013 Jun;25(6):288-92. PMID: 23735354.
64. Mugnai G, Chierchia GB, de Asmundis C, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *The American journal of cardiology*. 2014 May 1;113(9):1509-13. PMID: 24630388.

65. Schmidt M, Dorwarth U, Andresen D, et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol*. 2014 Jan;25(1):1-7. PMID: 24134539.
66. Bertaglia E, Fassini G, Anselmino M, et al. Comparison of ThermoCool Surround Flow catheter versus ThermoCool catheter in achieving persistent electrical isolation of pulmonary veins: a pilot study. *Journal of Cardiovascular Electrophysiology*. 2013 Mar;24(3):269-73. PMID: 23210452.
67. Verma A, Macle L, Cox J, et al. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: catheter ablation for atrial fibrillation/atrial flutter. *Can J Cardiol*. 2011 Jan-Feb;27(1):60-6. PMID: 21329863.
68. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. *European heart journal*. 2010;31.
69. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical research ed.)*. 2011;343:d4002. PMID: 21784880.
70. Bunch TJ, May HT, Bair TL, et al. Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. *Heart Rhythm*. 2013 Sep;10(9):1272-7. PMID: 23835257.
71. Chang CH, Lin JW, Chiu FC, et al. Effect of radiofrequency catheter ablation for atrial fibrillation on morbidity and mortality: a nationwide cohort study and propensity score analysis. *Circ*. 2014 Feb;7(1):76-82.
72. Hashimoto RE, Brodt ED, Skelly AC, et al. Administrative database studies: goldmine or goose chase? *Evidence-based spine-care journal*. 2014 Oct;5(2):74-6. PMID: 25278880.
73. AHRQ Methods for Effective Health Care. In: Gliklich RE, Dreyer NA, Leavy MB, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
74. Malmborg H, Lonnerholm S, Blomstrom P, et al. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. *Europace*. 2013 Nov;15(11):1567-73. PMID: 23703361.
75. Malmborg H, Christersson C, Lonnerholm S, et al. Comparison of effects on coagulation and inflammatory markers using a duty-cycled bipolar and unipolar radiofrequency pulmonary vein ablation catheter vs. a cryoballoon catheter for pulmonary vein isolation. *Europace*. 2013 Jun;15(6):798-804. PMID: 23362019.
76. Hummel J, Michaud G, Hoyt R, et al. Phased RF ablation in persistent atrial fibrillation. *Heart Rhythm*. 2014 Feb;11(2):202-9. PMID: 24239841.
77. Bordignon S, Chun KR, Gunawardene M, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. *Journal of Cardiovascular Electrophysiology*. 2013 Sep;24(9):987-94.
78. Jourda F, Providencia R, Marijon E, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. *Europace*. 2014 Sep 3 PMID: 25186456.
79. Koch L, Haeusler KG, Herm J, et al. Mesh ablator vs. cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation: results of the MACPAF study. *Europace*. 2012 Oct;14(10):1441-9. PMID: 22523379.

# Introduction

## Background

### Nature and Burden of Atrial Fibrillation

Atrial fibrillation (AF) is a major public health concern in the United States, affecting an estimated 2.3 million Americans.<sup>1</sup> The prevalence of AF is projected to reach 5.6 to 12.1 million by the year 2050.<sup>2</sup> AF is the most common sustained arrhythmia seen in clinical practice and accounts for approximately one third of hospitalizations for cardiac dysrhythmias.<sup>3</sup>

AF is characterized by uncoordinated atrial activation with resulting deterioration of atrial mechanical function.<sup>4</sup> While AF can occur in isolation, it may also be associated with other arrhythmias such as atrial flutter or atrial tachycardia. Atrial fibrillation can be paroxysmal, persistent, or permanent. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society AF guidelines<sup>4</sup> define paroxysmal AF as recurrent AF that terminates spontaneously or with intervention within 7 days of onset, persistent AF as one that is sustained beyond 7 days, and permanent AF as long-standing AF in which restoring and/or maintaining sinus rhythm has failed or has been foregone. Long-standing persistent AF is usually defined as AF that persists for over a year. Long-standing persistent and permanent AF are more commonly seen in older patients with structural heart disease.

A number of factors have been associated with increased risk of AF. The prevalence of AF increases with age; it affects 8 to 10 percent of patients 80 years of age and over.<sup>2, 5, 6</sup> AF is also more common in males: data from the Framingham Heart Study suggest that men are 1.5 times as likely to develop AF than are women after controlling for age and comorbidities.<sup>2</sup> Obesity increases the risk of developing AF. Data from community-based cohorts suggest that obese patients have a 1.5- to 2.3-fold greater risk of developing AF. Furthermore, obesity increases the likelihood that AF will progress from paroxysmal to permanent AF.<sup>6</sup> Additional factors that have been associated with an increased risk of AF include smoking, hypertension, hyperthyroidism, obstructive sleep apnea, diabetes, myocardial infarction, heart failure, and cardiac surgery.<sup>6</sup>

AF is associated with significant mortality, morbidity, and health care costs. Patients with AF have a twofold greater risk of death than do those without this disease. AF is associated with an increased risk of stroke, which affects 5 percent of nonrheumatic AF patients and nearly 7 percent of AF patients with heart failure each year.<sup>7</sup> Furthermore, ischemic stroke that occurs in the setting of AF tends to be either fatal or of moderate to high severity in most patients.<sup>8</sup> AF can also cause a number of cardiac conditions, including myocardial ischemia or infarction, exacerbation of heart failure, and cardiomyopathy if the ventricular rate is insufficiently controlled.<sup>9-12</sup> Although some patients with AF are asymptomatic, other patients experience symptoms like shortness of breath, intractable fatigue, and near-syncope, which can severely affect overall quality of life.<sup>13-16</sup> In total, the management of AF and its complications costs the U.S. health care system approximately \$26 billion each year.<sup>4, 17</sup>

### Management of Atrial Fibrillation

Treatment of AF involves rate control, rhythm control, prevention of thromboembolic events, and treating the underlying disease (e.g., hypertension) if applicable.<sup>4</sup> Typically, pharmacologic therapy is the primary treatment for rate and rhythm control, while pulmonary vein isolation with catheter ablation is reserved for second-line treatment but may be appropriate as a first-line

treatment in select populations when a rhythm control strategy is desired.<sup>4</sup> Discussion of strategies to prevent thromboembolic events or to treat underlying causes of AF are beyond the scope of this report.

While the initial management of AF often includes control of ventricular rate using pharmacological agents (i.e., beta-blockers or nonhydropyridine calcium channel blockers), it is common for the long-term management strategy to focus on restoring and maintaining normal heart rhythm.<sup>4</sup> AF patients who continue to have significant symptoms despite adequate rate control or who desire long-term rhythm control may be considered for treatment using a rhythm control strategy.

## **Pharmacological Rhythm Control**

The primary reason for rhythm control in patients with AF is to improve symptoms. In some patients, adequate rate control is enough to control symptoms, but if patients continue to have symptoms despite good rate control, then rhythm control should be considered. In the absence of symptoms, rhythm control can be used in patients with rapid ventricular response to AF when rate controlling medications are ineffective or cannot be tolerated. Rhythm control should not be used to allow patients to come off anticoagulation as the decision regarding anticoagulation should be based on their risks of thromboembolic events and bleeding.<sup>4</sup> Pharmacologic therapy is typically the first choice. Selection of the first-line antiarrhythmic medication is largely driven by the presence or absence of structural heart disease. For example, the 2014 Guidelines for the Management of Patients with Atrial Fibrillation give a Class I recommendation for treatment with flecainide, dofetilide, propafenone, dronedarone, sotalol and amiodarone; but for amiodarone, the guidelines emphasize that because of its potential toxicities, it should only be used after consideration of risks and when other agents have failed or are contraindicated. In patients with heart failure, the guidelines recommend one of two antiarrhythmic medications as first-line therapy (dofetilide and amiodarone).<sup>4</sup> Side effects can occur with the use of antiarrhythmic medications; some may actually cause more arrhythmias, and some may lose effectiveness over time. Patients on these medications therefore need to be monitored to assess the impact of medications on heart rhythm and the potential for side effects and interactions with any concomitant medications such as anticoagulants.

## **Catheter Ablation Rhythm Control**

Catheter ablation for the treatment of AF is increasingly being performed on symptomatic patients as an alternative to medical management, or when medical management has been ineffective or not tolerated.<sup>18-20</sup> AF ablation is typically recommended only for symptomatic patients; asymptomatic patients are usually managed with anticoagulation and/or rate control as needed.<sup>4</sup> The outcomes of this procedure may depend on patient characteristics such as age, AF type, and presence of structural heart disease, as well as on experience of the operator and methods and technologies used during the procedure. Relief of symptoms is a primary reason for considering catheter ablation as a treatment strategy.

In catheter ablation, energy is sent through an electrode at the tip of a catheter into specific areas of the heart to destroy (ablate) or electrically isolate small areas of tissue where abnormal electrical signals that trigger abnormal heart beats originate. The goal of catheter ablation for treatment of AF is to ablate or isolate triggers that mostly originate in the area of the pulmonary veins. Thus, the most commonly used and recommended catheter ablation procedure to treat AF is pulmonary vein isolation (PVI).<sup>18, 21</sup> For the procedure to be successful, complete bi-

directional electrical isolation of all pulmonary veins should be achieved. While other approaches may also be used, typically in addition to PVI, there is uncertainty regarding additional benefits or harms of such approaches.<sup>18</sup> Recent systematic reviews attempted to evaluate the efficacy of approaches relative to each other,<sup>22-24</sup> but significant heterogeneity with regard to the approaches compared precluded meaningful conclusions.<sup>22</sup>

Among methods and technologies used during the procedure, energy source is an important factor. Currently, there are two US Food and Drug Administration (FDA)-approved options for catheter ablation: radiofrequency energy, which heats the target sites, and cryoablation, which cools/freezes the sites. Cryoablation may be performed using either a focal catheter-tip (as in radiofrequency ablation) or a balloon catheter. Balloon catheters can ablate larger areas of abnormal tissue than single tip catheters which involve point-by-point application of energy. How cryoablation including use of a balloon catheter for ablation compares with traditional radiofrequency ablation in relation to efficacy and safety is also uncertain and is the subject of ongoing debate.

Imaging may be performed before or during the procedure, including magnetic resonance imaging, computed tomography imaging, and transthoracic, trans-esophageal, and intra-cardiac echocardiography. Electroanatomic mapping, which allows for a real-time three-dimensional view of the heart, is often used during the procedure to look for triggers of AF, confirm successful ablation, and allow characterization of its impact on overall left atrial (LA) function. Mapping techniques vary greatly and continue to evolve. Two examples of mapping systems available for use in clinical practice are CARTO (Biosense Webster Inc., CA, USA) and EnSite NavX (St. Jude Medical Inc., MN, USA). The comparative benefits or harms of these techniques are unclear as to date they have not been evaluated in a randomized controlled trial (RCT). Evaluation of imaging and mapping approach is beyond the scope of this report.

Three catheter ablation devices have been approved by the FDA for use in AF patients (see Appendix H; Table H5), with the first approved in 2009. One device employs radiofrequency energy and utilizes an irrigated catheter tip of 3.5 mm (Biosense Webster), while the other two are cryoablation catheters that use a balloon with a diameter of 23 to 28 mm (Medtronic Cryocath). A number of other radiofrequency ablation (RFA) and cryoablation catheter devices have been approved for the treatment of other types of arrhythmia and may be used “off-label” for the treatment of AF.

## Scope and Key Questions

In 2009, AHRQ published a comparative effectiveness review that evaluated both clinical effectiveness and harms of RFA for AF.<sup>21</sup> At that time, only six RCTs enrolling a total of 693 patients were available. There was moderate-strength evidence that patients treated with RFA after failing medical therapy had a threefold greater likelihood of maintaining freedom from AF recurrence at 12 months compared with patients who received medical therapy alone. There was low strength evidence that RFA resulted in greater quality of life and less need for anticoagulation but no difference in the risk of stroke and the rate of readmission. High strength evidence indicated that age wasn't significantly associated with AF recurrence after ablation; however, most patients studied were in their fifties (age range, 40 to 70 years) and the evidence was insufficient to estimate whether older age affected outcomes. At the time of the 2009 report, evidence was lacking for a number of issues, including health outcomes beyond 1 year, whether ablation reduces the risk of death and stroke, and the comparative effectiveness and harms of catheter ablation in the Medicare population ( $\geq 65$  years of age; or  $< 65$  years of age and

permanently disabled). The 2009 report did not compare cryoablation with medical therapy or compare catheter ablation energy sources with one another.

Based on Medicare Provider Analysis and Review (MedPAR) files, use of catheter ablation for the treatment of AF in the Medicare population increased substantially between 2001 and 2006 from an annual total procedural volume of 135 to 1975 cases and an increase in the number of hospitals performing RFA from 100 to 162.<sup>25</sup> Annual complication rates increased from 6.7 to 10.1 percent during the same time period, but increasing age was not associated with a higher rate of complications. Procedural volume was associated with probability of in-hospital death but not with overall risk of complications. An almost two-fold increase in the number of patients treated with catheter ablation was reported between 2003 and 2006 compared with the number treated between 1995 and 2002 based on a world-wide survey of electrophysiology centers.<sup>26</sup> The authors also report that catheter ablation was increasingly being offered to sicker AF patients. Catheter ablation was reported to be effective in approximately 80 percent of patients. A risk of 4.5 percent for major complications was also reported. Anecdotally, utilization has continued to increase in the Medicare and general populations.

Since the publication of the 2009 AHRQ report, the Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial was initiated to directly compare various methods of catheter ablation with medical therapy in a large, multi-center, multi-national trial that includes older patients (over 60 years old) with paroxysmal and persistent AF (ClinicalTrials.gov identifier NCT00911508); however, final data collection for the primary outcome measure will not be completed until September 2017.

Because there is increasing use of catheter ablation to treat AF patients in the Medicare population as well as uncertainty regarding the efficacy and harms of this procedure in this population in particular, and given that results from CABANA will not be available until 2018 at the earliest, the Centers for Medicare and Medicaid (CMS) has partnered with AHRQ to commission this systematic review to evaluate the current state of comparative evidence, with the aims of informing clinical practice and policy and to providing insight into research needs and general approaches for addressing identified evidence gaps.

## Key Questions

The objectives of this review include evaluating the comparative efficacy, effectiveness, and safety of catheter ablation and medical therapy for the treatment of AF. For the purposes of this report, efficacy refers to the ability of a treatment to produce a desired effect under optimum controlled conditions, such as during a randomized controlled trial. Effectiveness refers to the effect of treatment in actual clinical practice as evaluated by observational studies or comparative pragmatic trials. Comparative effectiveness review is a general term and in this report refers to the conduct and synthesis of systematic research to compare the interventions of interest, incorporating information on efficacy from RCTs and on effectiveness from comparative observational studies. Comparative effectiveness also includes evaluation of adverse events and harms. The Key Questions to be explored are as follows:

Key Question 1. What is the comparative efficacy and effectiveness of AF catheter ablation on short-term (6–12 months) and long-term (>12 months) outcomes in the general adult and Medicare populations? Comparisons of interest include:

- a) Catheter ablation compared with medical therapy

- b) Comparing ablation using different energy sources

Key Question 2. What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation in the general adult and Medicare populations? Comparisons of interest include:

- a) Catheter ablation compared with medical therapy
- b) Comparing ablation using different energy sources

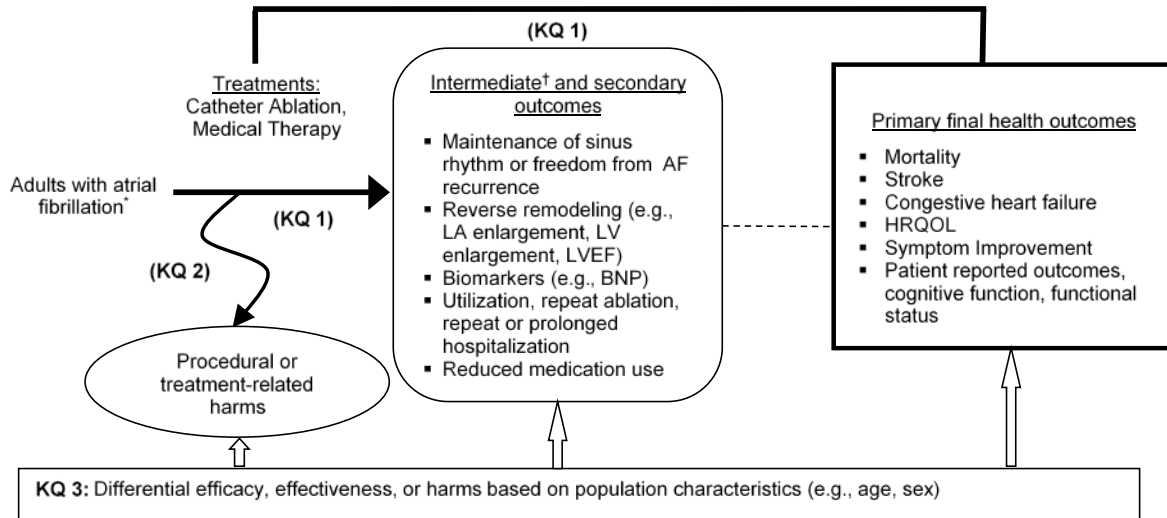
Key Question 3. Are there modifications of efficacy, effectiveness, or harms of catheter ablation by patient-level characteristics such as age, sex, type of AF, comorbidities, risk for stroke or bleeding events, condition (i.e., patients with significant left ventricular dysfunction/heart failure or patients with significant left atrial enlargement or left ventricular hypertrophy), provider/setting characteristics or technique/approach? Comparisons of interest include:

- a) Catheter ablation compared with medical therapy
- b) Comparing ablation using different energy sources

## **Analytic Framework**

The analytical framework for the systematic review is presented in Figure 1. This figure depicts the Key Questions addressed in this review. In general, the figure illustrates how the treatments relate to the outcomes and how the outcomes relate to each other. For example, a patient (far left of diagram) presents with AF and may receive medical therapy or catheter ablation (radiofrequency or cryoablation). The treatment can lead to long-term health outcomes (far right of the diagram), intermediate outcomes and harms. The solid lines marked with Key Question numbers represent the questions that this review will evaluate in a comparative way (intervention vs. intervention). The dotted line represents the evidence of a relationship between intermediate and health outcomes (which is beyond the scope of this review). The bottom box represents Key Question 3, which examines evidence on variation in outcome based on specific patient characteristics.

**Figure 1. Analytic framework for catheter ablation for atrial fibrillation**



\* Patients with longstanding persistent atrial fibrillation, persistent atrial fibrillation, or paroxysmal atrial fibrillation (considered

†Intermediate outcomes are those which may be along the causal pathway to final health outcomes.

BNP = brain natriuretic peptides; HRQOL = health-related quality of life; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction.



## Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>). The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA checklist.<sup>27</sup> All methods and analyses were determined *a priori*.

### Topic Refinement and Systematic Review Protocol

This topic was nominated by Centers for Medicare and Medicaid (CMS) as an update to a previous report published in 2009,<sup>21</sup> particularly to examine longer-term efficacy of catheter ablation and application to the Medicare population in order to inform CMS policy. The AHRQ Task Order Officer functioned as a liaison between the Evidence-based Practice Center (EPC) and CMS and helped resolve any ambiguities regarding the processes or scope of the project. The EPC drafted the initial Key Questions, Analytic Framework, and inclusion/exclusion criteria and refined them with input from a panel of Key Informants, all of whom were required to disclose any financial or other conflicts of interest prior to participation. The Key Informant panel included experts in cardiology primarily (with specialties in electrophysiology, heart failure, and cardiovascular aging/cardiovascular disease in older adults) and internal medicine; representatives from relevant specialty societies; government representatives (i.e., Department of Veterans' Affairs, National Heart, Lung and Blood Institute); and a patient advocate. After review from AHRQ, the draft questions and framework were posted for public review in December 2013 for 3 weeks. Following review of the public commentary, the EPC drafted a final topic refinement document which was approved by AHRQ and posted to their Web site. In place of a Technical Expert Panel, CMS provided input to the Key Questions and scope of the report. The final topic refinement document served as the basis for the review protocol with minor changes. Both the final topic refinement document and the systematic review protocol can be found on the AHRQ Web site at <http://www.ahrq.gov/research/findings/ta/>. The protocol was also registered with the PROSPERO international database of prospectively registered systematic reviews.

### Literature Search Strategy

A research librarian conducted searches for primary studies in the following databases: Ovid MEDLINE<sup>®</sup> (from 2005 to November 2014), Cochrane Central (J November 2014), and Cochrane Database of Systematic Reviews (from 2005 to November 2014). Searches were limited to a beginning date of January 2005 as there are multiple recent systematic evidence reviews, including good-quality reviews from AHRQ (2013, 2009)<sup>21, 22</sup> and the Washington State Health Technology Assessment Program (2013),<sup>24</sup> that have addressed aspects of the Key Questions for this current review, with searches conducted through late 2013. Key Informant input during topic refinement confirmed that this was a logical approach. The search strategy was developed based on an analysis of the medical subject headings (MeSH), terms, and text words of key articles identified *a priori* (the full search strategy is available in Appendix A). Reference lists of included articles and relevant review articles were inspected for relevant publications. All citations were downloaded and imported into an electronic database (EndNote<sup>®</sup> X7 Thomson Reuters, Philadelphia, PA).

All citations were reviewed independently by two individuals at both the title/abstract and full-text level and differences were resolved by consensus.

## **Inclusion and Exclusion Criteria**

Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach as described in Table 1. Briefly, studies of adult patients with paroxysmal, persistent, or permanent/long-standing atrial fibrillation (AF) treated with catheter ablation were sought. For all Key Questions, the focus was on evidence from comparative studies with the least potential for bias. Comparative observational studies were required to have a minimum of 100 patients to be included. Registry and administrative data studies were considered if inclusion criteria were met. Comparators of interest included medical therapy only (i.e., pharmacological agents for rate or rhythm control) and comparisons of different energy sources for catheter ablation (e.g., radiofrequency vs. cryoablation). Comparisons of different techniques and/or approaches and mapping were beyond the scope of this report and thus were excluded. For Key Question 2, case series that were specifically designed to evaluate harms and/or adverse events following ablation, had a minimum of 1000 patients and at least 80 percent followup were included because all included comparative studies were relatively small in size. Including these large case series of ablation patients allowed for the calculation of risk estimates of adverse events based on a larger number of patients.

For all Key Questions, both long-term (>12 months) and short-term ( $\leq$ 12 months) outcomes were identified in included studies. The primary outcomes listed in the PICOTS table (Table 1) were considered to be the most clinically important and were the focus of reporting, decisions for data pooling and determination of overall strength of evidence. Additional outcomes are reported in the detailed evidence synthesis sections of the Key Questions with a focus on outcomes common across studies. Where applicable and where data were available, results from short-term ( $\leq$ 12 months) and long-term (>12 months) followup were described.

Studies published only as conference abstracts, non-English-language articles, and studies of nonhuman subjects were excluded. Studies had to report original data to be included.

**Table 1. Summary of inclusion and exclusion criteria**

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	<p>For all KQs:</p> <ul style="list-style-type: none"> <li>• Adult patients (age ≥18 years) with AF (long-standing, persistent, or paroxysmal)</li> <li>• Medicare population ( ≥65 years of age; or &lt;65 years of age and permanently disabled)</li> </ul>	<ul style="list-style-type: none"> <li>• Patients &lt;18 years of age with isolated atrial flutter, isolated atrial tachycardia, AV nodal reentrant tachycardia or AV reentrant tachycardia, focal junctional ectopic tachycardia and nonparoxysmal junctional tachycardia, ventricular tachycardia and paroxysmal ventricular tachycardia, bradycardia</li> <li>• Patients in whom treatment of AF is not the primary goal, with prior catheter ablation, or who have known reversible causes of AF (including but not limited to postoperative, postmyocardial infarction, hyperthyroidism)</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>• For all KQs: Catheter ablation using devices available for use in the U.S., including ablation methods using different energy sources. Any FDA-approved devices (or devices in final stages of approval) that were used for catheter ablation in patients with AF were included whether or not they have been specifically approved for treatment of AF.</li> </ul>	<ul style="list-style-type: none"> <li>• Use of non-FDA approved devices or devices not in final stages for FDA approval (except as noted above),</li> <li>• Ablation as an adjunct to surgery or intraoperative ablation, surgical ablation, right atrial ablation for atrial flutter, ablation in which PV electrical isolation is not the goal, or complete AV node ablation requiring pacemaker implantation</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>• For all KQs:</li> <li>• Medical therapy only, including pharmacological agents for rate control (beta-blockers, nondihydropyridine calcium channel blockers), or pharmacological agents for rhythm control (amiodarone, disopyramide, dofetilide, dronedarone, flecainide, propafenone, sotalol)</li> <li>• Comparison of different energy sources for catheter ablation (e.g., radiofrequency vs. cryoablation)</li> </ul>	<ul style="list-style-type: none"> <li>• Uncontrolled or pre-post studies</li> <li>• Comparisons of different techniques used in catheter ablation (i.e., use of imaging, types of catheter tips, hybrid strategies); Comparisons of different approaches used in catheter ablation with each other (e.g., PVI vs. PVI plus additional catheter lines)</li> <li>• Diagnostic evaluations, and studies focused on mapping or those comparing mapping techniques</li> <li>• Cardioversion alone (i.e., in the absence of antiarrhythmic medical therapy)</li> <li>• Cox-Maze procedure; surgical ablation</li> <li>• Antiarrhythmic agents: quinidine, procainamide</li> </ul>

<b>PICOTS Element</b>	<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
Outcomes	<ul style="list-style-type: none"> <li>• For KQs 1, 3: Primary efficacy/effectiveness: prevention of mortality or other serious adverse events, improvement of symptoms, quality of life or functional status.</li> <li>• For KQs 1, 3: Intermediate outcomes: freedom from recurrence of AF, maintenance of sinus rhythm, repeat ablation for AF, parameters suggesting reverse remodeling, effect on biomarkers, health care utilization (hospitalization/ readmission for cardiovascular events), reduced medication use</li> <li>• For KQs 2, 3: Harms or adverse events (procedure or pharmacologic treatment related): in hospital and 30-day mortality, stroke, TIA, embolic events, myocardial infarction, other procedural complications, arrhythmias potentially secondary to catheter ablation (within 3 months of procedure), adverse events from drug therapies, hemorrhage, radiation exposure</li> </ul>	<ul style="list-style-type: none"> <li>• Nonclinical outcomes</li> </ul>
Timing	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>
Setting	<ul style="list-style-type: none"> <li>• For all KQs: No restrictions (inpatient and outpatient)</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>
Study design	<p>For KQs 1, 2:</p> <ul style="list-style-type: none"> <li>• RCTs or controlled cohort studies, focus was on evidence from comparative studies with the least potential for bias; Comparative observational studies required to have a minimum of 100 patients</li> </ul> <p>For KQ 2:</p> <ul style="list-style-type: none"> <li>• Case series or uncontrolled observational studies were considered in the evaluation of harms if they were specifically designed to evaluate adverse events, had a minimum of 1000 patients and a followup of at least 80%</li> </ul> <p>For KQ 3: RCTs</p>	<ul style="list-style-type: none"> <li>• Nonclinical studies of technique, studies reporting only on technical aspects of ablation, uncontrolled observational studies, nonsystematic reviews, narrative reviews, abstracts, editorials, letters, white papers, articles identified as preliminary reports when results are published in later versions, case series, case-reports</li> </ul>
Publication	<ul style="list-style-type: none"> <li>• Studies published in English in scholarly journals, published health technology assessments, or publicly available FDA reports</li> <li>• Gray literature (e.g., ongoing or unpublished clinical trial data)</li> </ul>	<ul style="list-style-type: none"> <li>• Studies with a publication date prior to 2005 (to exclude outdated technologies)</li> <li>• Single site reports from multicenter trials</li> <li>• Duplicate publications of the same study which do not report on unique outcomes or time points</li> </ul>

AF = atrial fibrillation; AV = atrioventricular; FDA = U.S. Food and Drug Administration; KQ = Key Question; PV = pulmonary vein; PVI = pulmonary vein isolation; RCT = randomized controlled trial; TIA = transient ischemic attack.

## Study Selection

Abstracts for all citations from the literature searches were independently reviewed by two team members and results were recorded in EndNote. All citations found to be potentially appropriate for inclusion by either reviewer underwent full-text review. Each full-text article was

independently evaluated for final inclusion by two investigators. For inclusion, both reviewers had to agree that inclusion criteria were met. Differences between reviewers were resolved through consensus and discussion. A record of studies excluded at the full-text level with reasons for exclusion is included in Appendix C.

## Data Extraction

After studies were selected for inclusion, a total of five experienced team members trained in using the Systematic Review Data Repository (SRDR) database (AHRQ, Rockville, MD; accessed at <http://srdr.ahrq.gov/>) entered data. After data extraction, at least one other staff member and one investigator each verified the accuracy and completeness of abstraction for each study included. Discrepancies were resolved by discussion and consensus. SRDR was used to maintain the data and to create detailed evidence tables and summary tables.

Reviewers extracted information on general study characteristics (e.g., study design, study period, followup, study setting, funding, and authors' conflicts of interest), study patients (patients approached/eligible/enrolled, age, sex, comorbidities, echocardiographic parameters), treatment arm details (patients treated, patients with followup, first-/second-line therapy, pharmacologic dose, ablation technique and procedural details, imaging performed), outcome measures, adverse events, and information related to study quality. Outcome measures and adverse events were prespecified during the creation of the extraction form to maintain consistency in data reporting. However, unique results were added during the abstraction process as needed. Special care was taken in the abstraction of information regarding crossover, the blanking period, reablation, and risk of bias. For harms attributable to ablation but not medical therapy (e.g., cardiac tamponade), data were reported on an as-treated basis in order to include data from patients who crossed over from medical therapy to ablation. Basic information regarding technique, approach, provider and setting was also abstracted when reported in included studies. Limited data were extracted from case series with a focus on safety outcomes of interest. An outline of the specific information included in the data extraction forms are available in Appendix D and detailed evidence tables are included in Appendix E. Tables are organized in order of comparison: radiofrequency ablation (RFA) versus medical therapy (Tables E1–E12), cryoballoon ablation versus medical therapy (Tables E13–E14), and studies comparing ablation with different energy types (Tables E15–E18). Within each comparison of interest, there are separate tables for randomized controlled trial (RCT) and observational data, which are further separated by the different atrial fibrillation (AF) patient populations: those with paroxysmal AF, those with persistent AF, and mixed populations.

## Quality Assessment of Individual Studies

Predefined criteria were used to assess the quality (risk of bias) of included RCTs and observational studies by using clearly defined templates and criteria as appropriate and following guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>28</sup> Assessment of RCTs followed appropriate criteria and methods established in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>29</sup> Comparative observational studies were assessed for study design features and sources of potential bias. Briefly, the quality of each comparative study was rated based on the following: methods used for randomization (RCTs only, requirement of computer-generated random numbers, random numbers tables, coin toss, or opaque sequentially numbered envelopes), allocation concealment (RCTs only, requirement of sealed opaque envelopes,

centralized randomization, on-site computer based system with a randomization sequence that is not readable until allocation, or blocked randomization), intention-to-treat analysis (RCTs), independent or blind outcome assessment, acceptable attrition ( $\leq 20\%$ ), comparable attrition between treatment groups ( $\leq 20\%$  difference between groups), controlling for possible confounding, full reporting on prespecified outcomes, and whether patients were blinded to treatment received. These criteria and methods were used in concordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions, in the AHRQ Methods Guide *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, wherein each study was rated as being “good”, “fair” or “poor” quality.<sup>30</sup> Two investigators independently assessed the quality of each study and any discrepancies were resolved through discussion and consensus.

Studies rated “good” are considered to have the least risk of bias, and their results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated “fair” are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are least as likely to reflect flaws in the study design as the true difference between the compared interventions. Studies rated as being poor in quality *a priori* were not excluded, but considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies were present.

Each study evaluated was dual-reviewed for quality by two team members. Any disagreements were resolved by consensus. The final risk of quality assessments are described in detail in Appendix F (Tables F1–F5).

## Data Synthesis

When adequate data were reported in studies, meta-analysis was conducted in order to provide more precise estimates for outcomes. To determine the appropriateness of conducting meta-analysis, clinical and methodological diversity and assessed statistical heterogeneity were considered. A random-effects model was used to combine risk ratios for binary outcomes, mean differences for continuous outcomes (e.g., SF-36), and proportions of adverse events that only occurred in the ablation arm, while incorporating variation among studies. For proportions of adverse events, a generalized linear random effects model was used due to sparse data with zero or small number of events. Random effects across studies were assumed and heterogeneity among the studies was tested based on the random effect variance ( $\tau^2$ ). Otherwise, a profile-likelihood model was used to combine studies,<sup>31</sup> and the presence of statistical heterogeneity among the studies was assessed using the standard Cochrane’s chi-square tests and the magnitude of heterogeneity by using the  $I^2$  statistic.<sup>32</sup>

To reduce the potential impact of clinical heterogeneity, analyses were stratified by type of AF (paroxysmal, persistent, or mixed population) and length of followup (>12 months vs. ≤12 months). Sensitivity analyses were conducted to assess the robustness of results in regards to treatment type (first-line vs. second-line therapy) across all types of atrial fibrillation. For continuous outcomes, results using the mean differences between followup scores were reported as they are slightly more conservative<sup>33</sup> and as the results based on mean difference in change score were similar. The number of studies was too small for exploring heterogeneity based on study level characteristics (aggregated patient characteristics, comorbidities, quality indicators, etc.). All analyses were performed using Stata/IC 12.1 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute Inc., Cary, NC).

The outcomes listed below were considered to be the most relevant and were the focus of reporting, data pooling, and determination of overall strength of evidence. Mortality, stroke, and myocardial infarction (MI) occurring after the 30-day peri-procedural period were considered to be efficacy or effectiveness outcomes while such events occurring within the 30 day peri-procedural period were considered adverse events. Primary outcome measures of interest included: mortality (all cause) >30 days post procedure, stroke (>30 days), MI (>30 days), congestive heart failure, and health-related quality of life. Intermediate outcome measures of interest included: freedom from recurrence, maintenance of sinus rhythm, and reablation for any arrhythmia (one or more repeat procedures). Primary safety outcomes of interest included: AF (<3 months), mortality (<30 days), stroke (<30 days), cardiac tamponade, pericardial effusion, pulmonary vein stenosis, and adverse drug events. Outcomes such as pulmonary vein stenosis, cardiac tamponade, and pericardial effusion were considered to be attributable to ablation.

Continuous outcome measures reported in this review include: health-related quality of life (HRQOL) questionnaires, exercise capacity (e.g., 6-minute walk test, stress tests), cardiac chamber size/function (e.g., left atrium [LA] enlargement, left ventricle [LV] enlargement, left ventricular ejection fraction [LVEF]), biomarkers (e.g., brain natriuretic peptide [BNP], coagulation, and inflammatory markers), and AF burden. Of the eight HRQOL measures reported, four were specific to populations with heart disease (Atrial Fibrillation Quality of Life [AF-QOL], Kansas City Cardiomyopathy [KCCQ], Minnesota Living with Heart Failure Questionnaires [MLHFQ], and the Symptom Checklist Frequency and Severity Scales) and four were general surveys of health status (Short Form-36 [SF-36], European Quality of Life-5 Dimensions [EQ-5D], Zung Self-Rating Depression Scale [SDS], and Zung Self-Rating Anxiety Scale [SAS]). All questionnaires were self-administered and all but one (MLHFQ) are scored so that higher scores reflect better health status (see Appendix H, Table H1 for details). The SF-36 was the most frequently reported HRQOL measure, in particular the SF-36 Mental Component Score (MCS) and the SF-36 Physical Component Score (PCS). Repeat ablations (i.e., reablation for arrhythmia recurrence) were included as an intermediate outcome only if they occurred after the blanking period, which was typically 4 to 6 weeks. Outcomes were reported as defined and definitions have been clarified as needed throughout the report. Detailed descriptions of these outcomes are available in the study characteristics tables in Appendix E. Some outcomes, particularly adverse events such as cardiac tamponade and pericardial effusion, are attributed to ablation, thus denominators for these outcomes reflect only patients who received ablation (either as randomized or after crossover from medical therapy).

## Strength of the Body of Evidence

The strength of evidence for each primary efficacy/effectiveness and safety outcome described above was initially assessed by one researcher using the approach described in the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, also available from the AHRQ Web site.<sup>28,30</sup>

In determining the strength of a body of evidence regarding a given outcome, the following domains are considered:

- Study limitations: the extent to which studies reporting on a particular outcome are likely to be protected from bias; graded as low, medium, or high level of study limitations
- Consistency: the extent to which studies report the same direction of effect for a particular outcome; graded as consistent, inconsistent, or unknown (in the case of a single study)
- Directness: reflects whether the outcome is directly or indirectly related to health outcomes of interest
- Precision: describes the level of certainty of the estimate of effect for a particular outcome and includes consideration of the sample size and number of events; graded as precise or imprecise
- Reporting bias: suspected if there was evidence of selective reporting, otherwise considered to be undetected.

A final strength of evidence grade was assigned by evaluating and weighing the combined results of the above domains; final grades are presented in the Discussion, and tables detailing how final grades were determined are available in Appendix G. To ensure consistency and validity of the evaluation, the strength of evidence ratings for all key outcomes were reviewed by the entire team of investigators, and discrepancies were resolved by consensus.

Briefly, bodies of evidence consisting of RCTs started as high strength while bodies of comparative observational studies began as low-strength evidence. The strength of the evidence was then downgraded based on the limitations described above. There are also situations where the observational evidence may be upgraded (e.g. very large size of effect), but we found no instances where these could be applied in this body of evidence (see AHRQ's *Methods Guide* for details on upgrading). The overall grades and their definitions are as follows:

- High — We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate — We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low — We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient — We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.



## **Applicability**

Applicability of the evidence was considered by examining the characteristics of the patient populations included in studies (e.g., demographic characteristics, type of AF, presence of medical comorbidities, stroke risk); the sample size of the studies; and clinical settings (e.g., academic setting, provider experience) in which the studies are performed, as outlined in the *AHRQ Methods Guide*.<sup>28, 34</sup> Variability in the studies may limit the ability to generalize the results to other populations and settings, for example studies enrolling relatively younger patients with few comorbidities may be less applicable to older patients (i.e., those in the Medicare population).

## **Peer Review and Public Commentary**

Experts in atrial fibrillation and catheter ablation as well as individuals representing other important stakeholder groups were invited to provide external peer review of this Technology Assessment. Comments and editorial review were provided by the AHRQ Task Order Officer. The draft report will be published on the AHRQ Web site for 2 weeks in order to solicit public comments. At the end of this period, the authors considered both the peer and public review comments and generated a final report. A disposition of comments report detailing the author response to the peer and public review comments will be made available after AHRQ posts the final report on the public Web site.

# Results

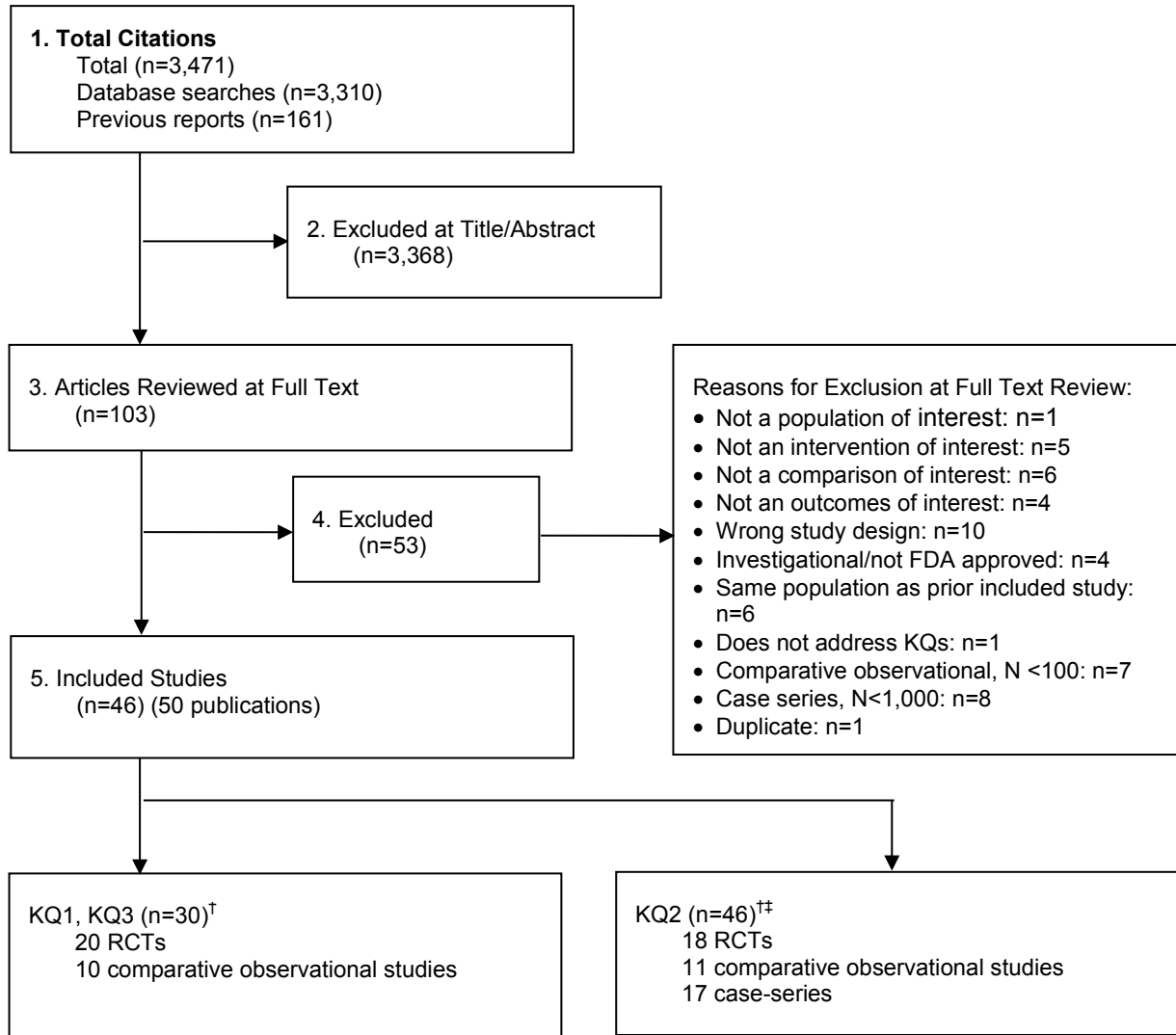
## Results of Literature Searches

The results of the literature search and study selection are summarized in the flow chart below (Figure 2). A total of 3,471 potentially relevant citations were identified, of which 3,310 came from database searches and 161 were added after reviewing the bibliographies of previous reports and relevant articles. After dual review of abstracts and titles, 3,368 articles were excluded (14 of which were identified from the updated literature search and were already included in the report). The remaining 103 articles underwent dual review at the full-text level and 46 studies (in 50 publications) met the inclusion criteria and were included in this report: 16 randomized controlled trials (RCTs), 13 comparative observational studies, and 17 case series.

For the comparison of radiofrequency ablation with medical therapy a total of 20 studies (23 publications) were included: 13 RCTs<sup>35-47</sup> and 7 comparative observational studies.<sup>48-54</sup> Also summarized under this comparison for Key Question 2 only were an additional 17 case-series, included specifically for information regarding the safety of catheter ablation.<sup>55-71</sup> For the comparison of cryoablation with medical therapy, only one RCT (2 publications) was included.<sup>72, 73</sup> For the comparison of ablation using different energy sources, a total of eight studies were included: two RCTs<sup>74, 75</sup> and six comparative observational studies.<sup>76-81</sup> A list of included studies can be found in Appendix B.

A total of 53 articles that did not meet one or more of the inclusion criteria were excluded after full-text review. Appendix C provides a list of these articles with reasons for exclusion. One, five, six, and four studies were excluded because they did not include populations, interventions, comparisons, and outcomes of interest, respectively. Ten studies were excluded because they were the wrong study design. Four examined investigational or non-US Food and Drug Administration (FDA)-approved devices (e.g., laser balloon ablation, phased RFA). The remainder were excluded for the following reasons: cases series with less than 1000 patients (n=8); comparative observational study with less than 100 patients (7 studies); same population as prior included study (6 studies); did not address any of the Key Questions (1 study); and duplicate publication (1 study).

**Figure 2. Flow chart showing results of literature search\***



Cryo = cryoablation; FDA = US Food and Drug Administration; KQ = Key Question; Med = medical therapy; RCT = randomized controlled trial; RFA = radiofrequency Ablation.

\*This is a modified PRISMA flow diagram.<sup>27, 82</sup>

<sup>†</sup>Some RCTs have multiple publications.

<sup>‡</sup>All of the randomized trials, and 11 of the 13 comparative observational studies included in KQ1 and KQ3 also provided data for KQ2.

## Organization of Results

For each Key Question, key points were presented followed by detailed information from evidence synthesis for the following comparisons: radiofrequency ablation versus medical therapy, cryoablation versus medical therapy, and comparisons between ablation energy sources. All included studies that investigated cryoablation used a cryoballoon catheter; therefore, this intervention is referred to throughout as “cryoballoon ablation”. Results are presented overall if appropriate and then by atrial fibrillation (AF) type with the focus on the outcomes considered to be most clinically important as previously described. With regard to AF type, results are reported for paroxysmal AF, persistent AF and, for studies which did not separate results by AF type, these were termed mixed.

**Key Question 1a. What is the comparative efficacy and effectiveness of AF catheter ablation versus medical therapy on short-term (6-12 months) and long-term (>12 months) outcomes in the general adult and Medicare populations?**

### Key Points

#### Radiofrequency Ablation Versus Medical Therapy

No RCTs in Medicare patients were identified for any of the following key outcomes. Of the comparative observational studies, two included Medicare populations (patients  $\geq 65$  years of age). Overall, findings from the comparative observational studies were consistent with those reported by the RCTs unless otherwise noted below.

There was substantial crossover from medical treatment to radiofrequency (RFA) in most RCTs.

### Primary Outcomes

#### All-Cause Mortality (>30 days)

- Short term ( $\leq 12$  months):
  - Overall: All-cause mortality was rare across seven RCTs (RFA: 0%–3.8%; medical therapy: 0%–2.9%) (low strength of evidence). RFA does not appear to affect all-cause mortality, and no statistical difference between treatments was reported.
  - Paroxysmal AF: Based on data from three RCTs, RFA does not appear to affect all-cause mortality in patients with paroxysmal AF (RFA: 0%–1.0%; medical therapy: 0%–3.6%) (low strength of evidence).
  - Persistent AF: Based on data from three RCTs, RFA does not appear to affect all-cause mortality in patients with persistent AF (RFA: 0%–3.8%; medical therapy: 0%) (low strength of evidence).
  - Medicare subpopulation: No RCTs or comparative observational studies were available (insufficient strength of evidence)
- Long term (>12 months):
  - Paroxysmal AF: Based on data from two RCTs, RFA does not appear to affect all-cause mortality in patients with paroxysmal AF (RFA: 0%–1.4%; medical therapy: 0%–2.8%) (low strength of evidence).

- Persistent AF: No data were reported for the general population (insufficient strength of evidence).
- Medicare subpopulation: All-cause mortality was comparable between groups in one observational study in patients with persistent AF (RFA: 1.3%; medical therapy: 1.9%) but was greater in the medical therapy arm in another observational study (RFA: 2.1%; medical therapy: 16.5%) that included those with both paroxysmal and persistent AF (insufficient strength of evidence).

### **Stroke (>30 days)**

- Short term ( $\leq 12$  months):
  - Paroxysmal AF: No strokes were observed in either treatment group in one RCT (insufficient strength of evidence).
  - Persistent AF: No strokes were observed in either treatment group in one RCT (insufficient strength of evidence).
  - Medicare subpopulation: No evidence available (insufficient strength of evidence).
- Long term ( $> 12$  months):
  - Paroxysmal AF: No strokes were observed in either treatment group one RCT (insufficient evidence).
  - Persistent AF: No evidence available (insufficient strength of evidence).
  - Mixed: Four observational studies assessed stroke and consistently found greater stroke rates in the medical therapy groups (insufficient strength of evidence).
  - Medicare subpopulation: Comparable frequency of stroke or transient ischemic attack (TIA) in both groups (RFA: 1.3%; medical therapy: 1.9%) in those with persistent AF, but in a single study in a mixed population frequency of stroke was greater following medical therapy (RFA: 0%; medical therapy: 1.5 %) (insufficient strength of evidence).

### **Myocardial Infarction (>30 days)**

- Short term ( $\leq 12$  months):
  - Paroxysmal AF: Myocardial infarction (MI) was rare across two RCTs (RFA: 0%–1.0%; medical therapy: 0%–1.8%) (low strength of evidence). All MIs were fatal and included in the results for mortality.
  - Persistent AF: No data reported (insufficient strength of evidence).
  - Medicare subpopulation: No evidence available (insufficient strength of evidence)
- Long term ( $> 12$  month):
  - Paroxysmal AF: MI was rare in both treatment groups as reported by one RCT (insufficient strength of evidence).
  - Persistent AF: No evidence available (insufficient strength of evidence).
  - Medicare subpopulation: Comparable MI events in both groups (RFA: 0%; medical therapy: 0.4%) in those with persistent AF, but higher frequency of MI for the ablation group (RFA: 1.4%; medical therapy: 0%) in the mixed population (insufficient strength of evidence).

### **Congestive Heart Failure**

- Short term ( $\leq 12$  months): No data on congestive heart failure (CHF) was reported for the general population or Medicare subpopulation (insufficient strength of evidence).

- Long term (>12 months):
  - Paroxysmal AF: No difference between groups in risk of congestive heart failure (CHF) development by 24 months in one RCT (insufficient strength of evidence).
  - Persistent AF: No data reported (insufficient strength of evidence).
  - Mixed AF: Three observational studies demonstrated greater heart failure hospitalizations in with medical therapy as compared to RFA (insufficient strength of evidence).
  - Medicare subpopulation: CHF development was comparable between groups (RFA: 0%; medical therapy 1.2%) in those with persistent AF, in contrast to the significantly higher frequency in the medical treatment group in a study with a mixed population (RFA: 0.7%; medical therapy: 9.8%) (insufficient strength of evidence).

### Health-Related Quality of Life

- A variety of health-related quality of life (HRQOL) measures were used at varied time frames across trials. This, combined with possible clinical heterogeneity across studies, limits the ability to draw firm conclusions. The Short-Form 36 (SF-36) was the most frequently used measure but was reported in a variety of ways across different time frames, which limited the ability to pool results. Overall, statistical differences between treatments were not consistently seen across HRQOL measures, time frames, or types of AF.
- Short term ( $\leq 12$  months):
  - Paroxysmal AF: No differences in SF-36 Mental Component Scores (MCS) (pooled estimate for difference in change scores 1.88; 95% confidence interval [CI] -0.47 to 4.50) and SF-36 Physical Component Scores (PCS) (pooled estimate for difference in change scores 2.88; 95% CI -0.18 to 5.25) were seen in two RCTs (insufficient strength of evidence) or in EuroQOL five dimensions (EQ5D) or Symptom Checklist frequency scale scores in one RCT; however, in the latter RCT, a difference favoring RFA in the Symptom Frequency severity scale was reported (insufficient strength of evidence for EQ5D and the Symptom Checklist).
  - Persistent AF: No differences between treatment groups were seen in change from baseline for SF-36 MCS (1 RCT) or in the Atrial Fibrillation Quality of Life Questionnaire (AF-QOL) or Kansas City Cardiomyopathy (KCCQ) scores (1 RCT each); however, for the SF-36 PCS a greater change was observed for the RFA group in one RCT and one trial reported improved New York Heart Association (NYHA) Functional Classification scores for the RFA group (insufficient strength of evidence for all). Across three trials in patients with heart failure, two reported a difference favoring RFA at 6 months in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and while not statistically significant, a third tended to favor RFA (low strength of evidence). Only one trial reported that this persisted to 12 months (low strength of evidence).
  - Medicare subpopulation: No evidence available (insufficient strength of evidence).
- Long term (>12 months):
  - Paroxysmal AF: SF-36 MCS and PCS were similar between groups at 24 months (one RCT) and at 48 months (one RCT) (insufficient strength of evidence at both time frames).

- Persistent AF: No RCTs reported HRQOL past 12 months (insufficient strength of evidence).
- Medicare Subpopulation: No evidence available (insufficient strength of evidence).

## Intermediate Outcomes

### Freedom From Recurrence (>30 days)

- Short term ( $\leq 12$  months):
  - Overall: Freedom from recurrence of any arrhythmia was greater for RFA versus medical therapy based on data from nine RCTs (pooled relative risk [RR] 2.62; 95% CI 1.90 to 3.96) (moderate strength of evidence).
  - Paroxysmal AF: Based on data from four RCTs, catheter ablation is superior to medical therapy at improving freedom from recurrence of any atrial arrhythmia (pooled RR 3.06; 95% CI 2.35 to 3.90) (moderate strength of evidence).
  - Persistent AF: Based on data from three RCTs, catheter ablation is superior to medical therapy at improving freedom from recurrence of any atrial arrhythmia (RFA: 58%–75%; medical therapy: 4%–58%) (low strength of evidence).
- Long term ( $> 12$  months):
  - Paroxysmal AF: Based on data from three RCTs, catheter ablation is superior to medical therapy at improving freedom from recurrence of any atrial arrhythmia (pooled RR 1.24; 95% CI 1.11 to 1.47) (moderate strength of evidence).
  - Persistent AF: No data reported (insufficient strength of evidence).

### Maintenance of Sinus Rhythm

- Short term ( $\leq 12$  months):
  - Paroxysmal AF: One RCT found that RFA is superior to medical therapy at improving maintenance of sinus rhythm while a second found no difference between groups (RFA: 88%–92%; medical therapy: 35.4%–87%) (low strength of evidence).
  - Persistent AF: Based on two RCTs of heart failure patients, catheter ablation is superior to medical therapy at improving maintenance of sinus rhythm (RFA: 50%–88%; medical therapy: 0%–7.7%) (low strength of evidence).
- Long term ( $> 12$  months): No data reported in the general population (insufficient strength of evidence).
  - Medicare subpopulation: In patients with persistent AF sinus rhythm was maintained in 58 percent of the RFA group versus 43 percent of the medical therapy group. (insufficient strength of evidence)

### Reablation (>30 days)

- Short term ( $\leq 12$  months):
  - Overall: The frequency of reablation following RFA varied across seven RCTs (range, 0%–43%) (low strength of evidence).
  - Paroxysmal AF: Based on data from three RCTs, the frequency of reablation following RFA ranged from 0 percent to 43 percent (low strength of evidence).
  - Persistent AF: The frequency of reablation following RFA varied across four RCTs (pooled risk 20.1%; 95% CI 11.0 to 34.1) (low strength of evidence).
- Long term ( $> 12$  months):

- Paroxysmal AF: The frequency of reablation following RFA varied across four RCTs (pooled risk 24.2%; 95% CI 12.6 to 41.5) (low strength of evidence).
- Persistent AF: No data reported (insufficient strength of evidence).
- Medicare subpopulation: 18.3 percent of patients with persistent AF required reablation in a single observational study (insufficient strength of evidence)

## **Cryoablation Versus Medical Therapy**

No RCTs or comparative observational studies in Medicare patients were identified for cryoballoon ablation or focal cryoablation versus medical therapy. One fair-quality RCT was identified comparing cryoballoon ablation which reported only short-term ( $\leq 12$  months) outcomes in patients with paroxysmal or persistent AF. This study had substantial crossover from medical therapy to cryoballoon ablation.

### **Primary Outcomes**

- In the cryoballoon ablation group, one death occurred, due to an MI at 10 months postprocedure (this event was counted as both all-cause mortality and MI, 0.6% for both); three strokes (1.8%) and no TIAs were reported; and one patient (0.6%) was hospitalized with AF-related CHF. None of these events occurred in the medical therapy group. For HRQOL, no comparative data were reported (insufficient strength of evidence for all outcomes).

### **Intermediate Outcomes**

- Freedom from protocol-defined treatment failure was significantly greater in the cryoablation group (69.9%) compared with the group treated medically (7.3%) (low strength of evidence).

## **Radiofrequency Ablation Versus Medical Therapy**

### **Description of Included Studies**

#### **Randomized Controlled Trials**

Thirteen RCTs compared RFA with medical therapy. Short-term outcomes were reported by 11 RCTs,<sup>36-41, 43-47</sup> with followup past the blanking period of 12 months available in 10 and 13 months available in one trial.<sup>45</sup> Three RCTs reported on long-term outcomes, with followup ranging from 24 to 48 months.<sup>35, 42, 83</sup> One trial published 12 and 48 month outcomes in two separate articles.<sup>44, 83</sup> The blanking period ranged from 1 to 3 months across 12 RCTs; one RCT<sup>43</sup> did not report on the length of the blanking period. Six RCTs only included patients with paroxysmal AF,<sup>35, 38, 42, 44, 46, 47, 83</sup> five only included patients with persistent AF,<sup>37, 39-41, 43</sup> and two trials included patients with either paroxysmal or persistent AF (“mixed”),<sup>36, 45</sup> study characteristics are presented in Tables 2, 3, and 4, respectively. Eleven RCTs were multicenter<sup>35, 36, 38-43, 45-47</sup> and two single center;<sup>37, 44, 83</sup> study centers were located primarily in North America and Europe. The majority of trials received funding from industry.<sup>35, 38, 41, 42, 45-47</sup> Conflicts of interest were mainly in the form of grants or consulting fees from biomedical companies (e.g. Biosense Webster) and were disclosed by eight trials.<sup>35, 36, 38, 39, 42-44, 47, 83</sup> Four RCTs reported no conflicts of interest<sup>37, 40, 41, 45</sup> and one did not report whether any conflicts existed among its authors.<sup>46</sup>



Trial sample sizes ranged from 41 to 294 patients. The trial populations were predominantly male (59%–96%) and mean ages ranged from 51 to 64 years (Tables 2–4 below; detailed tables available in Appendix E, Tables E1–E3, E7–E9). Patients underwent treatment as a first-line therapy in three trials,<sup>35, 40, 42, 46</sup> as a second-line therapy (i.e., had failed previous medical therapy) in eight<sup>36, 38, 40, 41, 43–45, 47, 83</sup> and two studies included patients for whom treatment was either a first- or second-line therapy.<sup>37, 39</sup> Four RCTs investigated outcomes in populations with comorbidities often seen in conjunction with AF: three were conducted specifically in patients with CHF (all with persistent AF)<sup>37, 39, 40</sup> and one in patients with type 2 diabetes.<sup>36</sup> No studies specifically targeted the Medicare population. The majority of studies required discontinuation of antiarrhythmic drug (AAD) use after the blanking period for the RFA group, while two studies permitted patients in the RFA group to remain on AADs throughout the followup period.<sup>40, 45</sup> The most common AADs used in both the RFA and medical groups were amiodarone, propafenone, flecainide, and sotalol. Of the RCTs that included patients undergoing second-line therapy, medically-treated patients received new/previously unused AADs in four trials<sup>38, 40, 44, 47, 83</sup> but it was unclear if this was the case in the other six.<sup>36, 37, 39, 41, 43, 45</sup> The timing, duration and intensity of anticoagulation were variably reported across RCTs. In many studies, the adequacy of anticoagulation in the ablation group, particularly before ablation, was not clear. Limited detail regarding anticoagulation in the medical treatment groups was available.

Ablation strategies varied across studies. Pulmonary vein isolation (PVI) only was performed in one study,<sup>46</sup> PVI plus additional lines (including the atrial roof, cavotricuspid and mitral isthmus, superior vena cava, foci from nonvenous structures, and other right and/or left atrial foci) in eleven,<sup>35, 36, 38–45, 47, 83</sup> and PVI plus complex fractionated atrial electrogram (CFAE) and additional lines if necessary in one.<sup>37</sup> PVI plus complex fractionated atrial electrogram (CFAE) was less common, but was completed in a subset of patients in four studies.<sup>39–42</sup> In one study, additional RFA was performed specifically to resolve atrial flutter in combination with ablation for AF.<sup>40</sup> Mapping systems were utilized in all studies. Details regarding ablation and mapping techniques used in each trial are outlined in Table H6 in the Appendix.

There was substantial crossover (37.0%–87.9%) from medical therapy to RFA in six trials<sup>35, 42–45, 47, 83</sup> and two trials reported lower crossover rates of 9.4 percent<sup>38</sup> and 3.8 percent.<sup>39</sup> In some studies, a patient had to fail at least two drug treatments in order to be eligible for crossover. One trial did not provide the number of patients that crossed over, but indicated that followup could not be extended to 12 months in the medical therapy group because many went on to have ablation.<sup>37</sup> One study did not report if crossover occurred<sup>40</sup> and two did not allow crossover during the 12-month study period.<sup>36, 46</sup> One RCT reported a crossover rate of 0 percent in the medical group compared with 35.7 percent in the ablation group during the study period; however, at the end of followup, 47.9 percent in the medical therapy group underwent RFA.<sup>41</sup> A considerably smaller number of patients crossed over from ablation to medical therapy (0%–9.4%) in seven RCTs.<sup>35, 38, 39, 41–44, 47</sup>

Only one trial was considered to be good quality,<sup>45</sup> the remaining trials were all considered fair quality. Common methodological shortcomings included unclear allocation concealment (only one documented concealed allocation)<sup>45</sup> and lack of assessor blinding for primary outcomes. Four RCTs did not report information on random sequence generation.<sup>38, 41, 44, 83</sup> One RCT did not perform an intention-to-treat analysis.<sup>47</sup> Discrepancies in baseline characteristics as well as unclear randomization methods were observed, although rarely.

**Table 2. Patient characteristics and overview of study characteristics for RCTs comparing RFA with medical therapy in patients with paroxysmal atrial fibrillation**

Author (Year) Therapy Sample Size		Cosedis Nielsen (2012) <sup>35</sup> RFA (n=146)	Cosedis Nielsen (2012) <sup>35</sup> Medical (n=148)	Jais (2008) <sup>38</sup> RFA (n=53)	Jais (2008) <sup>38</sup> Medical (n=59)	Morillo (2014) <sup>42</sup> RFA (n=66)	Morillo (2014) <sup>42</sup> Medical (n=61)	Pappone (2006/ 2011) <sup>44, 83</sup> RFA (n=99)	Pappone (2006/ 2011) <sup>44, 83</sup> Medical (n=99)	Wilber (2010) <sup>47</sup> RFA (n=106)	Wilber (2010) <sup>47</sup> Medical (n=61)	Wazni (2005) <sup>46</sup> RFA (n=33)	Wazni (2005) <sup>46</sup> Medical (n=37)
<b>Patient Demographics</b>	Male, % (n)	68.5 (100)	71.6 (106)	84.9 (45)	83.1 (49)	77.3 (51)	73.8 (45)	69.7 (69)	64.6 (64)	68.9 (73)	62.3 (38)	NR	NR
	Age (years); mean ± SD, mean (95% CI)	56 ± 9	54 ± 10	49.7 ± 10.7	52.4 ±11.4	56.3 ± 9.3	54.3 ± 11.7	55 ± 10	57 ± 10	55.5 (53.7– 57.3)	56.1 (52.9– 59.4)	53 ± 8	54 ± 8
	AF duration; mean ± SD, median (IQR)	6 ± 4 Years	6 ± 5 years	4.0 (1.0 - 12.0) hours* (median, IQR)	6.0 (2.0 - 15.0) hours* (median, IQR)	NR	NR	6 ± 4 Years	6 ± 6 Years	5.4 (4.3– 6.5) years	6.2 (4.6– 7.9) years	5 ± 2 months	5 ± 2.5 months
	Left atrial size (mm); mean ± SD, mean (95% CI)	40 ± 6	38 ± 6	39.5 ± 5.6	40.0 ± 5.7	40 ± 5	43 ± 5	40 ± 6	38 ± 6	40.0 (38.9– 41.1)	40.5 (39.0– 41.9)	41 ± 8	42 ± 7
	LVEF (%), mean ± SD, mean (95% CI)	>60%: 79.5 (n=116) 40-60%: 19.9 (n=29)	>60%: 81.8 (n=121) 40-60%: 17.6 (n=26)	63.1 ± 11.0	65.6 ± 7.2	61.4 ± 4.8	60.8 ± 7.0	60 ± 8	61 ± 6	62.3 (60.4– 64.3)	62.7 (60.7– 64.7)	53 ± 5	54 ± 6
	1st/2nd line therapy	1 <sup>st</sup> line	1 <sup>st</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	1 <sup>st</sup> line	1 <sup>st</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	1 <sup>st</sup> line	1 <sup>st</sup> line
	Special population	None	None	None	None	None	None	None	None	None	None	None	None
<b>Comorbidities, % (n)</b>	Heart failure	NR	NR	NR	NR	3.0 (2)	1.6 (1)	NR	NR	NR	NR	NR	NR
	Hypertension	29 (43)	36 (53)	21.6 (11)	30.5 (18)	42.4 (28)	41.0 (25)	56 (55)	57 (56)	48.6 (51)	50.0 (30)	NR	NR
	Coronary artery disease	4 (6)	1 (2)	NR	NR	9.1 (6)	3.3 (2)	2 (2)	2 (2)	NR	NR	NR	NR
	Thyroid disease	7 (10)	7 (10)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Pulmonary disease	5 (8)	4 (6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Valvular disease (moderate/severe)	5 (7)	10 (15)	NR	NR	NR	NR	3 (3)	1 (1)	NR	NR	NR	NR
	History of prior stroke	4 (6)	3 (5)	NR	NR	4.6 (3)	6.6 (4)	NR	NR	1.9 (2) <sup>†</sup>	5.0 (3) <sup>†</sup>	NR	NR
	Prior embolic/ thromboembolic event	NR	NR	1.9 (1)	11.9 (7)	NR	NR	NR	NR	1.9 (2)	3.3 (2)	NR	NR

Author (Year) Therapy Sample Size		Cosedis Nielsen (2012) <sup>35</sup> RFA (n=146)	Cosedis Nielsen (2012) <sup>35</sup> Medical (n=148)	Jais (2008) <sup>38</sup> RFA (n=53)	Jais (2008) <sup>38</sup> Medical (n=59)	Morillo (2014) <sup>42</sup> RFA (n=66)	Morillo (2014) <sup>42</sup> Medical (n=61)	Pappone (2006/ 2011) <sup>44, 83</sup> RFA (n=99)	Pappone (2006/ 2011) <sup>44, 83</sup> Medical (n=99)	Wilber (2010) <sup>47</sup> RFA (n=106)	Wilber (2010) <sup>47</sup> Medical (n=61)	Wazni (2005) <sup>46</sup> RFA (n=33)	Wazni (2005) <sup>46</sup> Medical (n=37)
	CHADS2 score 2+	12 (17)	13 (19)	NR	NR	6.1 (4)	11.5 (7)	NR	NR	NR	NR	NR	NR
	Diabetes	4 (6)	10 (10)	1.9 (1)	3.4 (2)	1.5 (1)	6.6 (4)	5.1 (5)	4.0 (4)	9.5 (10)	11.7 (7)	NR	NR
	Structural heart disease	NR	NR	19 (10)	24 (14)	NR	NR	2.0 (2)	1.0 (1)	9.5 (10)	15.0 (9)	25 (8)	28 (10)
Study Characteristics	Followup period	24 months	24 months	12 months	12 months	24 months	24 months	2006: 12 months 2011: 48 months	2006: 12 months 2011: 48 months	12 months	12 months	12 months	12 months
	Completed followup, % (n)	94.5 (138)	92.6 (137)	98.1 (52)	93.2 (55)	86.4 (57)	78.7 (48)	2006: 100 2011: 95 (94) <sup>‡</sup>	2006: 100 2011: 95 (94) <sup>‡</sup>	NR	NR	97 (32)	94.6 (35)
	Blanking period	3 months	3 months	3 months	3 months	3 months	3 months	6 weeks	6 weeks	3 months	14 days	2 months	2 months
	Crossover, % (n)	9 (13)	37 (54)	9.4 (5)	62.7 (37)	9.1 (6)	42. (26)	5.1 (5)	42.4 (42)	4.8 (5)	60 (36)	Not allowed during F/U (>1 year: 3.1 (1))	Not allowed during F/U (>1 year: 51.4 (18))
	Use of AADs in RFA group	NR	---	NR	---	Stopped after blanking period	---	Stopped after blanking period	---	Previously ineffective drug <sup>§</sup>	---	Beta-blocker <sup>§</sup>	---

AAD = antiarrhythmic drug; AF = atrial fibrillation; CHADS2: = Cardiac failure, Hypertension, Age, Diabetes, Stroke system; F/U = followup; IQR = interquartile range; LVEF = left ventricular ejection fraction; NR = not reported; RCTs = nonrandomized controlled trials; RFA = radiofrequency ablation; SD = standard deviation.

\*Authors report duration of episodes, not the length of time since the person was diagnosed with AF.

†Cerebrovascular accident/TIA.

‡95% followup for the entire study group at 4 years, 100% followup to 3 years.

§At physicians discretion during effectiveness period.

**Table 3. Patient characteristics and overview of study characteristics for RCTs comparing RFA with medical therapy in patients with persistent atrial fibrillation**

Author (Year) Therapy Sample Size		MacDonald (2011) <sup>40</sup> RFA (n=22)	MacDonald (2011) <sup>40</sup> Medical (n=19)	Mont (2013) <sup>41</sup> RFA (n=98)	Mont (2013) <sup>41</sup> Medical (n=48)	Oral (2006) <sup>43</sup> RFA (n=77)	Oral (2006) <sup>43</sup> Medical (n=69)	Jones (2013) <sup>39</sup> RFA (n=26)	Jones (2013) <sup>39</sup> Medical (n=26)	Hunter (2014) <sup>37</sup> RFA (n=26)	Hunter (2014) <sup>37</sup> Medical (n=24)
<b>Patient Demographics</b>	Male, % (n)	77.3 (17)	78.9 (15)	77.5 (76)	77.1 (37)	87.0 (67)	89.9 (62)	80.8 (21)	92.3 (24)	92.6 (25)	95.8 (23)
	Age (years); mean ± SD	62.3 ± 6.7	64.4 ± 8.3	55 ± 9	55 ± 9	55 ± 9	58 ± 8	64 ± 10	62 ± 9	55 ± 12	60 ± 10
	AF duration (years); mean ± SD	3.7 ± 3.0	5.3 ± 3.9	NR	NR	5 ± 4	5 ± 4	4.3 ± 3.3	4.3 ± 6.3	2.0 (IQ range, 1.4-2.8)	2.0 (IQ range, 1.0-4.0)
	Left atrial size (mm); mean ± SD	NR	NR	41.3 +/- 4.6	42.7 +/- 5.1	45 +/- 6	45 +/- 5	50 ± 6	46 ± 7	52 ± 11	50 ± 10
	LVEF (%), mean ± SD	16.1 ± 7.1	19.6 ± 5.5	61.1 ± 8.8	60.8 ± 9.7	55 ± 7	56 ± 7	22 ± 8	25 ± 7	31.8 ± 7.7	33.7 ± 12.1
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	Both	Both	Both	Both
	Special population	Heart Failure	Heart Failure	None	None	None	None	Heart failure	Heart failure	Heart failure	Heart failure
<b>Comorbidities, % (n)</b>	Heart failure	100 (22)	100 (19)	NR	NR	NR	NR	100 (26)	100 (26)	100 (26)	100 (24)
	Hypertension	64 (14)	58 (11)	46.9 (46)	39.5 (19)	NR	NR	NR	NR	31 (8)	33 (8)
	Coronary artery disease	50 (11)	53 (10)	NR	NR	4 (3)	6 (4)	42 (11)	50 (13)	23 (6)	29 (7)
	Cardiomyopathy	NR	NR	NR	NR	3 (2)	1 (1)	NR	NR	31 (8)	29 (7)
	Pulmonary disease	27 (6)	16 (3)	3.1 (3)	2.1 (1)	NR	NR	NR	NR	NR	NR
	Obstructive sleep apnea	NR	NR	10.2 (10)	16.6 (8)	NR	NR	NR	NR	NR	NR
	Valvular disease (moderate/severe)	NR	NR	NR	NR	1 (1)	0 (0)	NR	NR	NR	NR
	History of prior stroke	NR	NR	3.1 (3)	2.1 (1)	NR	NR	NR	NR	NR	NR
	History of prior TIA	NR	NR	1.0 (1)	2.1 (1)	NR	NR	NR	NR	NR	NR
	Diabetes	32 (7)	21 (4)	NR	NR	NR	NR	NR	NR	NR	NR
	NYHA functional class II	2 (9)	2 (11)	NR	NR	NR	NR	14 (54)	13 (50)	42 (11)	50 (12)
NYHA functional class III	20 (91)	17 (89)	NR	NR	NR	NR	12 (46)	13 (50)	58 (15)	50 (12)	
<b>Study Characteristics</b>	Followup period	6 Months	6 Months	12 months	12 months	12 months	12 months	12 months	12 months	6 months*	6 months*
	Completed followup, % (n)	90.9 (20)	94.7 (18)	91.8 (90)	100 (48)	100 (77)	100 (69)	92.3 (24)	100 (26)	96 (25)	96 (23)

Author (Year) Therapy Sample Size	MacDonald (2011) <sup>40</sup> RFA (n=22)	MacDonald (2011) <sup>40</sup> Medical (n=19)	Mont (2013) <sup>41</sup> RFA (n=98)	Mont (2013) <sup>41</sup> Medical (n=48)	Oral (2006) <sup>43</sup> RFA (n=77)	Oral (2006) <sup>43</sup> Medical (n=69)	Jones (2013) <sup>39</sup> RFA (n=26)	Jones (2013) <sup>39</sup> Medical (n=26)	Hunter (2014) <sup>37</sup> RFA (n=26)	Hunter (2014) <sup>37</sup> Medical (n=24)
Blanking period	3 months	NR	3 months	3 months	NR	NR	2 months	NR	3 months	3 months
Crossover, % (n)	NR	NR	35.7 (35)	47.9 (23)	0 (0)	77 (53)	3.8 (1)	3.8 (1)	NR	NR
Use of AADs in RFA group	Yes (amiodarone)	---	Yes (amiodarone, class Ic, or class III drugs)	---	1% (1/77) continued amiodarone.	---	NR	---	No (stopped post- ablation; AAD type NR)	---

AAD = antiarrhythmic drug; AF = atrial fibrillation; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association; RCT = randomized controlled trial; RFA = radiofrequency ablation; SD = standard deviation; TIA = transient ischemic attack.

\*Followup was extended to 1 year in the ablation group only; this could not be performed in the medical group because many went on to have pulmonary vein isolation, atrioventricular node ablation, and device implantation.

**Table 4. Patient characteristics and overview of study characteristics for RCTs comparing RFA with medical therapy in patients with paroxysmal or persistent atrial fibrillation**

Author (Year) Therapy Sample Size		Forleo (2009) <sup>36</sup> RFA (n=35)	Forleo (2009) <sup>36</sup> Medical (n=35)	Stabile (2006) <sup>45</sup> RFA (n=68)	Stabile (2006) <sup>45</sup> Medical (n=69)
<b>Patient demographics</b>	Male, % (n)	57.1 (20)	65.7 (23)	54.4 (37)	63.8 (44)
	Age (years); mean ± SD	63.2 ± 8.6	64.8 ± 6.5	62.2 ± 9	62.3 ± 10
	Paroxysmal AF, % (n)	45.7 (16)	37.1 (13)	61.8 (42)	72.5 (50)
	Persistent AF, % (n)	54.3 (19)	62.9 (22)	38.2 (26)	27.5 (19)
	AF duration (years); median (IQR) or mean ± SD	3.4 (1.5–5.5)	3.0 (1.4–4.6)	5.1 ± 3.9	7.1 ± 5.9
	Left atrial size (mm); mean ± SD	44.3 ± 5.6	45.2 ± 5.2	46 ± 5	45.4 ± 5.5
	LVEF (%), mean ± SD	54.6 ± 7	52.6 ± 8.6	59.1 ± 6.7	57.9 ± 5.8
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line
Special population	Diabetes	Diabetes	None	None	
<b>Comorbidities, % (n)</b>	Hypertension	62.9 (22)	68.6 (24)	52.9 (36)	49.3 (34)
	Coronary artery disease	20.0 (7)	20.0 (7)	NR	NR
	Hypertrophic cardiomyopathy	Dilated: 8.6 (3)	Dilated: 5.7 (2)	Dilated: 1.5 (1) Ischemic: 4.4 (3) Valvular: 4.4 (3)	Dilated: 2.9 (2) Ischemic: 7.2 (5) Valvular: 2.9 (2)
	Valvular disease (moderate/severe)	5.7 (2)	11.4 (4)	NR	NR
	History of prior stroke	14.3 (5)	8.6 (3)	NR	NR
	Diabetes	100 (35)	100 (35)	NR	NR
	Structural heart disease	45.7 (16)	54.3 (19)	63.2 (43)	62.3 (43)
Lung disease (asthma/COPD)	2.9 (1)	2.9 (1)	NR	NR	
<b>Study characteristics</b>	Followup period	12 months	12 months	12 months	12 months
	Completed followup, % (n)	100 (35)	100 (35)	97.1 (66)	97.1 (67)
	Blanking period	5 weeks	5 weeks	1 month	1 month
	Crossover, % (n)	None permitted	None permitted	NR	52.2 (36)
	Use of AADs in RFA group	NR	---	Yes-various	---

AAD = antiarrhythmic drug; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; LVEF = left ventricular ejection fraction; NR = not reported; RFA = radiofrequency ablation; SD = standard deviation.

## Comparative Observational Studies

Seven comparative observational studies, three prospective<sup>48, 49, 52</sup> and four retrospective<sup>50, 51, 53, 54</sup> compared RFA with medical therapy. Of these, three reported outcomes up to 12 months following the blanking period<sup>49, 52, 54</sup> and four reported on outcomes after 12 months (15 to 69 months).<sup>48, 50, 51, 53</sup> Three studies only included paroxysmal AF patients,<sup>49, 52, 54</sup> one only included persistent AF patients,<sup>48</sup> and three studies included patients with either paroxysmal or persistent AF;<sup>50, 51, 53</sup> study characteristics are presented in Tables 5, 6, and 7, respectively. All studies included patients receiving treatment as a second-line therapy (i.e., had failed previous medical therapy). Five studies reported blanking periods ranging from 1 to 3 months in the RFA group.<sup>48, 49, 51, 52, 54</sup> The remaining two studies did not report a blanking period.<sup>50, 53</sup> Funding was not reported for four studies;<sup>48, 51, 53, 54</sup> one study was supported by Biosense Webster<sup>50</sup> and two received government grants/funds (the Health Research Foundation/Health Bureau of Chongqing<sup>49</sup> and the National Science Foundation of China and Beijing Natural Science Foundation<sup>52</sup>). Two studies reported a conflict of interest (COI) regarding the first author's relationship with Biosense Webster,<sup>48, 50</sup> while three studies indicated they had no disclosures<sup>49, 52, 54</sup> and two did not report COI.<sup>51, 53</sup>

The study populations were predominantly male (49.5%–84.7%) and mean ages ranged from 55 to 75 years (Tables 5–7 below; detailed tables can be found in Appendix E, Tables E4–E6, E10–E12). Two studies were comprised of exclusively Medicare populations (age ≥65 years).<sup>48, 53</sup> All but two studies<sup>49, 50</sup> reported hypertension in over half of their patients; otherwise, the comorbidities and their prevalence varied across studies.

Ablation strategies varied (details regarding ablation and mapping techniques used in each study are outlined in Table H6 in the Appendix). All patients underwent PVI, with three studies reporting subsequent ablation of other areas (i.e., cavotricuspid isthmus, roofline, metrial annulus, superior vena cava).<sup>48, 50, 51</sup> Two studies allowed for the use of AADs throughout the study period,<sup>50, 53</sup> with the remaining five studies requiring patients to cease AAD use after the blanking period. Common AADs included amiodarone, flecainide, propafenone, and sotalol.

Of the seven studies, four were fair quality<sup>48-50, 52</sup> and three were poor quality.<sup>51, 53, 54</sup> The most common methodological shortcoming was a lack of assessor blinding for primary outcomes. Followup of at least 80 percent was reported by three studies<sup>48, 52, 54</sup> and all of them controlled for confounding (primarily in the form of similar baseline characteristics between groups).<sup>49-54</sup>

**Table 5. Patient characteristics and overview of study characteristics for comparative observational studies comparing RFA with medical therapy in patients with paroxysmal atrial fibrillation**

Author (Year) Therapy Sample Size	Lan (2009)* Prospective <sup>49</sup> RFA (n=120)	Lan (2009)* Prospective <sup>49</sup> Medical (n=120)	Sang (2013) <sup>†</sup> Prospective <sup>52</sup> RFA (n=85)	Sang (2013) <sup>†</sup> Prospective <sup>52</sup> Medical (n=90)	Yu (2012) <sup>†</sup> Retrospective <sup>54</sup> RFA (n=98)	Yu (2012) <sup>†</sup> Retrospective <sup>54</sup> Medical (n=112)	
<b>Patient Demographics</b>	Male, % (n)	66.7 (80)	64.2 (77)	67.1 (55)	69.1 (58)	49.5 (48)	52.0 (53)
	Age (years); mean ± SD	59.5	58.5	55.9 ± 6.1	57.2 ± 5.4	55.2 ± 6.5	54.9 ± 7
	AF duration (years); mean ± SD	2.6	2.6	7.5 ± 7.5	7.2 ± 7.6	2.4 ± 0.1	2.3 ± 0.1
	Left atrial size (mm); mean ± SD	34.7	34.7	39.0 ± 5.9	38.6 ± 6.2	31.7 ± 1.9	32 ± 2
	LVEF (%), mean ± SD	66.5	66.6	59.6 ± 7.5	58.9 ± 8.3	57.9 ± 6.4	56.9 ± 6
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	None	None	LVEF <35%	LVEF <35%	None	None
<b>Comorbidities, % (n)</b>	Hypertension	NR	NR	64.6 (53)	60.7 (51)	54.1 (53)	56.9 (58)
	Coronary artery disease	NR	NR	9.8 (8)	11.9 (10)	3.1 (3)	5.9 (6)
	Hypertrophic cardiomyopathy	NR	NR	Dilated: 2.4 (2)	Dilated: 4.8 (4)	NR	NR
	Valvular disease (moderate/severe)	NR	NR	3.7 (3)	6.0 (5)	NR	NR
	History of prior stroke	NR	NR	8.5 (7)	8.3 (7)	6.1 (6)	7.8 (8)
	BMI (kg/m <sup>2</sup> ), mean	23.9	24.5	NR	NR	NR	NR
	Diabetes	NR	NR	13.4 (11)	19.1 (16)	4.1 (4)	8.2 (9)
	Current smoker	NR	NR	NR	NR	38.8 (38)	33.3 (34)
Current drinker	NR	NR	NR	NR	18.4 (18)	20.6 (21)	
<b>Study Characteristics</b>	Followup period	12 months	12 months	312 months	12 months	12 months	12 months
	Completed followup, % (n)	NR	NR	96.5 (82)	93.3 (84)	98.9 (97)	91.1 (102)
	Blanking period	1 month	1 month	3 months	NR	3 months	NR
	Use of AADs in RFA group	NR	---	2 months after ablation and then discontinued if no AF recurred	---	Stopped after blanking period	---

AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; LVEF = left ventricular ejection fraction; NR = not reported; RFA = radiofrequency ablation; SD = standard deviation.

\*The circumferential pulmonary vein ablation (n=60) and the segmental pulmonary vein isolation (n=60) groups were combined to form one ablation group. Age, AF duration, left atrial size, LVEF, and BMI were calculated using weighted means.

†Demographics reported out of the number of patients who completed followup.



**Table 6. Patient characteristics and overview of study characteristics for comparative observational studies comparing RFA with medical therapy in patients with persistent atrial fibrillation**

Author (Year) Therapy Sample Size		Blandino (2013) Prospective <sup>48</sup> RFA (n=153)	Blandino (2013) Prospective <sup>48</sup> Medical (n=259)
<b>Patient Demographics</b>	Male, % (n)	71 (109)	72 (186)
	Age (years); mean ± SD	75 ± 5	76 ± 5
	AF duration (months); mean ± SD	6 ± 4 months	6 ± 4 months
	Left atrial size (mm); mean ± SD	47 ± 5	47 ± 6
	LVEF (%), mean ± SD	56 ± 6	56 ± 8
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	Medicare population	Medicare population
<b>Comorbidities</b>	Hypertension	70 (107)	74 (191)
	Prior thyroid dysfunction	27 (41)	21 (53)
	History of prior stroke or TIA	17 (26)	14 (36)
	Diabetes	3 (5)	6 (15)
	Dyslipidemia	24 (36)	26 (68)
	Structural heart disease	Ischemic: 14 (21) Valvular: 5 (8) Others: 5 (7)	Ischemic: 13 (34) Valvular: 9 (22) Others: 2 (5)
<b>Study Characteristics</b>	Followup period	mean 60 ± 17 months	mean 60 ± 17 months
	Complete followup, % (n)	100 (153)	100 (259)
	Blanking period	3 months	NR
	Use of AADs in RFA group	All patients continued the same AAD regimen during blanking period; then, according to AF/AT recurrence, referring physician's decision, and patient's will AADs were suspended or not	---

AAD = antiarrhythmic drug; AF = atrial fibrillation; LVEF = left ventricular ejection fraction; NR = not reported; RFA = radiofrequency ablation; SD = standard deviation.

**Table 7. Patient characteristics and overview of study characteristics for comparative observational studies comparing RFA with medical therapy in patients with paroxysmal, persistent or permanent atrial fibrillation**

Author (Year) Therapy Sample Size		Reynolds (2012) Retrospective <sup>50</sup> RFA (n=801)	Reynolds (2012) Retrospective <sup>50</sup> Medical (n=801)	Rossillo (2008) Retrospective <sup>51</sup> RFA (n=85)	Rossillo (2008) Retrospective <sup>51</sup> Medical (+Cardioversion) (n=85)	Sonne (2009) Retrospective <sup>53</sup> RFA <sup>*</sup> (n=146)	Sonne (2009) Retrospective <sup>53</sup> Medical (+ Cardioversion) (n=205)
<b>Patient Demographics</b>	Male, % (n)	60.9 (488)	62.6 (501)	84.7 (72)	84.7 (72)	67.8 (99)	68.8 (141)
	Age (years); mean ± SD	≥65 yrs: 48.2 (386)	≥65 yrs: 43.9 (352)	62.0 ± 7.6	62.0 ± 7.6	67.2 ± 8.0	66.7 ± 7.7
	Paroxysmal AF, % (n)	NR	NR	31.7 (27)	0 (0)	26.7 (39)	24.8 (51)

<b>Author (Year)</b> Therapy Sample Size		<b>Reynolds (2012) Retrospective<sup>50</sup></b> RFA (n=801)	<b>Reynolds (2012) Retrospective<sup>50</sup></b> Medical (n=801)	<b>Rossillo (2008) Retrospective<sup>51</sup></b> RFA (n=85)	<b>Rossillo (2008) Retrospective<sup>51</sup></b> Medical (+Cardioversion) (n=85)	<b>Sonne (2009) Retrospective<sup>53</sup></b> RFA* (n=146)	<b>Sonne (2009) Retrospective<sup>53</sup></b> Medical (+ Cardioversion) (n=205)
	Persistent AF, % (n)	NR	NR	50.5 (43)	100.0 (85)	NR <sup>†</sup>	NR <sup>†</sup>
	Permanent AF, % (n)	NR	NR	17.8 (15)	0 (0)	NR <sup>†</sup>	NR <sup>†</sup>
	AF duration (years); mean	NR	NR	8 (range, 1–24)	Unknown	NR	NR
	Left atrial size (mm); mean ± SD	NR	NR	44 ± 6	42 ± 7	55 ± 8.7	56 ± 8.7
	LVEF (%), mean ± SD	NR	NR	58 ± 6	56 ± 8	50 ± 9	50 ± 10
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	NR	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	None	None	None	None	Medicare population	Medicare population
<b>Comorbidities, % (n)</b>	Heart failure	17.4 (139)	15.7 (126)	NR	NR	NR	NR
	Hypertension	42.7 (342)	40.7 (326)	NR	NR	56.8 (83)	57 (117)
	Coronary artery disease	37.0 (296)	35.6 (285)	NR	NR	44.5 (65)	31.7 (65)
	Cardiomyopathy	7.5 (60)	7.2 (58)	NR	NR	NR	NR
	Kidney disease	1.9 <sup>§</sup> (15)	2.1 <sup>§</sup> (17)	NR	NR	6.1 (9)	4.9 (10)
	Valvular disease (moderate/severe)	24.6 (197)	21.5 (172)	2.4 (2)	2.4 (2)	NR	NR
	History of prior MI	1.6 (13)	2.1 (17)	NR	NR	17 (25)	15.1 (31)
	History of prior stroke/TIA	2.9 (23)	4.1 (33)	NR	NR	NR	NR
	Diabetes	18.7 (150)	15.2 (122)	NR	NR	19.8 (29)	20.0 (41)
	Structural heart disease	3.0 (24)	1.8 (15)	71.8 (61)	71.8 (61)	NR	NR
COPD	10.2 (82)	11.4 (91)	NR	NR	NR	NR	
<b>Study Characteristics</b>	Followup period (months)	Mean 27	Mean 27	mean 15 ± 7	mean 16 ± 7	mean: 69 ± 27	mean: 69 ± 27
	Completed followup, % (n)	NR	NR	NR	NR	97.9 (143)	83.4 (171)
	Blanking period	NR	NR	8 weeks	NR	NR	NR
	Use of AADs in RFA group	Yes, various	---	None unless recurrence developed	---	Yes, various	---

AAD = antiarrhythmic drug; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; RFA = radiofrequency ablation; SD = standard deviation.

\*Two ablation groups were reported in this paper. Only the group that underwent pulmonary vein antrum isolation was included; the atrioventricular junction ablation group was excluded from our analysis per our prespecified exclusion criteria.

†Reported as nonparoxysmal AF: ablation (73.2%, n=107); medical (75.1%; n=154).

## Detailed Synthesis

### Primary Outcomes

#### Mortality >30 days

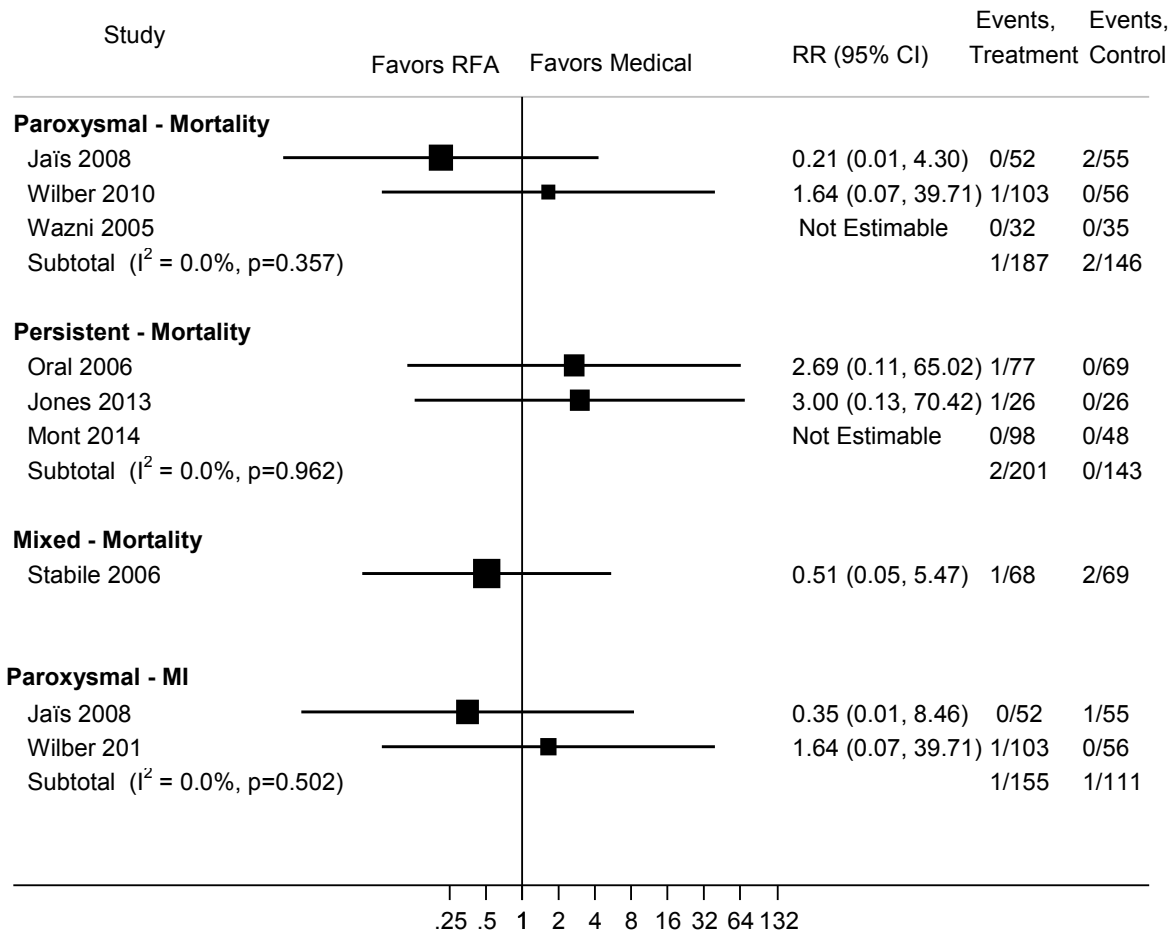
Seven RCTs comparing RFA with medical therapy reported all-cause mortality past the 30 day periprocedural time up to 12 (or 13)<sup>45</sup> months or for which timing of mortality was not reported.<sup>38, 39, 41, 43, 45-47</sup> RFA was used as a first-line treatment in only one of these trials.<sup>46</sup> Of the seven RCTs, three fair-quality trials evaluated patients with paroxysmal AF,<sup>38, 46, 47</sup> three fair-quality trials evaluated patients with persistent AF,<sup>39, 41, 43</sup> and one good-quality trial included both paroxysmal and persistent AF patients.<sup>45</sup> Two fair-quality trials evaluated all-cause mortality up to 24 months past the 30 day periprocedural period in patients with paroxysmal AF.<sup>35, 42</sup> The majority of patients across studies were male with mean ages ranging from 51 to 64 years old. Study sizes were likely insufficient to effectively determine the effect of AF ablation on mortality or detect statistical differences between treatment groups.

Overall, all-cause mortality within 12 months was rare across the seven trials, ranging from 0 to 3.8 percent in RFA groups and 0 to 2.9 percent in groups receiving medical therapy (Figure 3). Data for this outcome were sparse and were not pooled given inconsistency across studies with regard to which treatment may be favored for specific AF types and across AF types. Crossover from medical therapy to RFA was substantial in most studies, ranging from 37 to 88 percent across studies.

All-cause mortality within 24 months was also rare across two studies of patients with paroxysmal AF (Table 8). One trial reported no mortality in either treatment group,<sup>42</sup> the other reported two deaths (1.4%) in the RFA group and four (2.9%) in the medical treatment group.<sup>35</sup>

Of the six included observational studies, three reported all-cause mortality (Table 9). One fair-quality study, conducted in a Medicare-relevant population (age  $\geq 75$  years) of persistent AF patients, reported similar low rates of all-cause mortality in both groups at a mean followup of 60 months, all of which were cardiovascular-related.<sup>48</sup> The remaining two studies included patients with a mixture of AF types. In one poor-quality study with a mean followup of 16 months, no patient died in the ablation arm and one patient (1.2%) in the medical therapy arm died from a stroke (difference not statistically significant).<sup>51</sup> In the second study, conducted in a Medicare-relevant population (mean age 67 years), three patients (2.1%) in the ablation group and 34 patients (16.5%) in the medical therapy group had died at the end of 69 months of follow up (HR 0.20; 95% CI 0.06 to 0.69;  $p=0.01$ ).<sup>53</sup> All deaths in the ablation group were cardiovascular-related. Although this last study provided evidence of a survival benefit in the ablation arm, the limitations of this poor-quality study included lack of information about blinding of outcome assessor's regarding intervention, lack of full reporting of prespecified outcomes, and no reporting on attrition rates.

**Figure 3. Profile likelihood model meta-analysis of all-cause mortality and myocardial infarction within 12 months of followup in RCTs comparing RFA with medical therapy**



MI = myocardial infarction; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation; RR = relative risk.  
 \*For Stabile 2006, followup time included a 1-month blanking period, for a total of 13 months followup.

### Cardiovascular Mortality >30 Days

Cardiovascular mortality past the 30 day periprocedural time through 12 months followup was reported in five RCTs, three of which included only paroxysmal AF patients<sup>38, 46, 47</sup> and two of which included only persistent AF patients.<sup>39, 41</sup> One trial of persistent AF patients included only heart failure patients with an ejection fraction less than 50 percent.<sup>39</sup> Two studies reported cardiovascular mortality up to 24 months past the 30 day periprocedural time.<sup>35, 42</sup> All trials were rated as fair quality. Study sizes were likely insufficient to effectively determine risk of cardiovascular mortality or detect statistical differences between treatment groups.

Cardiovascular mortality was rare at both 12-month and 24-month time frames (Table 8). Across three RCTs of paroxysmal AF patients, one event in each treatment group was reported within 12 months of followup. Both deaths were from myocardial infarction and not attributed to

treatment.<sup>38, 46, 47</sup> Across two trials of paroxysmal patients with 24 months of followup, one cardiovascular death occurred in the medical therapy group and none in the RFA group.

In individuals with persistent AF, one cardiovascular death was reported in the RFA group across two RCTs with followup to 12 months.<sup>39, 41</sup> This death occurred in the study that was restricted to patients with heart failure.<sup>39</sup>

Two observational studies, both conducted in Medicare-relevant populations (age  $\geq 65$  years), assessed cardiovascular mortality greater than 30 days from treatment (Table 9). In one fair-quality study of patients with persistent AF, two patients (1.3%) in the RFA group and five patients (1.9%) in the medical therapy group died from cardiovascular causes during a mean followup of 60 months ( $p=0.714$ ).<sup>48</sup> In the second, poor-quality study of patients with mixed AF, after 69 months of followup, three patients (2.1%) in the RFA arm and 20 patients (9.8%) in the medical therapy arm had died from cardiovascular causes.<sup>53</sup>

### Stroke >30 Days

Four fair-quality trials comparing RFA with medical therapy reported on stroke past the 30 day periprocedural time, three of which had 12 months of followup<sup>36, 41, 46</sup> and one of which had 24 months of followup.<sup>42</sup> Of the trials reporting stroke up to 12 months, one was in patients with paroxysmal AF,<sup>46</sup> one in patients with persistent AF,<sup>41</sup> and the third trial did not separate data by AF type, resulting in a population that combined patients with paroxysmal and persistent AF (this trial included only patients with diabetes).<sup>36</sup> None of the trials provided criteria or definitions for stroke diagnosis although all distinguished it from TIA. Anticoagulation was used in all patients receiving RFA and its use was variably reported for the medical groups. Duration of anticoagulation use varied across studies. In three of the studies,<sup>41, 42, 46</sup> it was not clear that anticoagulation prior to ablation was adequate, but it appeared to be adequate during the procedure. Anticoagulation was discontinued in the absence of AF recurrence at 3 months (and no pulmonary vein narrowing  $\geq 50\%$ )<sup>46</sup> or 6 months (and no major risk factors),<sup>36</sup> a practice that is not supported by strong evidence.

No strokes were observed in any of the three trials with followup to 12 months or in the trial which followed patients to 24 months (Table 8). Study sizes were likely insufficient to effectively determine effect of AF ablation on stroke.

Four of the observational studies assessed stroke greater than 30 days from treatment (Table 9). Three studies were of patients with mixed AF. No strokes occurred in the ablation group in two poor-quality studies compared with four (4.7%)<sup>51</sup> and three (1.5%)<sup>53</sup> strokes in the medical therapy groups, during followup periods of 16 and 69 months, respectively. The latter study was comprised of patients with a mean age of 67 years (i.e., a Medicare-relevant population). In the third fair-quality administrative database study, patients in the ablation arm suffered any stroke/TIA at an annualized rate of 3.4 percent while those who underwent medical therapy had a rate of 5.5 percent.<sup>50</sup> Unadjusted hazard ratio for stroke/TIA of ablation versus medical therapy was 0.62 (95% CI 0.44 to 0.86;  $p=0.005$ ). The multivariable Cox proportional hazards model also demonstrated an association between age  $\geq 65$  years and stroke/TIA after adjustment for other variables. A fourth, fair-quality study conducted in a Medicare-relevant population (age  $\geq 75$  years) of persistent AF patients, reported the incidence of stroke or TIA; two patients in the ablation arm and five patients in the medical therapy group suffered an event after a mean of 60 months (1.3% vs. 1.9%, respectively;  $p=0.714$ ).<sup>48</sup> The adequacy of anticoagulation before and after ablation in two studies cannot be assessed based on authors' descriptions,<sup>51, 53</sup> but appeared to be adequate in the two studies that reported on the combined outcome of stroke or TIA.<sup>48, 50</sup>

### **Myocardial Infarction >30 Days**

Three trials reported on MI past the 30 day periprocedural time, two with followup to 12 months<sup>38,47</sup> and one with followup to 24 months.<sup>35</sup> RFA was a second-line treatment in both trials. None of the trials provided diagnostic criteria used for determining MI.

All trials were in patients with paroxysmal AF. A total of two patients experienced fatal MI, one in each treatment group, up to 12 months of followup across two studies (Figure 3, above; Table 8).<sup>38,47</sup> One fatal MI in the medical treatment group was reported in the one study with 24-month followup (Table 8).<sup>35</sup>

Two observational studies, both conducted in Medicare-relevant populations (age  $\geq 65$  years), assessed MIs occurring greater than 30 days from treatment (Table 9). In one fair-quality study of persistent AF,<sup>48</sup> no patients in the RFA arm and one patient (0.4%) in the medical therapy arm suffered an MI during a mean followup of 60 months ( $p=1.0$ ) while in the second poor-quality study (in a mixed AF population),<sup>53</sup> two patients in the RFA arm (1.4%) compared with no patients in the medical therapy arm had a MI after 69 months of followup.

### **Transient Ischemic Attack >30 Days**

Six trials comparing RFA with medical therapy reported frequency of TIA after the 30 day periprocedural period. All but one study was considered to be of fair quality. For followup to 12 months, there was one trial in patients with paroxysmal AF,<sup>46</sup> one trial in patients with persistent AF,<sup>41</sup> and two trials that enrolled patients with either paroxysmal or persistent AF.<sup>36,45</sup> One trial included a 1-month blanking period, for a total followup period of 13 months.<sup>45</sup> One of these trials consisted only of patients with diabetes.<sup>36</sup> Two trials in patients with paroxysmal AF reported on TIA at followup longer than 12 months.<sup>35,83</sup> None of the studies provided definitions or details regarding evaluation or diagnosis for TIA.

Across all RCTs, TIA was rare with a frequency ranging from 0.7 to 1.4 percent, regardless of treatment (Table 8).

Of the six included observational studies, none specifically assessed TIA greater than 30 days from treatment.

### **Congestive Heart Failure**

Only one fair-quality trial comparing RFA with medical therapy reported on development of CHF.<sup>35</sup> None of the patients receiving RFA developed CHF compared with two patients (1.4%) in the medical group by 24 months of followup (Table 8).

Two comparative observational studies, both in Medicare-relevant populations (age  $\geq 65$  years) assessed CHF. In one fair-quality study in persistent AF patients, no patient in the RFA group compared with three patients in the medical group suffered heart failure during a mean followup of 60 months ( $p=0.297$ ),<sup>48</sup> while in the second poor-quality study (in a mixed AF population)<sup>53</sup> one (0.7%) RFA patient compared with 20 (9.8%) medical therapy patients suffered heart failure (Table 9). A third fair-quality observational administrative database study in the general population reported a lower annualized rate of hospitalization for heart failure (1.5%) following RFA versus the medical treatment arm (2.2%). The Cox regression unadjusted hazard ratio for heart failure hospitalization in the ablation versus medical treatment cohorts was 0.69 (95% CI 0.42 to 1.15,  $p=0.158$ ). In multivariable models, there was no association between age  $\geq 65$  years and rates of hospitalization for heart failure at 27 months.

### **Progression from Paroxysmal to Persistent Atrial Fibrillation**

One small, fair-quality trial, in which RFA was used as a second-line therapy, followed patients up to 48 months and reported the progression from paroxysmal AF to persistent AF.<sup>83</sup> Significantly more patients originally randomized to the medical therapy group had progression to persistent AF compared with those receiving RFA (19.2% vs. 1.0%; RR 0.09, 95% CI 0.01 to 0.61,  $p < 0.0001$ ) (Table 8). Crossover from medical therapy to RFA in this study was 42 percent and it is not clear how this may have been considered in determining progression.

Of the six included observational studies, none assessed progression from paroxysmal to persistent AF.

**Table 8. Primary efficacy outcomes for RCTs comparing RFA with medical therapy\***

Outcome <sup>†</sup>	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)
<b>Mortality (all-cause) &gt;30 days</b>	Paroxysmal (1 <sup>st</sup> line)	Morillo 2014 <sup>42</sup>	24 months	0% (0/66)	0% (0/61)
		Cosedis Nielsen 2012 <sup>35</sup>	24 months	1.4% (2/140) <sup>‡</sup>	2.9% (4/141) <sup>‡</sup>
<b>Mortality (cardiovascular) &gt;30 days</b>	Paroxysmal (1 <sup>st</sup> line)	Wazni 2005 <sup>46</sup>	12 months	0% (0/32)	0% (0/35)
		Morillo 2014 <sup>42</sup>	24 months	0% (0/66)	0% (0/61)
		Cosedis Nielsen 2012 <sup>35</sup>	24 months	0% (0/138)	0.7% (1/138) <sup>‡</sup>
		Jais 2008 <sup>38</sup>	12 months	0% (0/52)	1.8% (1/55) <sup>§</sup>
	Paroxysmal (2 <sup>nd</sup> line)	Wilber 2010 <sup>47</sup>	12 months	1.0% (1/103) <sup>**</sup>	0% (0/56)
		Jones 2013 <sup>39</sup> (Heart failure)	12 months	3.8% (1/26) <sup>††</sup>	0% (0/26)
Persistent (2 <sup>nd</sup> line)	Mont 2014 <sup>41</sup>	12 months	0% (0/98)	0% (0/48)	
<b>Stroke (any type) &gt;30 days</b>	Paroxysmal (1 <sup>st</sup> line)	Wazni 2005 <sup>46</sup>	12 months	0% (0/32)	0% (0/35)
		Morillo 2014 <sup>42</sup>	24 months	0% (0/66)	0% (0/61)
	Persistent (2 <sup>nd</sup> line)	Mont 2014 <sup>41</sup>	12 months	0% (0/98)	0% (0/48)
	Mixed (2 <sup>nd</sup> line)	Forleo 2009 (Diabetes)	12 months	0% (0/35)	0% (0/35)
<b>Myocardial infarction &gt;30 days</b>	Paroxysmal (1 <sup>st</sup> line)	Cosedis Nielsen 2012 <sup>35</sup>	24 months	0% (0/146)	0.7% (1/148)
<b>Transient ischemic attack &gt;30 days</b>	Paroxysmal (1 <sup>st</sup> line)	Wazni 2005 <sup>46</sup>	12 months	0% (0/32)	0% (0/35)
		Cosedis Nielsen 2012 <sup>35</sup>	24 months	0.7% (1/146)	0.7% (1/148)
		Pappone 2011 <sup>83</sup>	48 months	0% (0/99)	0% (0/99)
	Paroxysmal (2 <sup>nd</sup> line)	Mont 2014 <sup>41</sup>	12 months	0% (0/98)	0% (0/48)
		Forleo 2009 <sup>36</sup> (Diabetes)	12 months	0% (0/35)	0% (0/35)
	Mixed (2 <sup>nd</sup> line)	Stabile 2006 <sup>45</sup>	12 months <sup>**</sup>	0% (0/68)	1.4% (1/69)
<b>Intracranial hemorrhage</b>	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line)	Hunter 2014 <sup>37</sup>	6 months	0% (0/26)	4.2% (1/24)
<b>Congestive heart failure</b>	Paroxysmal (1 <sup>st</sup> line)	Cosedis Nielsen 2012 <sup>35</sup>	24 months	0% (0/146)	1.4% (2/148)
<b>Progression from paroxysmal to persistent AF</b>	Paroxysmal (2 <sup>nd</sup> line)	Pappone 2011 <sup>83</sup>	48 months	1.0% (1/99)	19.2% (19/99)

AF = atrial fibrillation; CI = confidence interval; RCT = randomized controlled trial; RFA = radiofrequency ablation; RR = risk ratio.

\*A meta-analysis was performed on the outcomes all-cause mortality >30 days and MI >30 days in RCTs with followup of ≤12 months (see Figure 3).

†Mortality, stroke, transient ischemic attack, and congestive heart failure all had to occur at a time point >30 days (or timing NR) to be considered an efficacy outcome.

‡Mortality (all-cause): In the ablation group, 138 patients completed 24 month followup – the 2 patients with all-cause death (1 prostate cancer, 1 sudden death, cause unknown) were included in the loss-to-followup and have been added back into the denominator; in the medical therapy group, 137 patients completed 24 month followup – the 4 patients with all-cause death (2 lung cancer, 1 MI, 1 sudden death, cause unknown) were included in the loss-to-followup and have been added back into the denominator. Mortality (cardiovascular): 137 patients completed 24 month followup; the 1 patient with cardiovascular death (due to MI) was included in loss-to-follow and has been added back into the denominator for this outcome (also included under the outcome MI >30 days).

§MI deemed not related to AADs. Also included under the outcome MI >30 days.

\*\*284 days postprocedure; acute MI deemed unrelated to ablation procedure. Also included under the outcome MI >30 days.

††Patient with chronic lung disease, dilated cardiomyopathy, and a biventricular pacemaker.

‡‡Followup time included a 1-month blanking period, for a total of 13 months followup.



**Table 9. Primary effectiveness outcomes for comparative observational studies comparing RFA with medical therapy**

Outcome*	AF Type†	Study‡	Followup	RFA % (n/N)	Medical Therapy % (n/N)	p-value
<b>Mortality (all-cause) &gt;30 days</b>	Persistent	Blandino 2013 <sup>48</sup>	Mean 60 months	1.3% (2/153) <sup>§</sup>	1.9% (5/259) <sup>§</sup>	0.71
	Mixed	Sonne 2009 <sup>53</sup>	Mean 69 months	2.1% (3/146) <sup>§</sup>	16.5% (34/205)	0.01
		Rossillo 2008 <sup>51</sup>	Mean 16 months	0% (0/85)	1.2% (1/85) <sup>**</sup>	NR
<b>Mortality (cardiovascular) &gt;30 days</b>	Persistent	Blandino 2013 <sup>48</sup>	Mean 60 months	1.3% (2/153)	1.9% (5/259)	0.71
	Mixed	Sonne 2009 <sup>53</sup>	Mean 69 months	2.1% (3/146)	9.8% (20/205)	0.003 <sup>††</sup>
<b>Stroke (any type) &gt;30 days</b>	Mixed	Sonne 2009 <sup>53</sup>	Mean 69 months	0% (0/146)	1.5% (3/205)	NR
		Rossillo 2008 <sup>51</sup>	Mean 16 months	0% (0/85)	4.7% (4/85)	NR
<b>Stroke/TIA &gt;30 days</b>	Persistent	Blandino 2013 <sup>48</sup>	Mean 60 months	1.3% (2/153)	1.9% (5/259)	0.71
	Mixed	Reynolds 2012 <sup>50</sup>	Mean 27 months	Annualized rate <sup>‡‡</sup> : 3.4% Kaplan-Meier estimate <sup>§§</sup> : 8.3%	Annualized rate <sup>‡‡</sup> : 5.5% Kaplan-Meier estimate <sup>§§</sup> : 14.1%	0.005 HR: 0.62 95% CI (0.44-0.86) <sup>***</sup>
<b>Myocardial infarction &gt;30 days</b>	Persistent	Blandino 2013 <sup>48</sup>	Mean 60 months	0% (0/153)	0.4% (1/259)	1.0
	Mixed	Sonne 2009 <sup>53</sup>	Mean 69 months	1.4% (2/146)	0% (0/205)	NR
<b>Thromboembolic events &gt;30 days</b>	Paroxysmal	Sang 2013 <sup>52</sup>	12 months	0% (0/82)	3.6% (3/84)	NR
<b>Peripheral embolism &gt;30 days</b>	Persistent	Blandino 2013 <sup>48</sup>	Mean 60 months	0.6% (1/153)	0.4% (1/259)	1.0
<b>Congestive heart failure</b>	Persistent	Blandino 2013 <sup>48</sup>	Mean 60 months	0% (0/153)	1.2% (3/259)	0.30
	Mixed	Sonne 2009 <sup>53</sup>	Mean 69 months	0.7% (1/146)	9.8% (20/205)	0.002 <sup>††</sup>
<b>Hospitalization for heart failure</b>	Mixed	Reynolds 2012 <sup>50</sup>	Mean 27 months	Annualized rate <sup>‡‡</sup> : 1.5% Kaplan-Meier estimate <sup>§§</sup> : 4.5%	Annualized rate <sup>‡‡</sup> : 2.2% Kaplan-Meier estimate <sup>§§</sup> : 5.5%	0.155 HR: 0.69 95% CI (0.42-1.15) <sup>***</sup>

AF = atrial fibrillation; NA = not applicable; NR = not reported; RFA = radiofrequency ablation; TIA = transient ischemic attack.

\*Mortality, stroke, TIA, MI, and embolic events all had to occur at a time point >30 days (or timing NR) to be considered an effectiveness outcome. Stroke, TIA, thromboembolic events and peripheral embolism were not defined further in their respective studies.

†All treatments were a second-line therapy for AF.

‡Blandino 2013 and Sonne 2009 represent the Medicare population (age ≥75 years and mean age 67 years, respectively); all other studies represent the general adult population. Also regarding Sonne 2009, only results from the group that underwent pulmonary vein antrum isolation are reported (the authors also included a group who underwent atrioventricular junction ablation which is an intervention excluded from our report).

§All cardiovascular-related.

\*\*Cause of death was stroke. This patient is also counted under stroke (any type).

††Based on t-test calculated by the EPC.

‡‡Annualized rate calculated as percentage (number of patients in the cohort who had an event within 3 years/average length of followup in the cohort). TIA indicates transient ischemic attack.

§§Product-limit estimates of the 3-year event rates (percentages) and P values of the nonparametric log-rank test comparing survival functions of the 2 cohorts.

\*\*\*Unadjusted Cox regression estimate of the hazard ratio for models with cohort as the only predictor variable and the Wald chi squared p value for significance of cohort.

## Health-Related Quality of Life

A variety of HRQOL measures were used at varied time frames across trials, which, combined with clinical heterogeneity across studies, limited this review's ability to pool data or draw firm conclusions regarding the HRQOL outcome. Further, trial sizes may have been insufficient to detect significant differences between treatments for most measures. The SF-36 was the most frequently used questionnaire, with eight trials reporting outcomes for at least one subscale. The MLHFQ was the second most commonly used HRQOL measure, with three trials in people with persistent AF and CHF reporting.

**SF-36.** Eight fair-quality trials comparing RFA with medical therapy in patients with paroxysmal AF reported SF-36 results but did so in a variety of ways across different time frames which limited the ability to pool results (Tables 10, 11, 12, and 14).<sup>35, 36, 38, 46, 47, 83</sup> 40 Five reported both the MCS and PCS.<sup>35, 38, 40, 47, 83</sup> Individual SF-36 domains were reported by five trials, including two of those that reported MCS and PCS scores.<sup>36-38, 46, 83</sup> Results are presented based on intention-to-treat analysis; however, substantial crossover from medical therapy to RFA in most studies (crossover frequency 37% to 88%) should be considered when interpreting these results.

Four of the five trials reporting the SF-36 MCS and PCS were in patients with paroxysmal AF;<sup>35, 38, 47, 83</sup> the fifth trial was in persistent AF patients with heart failure.<sup>40</sup> One trial in paroxysmal AF patients used RFA as a first line treatment and was the only trial to provide data on both short and long-term followup.<sup>35</sup>

One trial of paroxysmal AF patients reported that RFA patients saw greater improvements at 3 months in SF-36 MCS and PCS outcomes than did those who received medical therapy, however this time frame is likely too soon after the procedure (i.e., during post-procedure healing) to be an accurate reflection of quality of life.<sup>47</sup> Across the remaining three trials of paroxysmal AF patients, data were reported between 12 and 48 months. For the MCS, only one of three found statistically greater improvement following RFA versus medical therapy<sup>38</sup>; for the PCS, two of three reported significant results that favored RFA.<sup>35, 38</sup> The one trial of persistent AF patients with heart failure showed that quality of life tended to be better at 6 months following RFA than medical therapy, although the results were only statistically significant for the PCS (Table 10).<sup>40</sup>

Pooled analysis was possible across two fair-quality trials comparing RFA with medical therapy in patients with paroxysmal AF.<sup>35, 38</sup> These studies contained sufficient data on the SF-36 MCS and PCS at 12 months based on intention-to-treat analyses (Table 11). No statistical differences between treatment groups were observed for the SF-36 MCS at 12 months; this held true whether the analysis was done using the mean scores at followup or using the change from baseline scores. In terms of individual study results, neither study reported an effect based on change from baseline scores, but the smaller study<sup>38</sup> found a significant effect favoring RFA based on followup scores only. For PCS, RFA was favored over medical therapy when the pooled estimate was calculated using differences in mean followup scores (overall effect 2.85; 95% CI 0.93 to 4.82;  $I^2=0\%$ ), however when the analysis was based on the change from baseline the effect was no longer statistically meaningful (overall effect 2.88; 95% CI 0.18 to 5.25,  $I^2=32.89\%$ ). Individual study data suggested that quality of life based on SF-36 scores may be significantly better following RFA than medical therapy, although the smaller study<sup>38</sup> showed no treatment effect in one analysis. Because these results are only based on two studies, and because one trial employed catheter ablation as a first line therapy while the other used the treatment as a second line therapy, it is difficult to arrive at firm conclusions regarding this outcome. No

difference between treatments in baseline scores were seen in either study. Although the timing of cross-over for the two pooled studies is unclear, it appears that the average timing of cross over may have been around 6 months in both studies.

A followup report to the Wilber trial reported HRQOL outcomes at six and twelve months, but data were not analyzed based on intention to treat (the 65% [31/48] of AAD patients who crossed over and received ablation were excluded from the analysis).<sup>84</sup> Based on this analysis, authors reported that QOL outcomes were significantly better in those randomized to RFA than those who received only medical therapy at both six and twelve months.

Outcomes from additional SF-36 domains were reported in five trials,<sup>36-38, 46, 83</sup> though one of these trials did not provide any data-(Table 12).<sup>38</sup> Three trials reported on patients with paroxysmal AF. While one trial reported statistical differences favoring RFA were noted for most domains (physical functioning, role physical, bodily pain, general health, social functioning) at 6 months,<sup>46</sup> a second trial found no differences between treatments at 48 months for any domain.<sup>83</sup> A third trial reported statistically greater improvements following RFA vs. medical therapy for six of the eight domains, however no other information (i.e., which domains improved, timing of the evaluation, data) was provided.<sup>38</sup> One trial in diabetic patients with either type of AF reported statistical differences in mean change between groups favoring RFA for some domains (physical functioning, bodily pain, general health, social functioning, and role emotional).<sup>36</sup> One trial in persistent AF patients with concomitant CHF reported statistically significant improvement in four domains (physical functioning, role physical, bodily pain and vitality) at 6 months.<sup>37</sup> Across the four clinically heterogeneous trials that provided data at discrepant time frames, bodily pain was significantly better in the RFA groups in three of the four trials.<sup>36, 37, 46</sup> Two heterogeneous trials reported greater improvement in RFA patients in the role physical domain, and two reported improvement in the general health domain.

Three comparative observational studies reported SF-36 outcomes (Table 13).<sup>48, 52, 54</sup> Two studies were on paroxysmal patients. The fair-quality study of paroxysmal AF patients found that the SF-36 PCS and MCS scores increased significantly more 12 months following ablation compared with medical therapy).<sup>52</sup> A poor-quality study in these patients reported that the total SF-36 score increased in the ablation group after 12 months but not in the medical therapy group.<sup>54</sup> Authors do not report whether there was a significant difference between groups for total score or individual domain scores and there were significant differences between groups at baseline. A fair-quality study of elderly ( $\geq 75$  years) persistent AF patients showed statistically meaningful improvements in all SF-36 domain scores (except bodily pain) between groups over a mean followup period of 60 months; again substantial differences at baseline between groups for most domains were noted.<sup>48</sup> The limitations of these studies should be considered in interpreting these findings. Individual SF-36 domain scores for the comparative observational studies can be found in Table H3 of the Appendix.

**Minnesota Living with Heart Failure Questionnaire.** The MLHFQ was reported in three trials, all of which were in patients with persistent AF and concomitant heart failure (Table 14).<sup>37, 39, 40</sup>

All three trials evaluated patients at 6 months. Two of the trials reported statistically significant differences favoring RFA at 6 months (Hunter: 23.7 versus 47.0,  $p=0.001$ ; Jones: data not reported,  $p=0.02$ ),<sup>37, 39</sup> while the third trial tended to favor RFA, results did not reach statistical difference (change from baseline  $-5.7 \pm 19.7$  for RFA vs.  $-2.8 \pm 17.9$ ).<sup>40</sup> One trial reported that the significantly greater improvement seen 6 months after RFA versus medical therapy found a similar effect at 12 months (mean  $21 \pm 19$  for RFA vs.  $41 \pm 21$ ,  $p=0.02$ ).<sup>39</sup>

**Other quality-of-life measures.** A variety of other HRQOL measures were used at varied time frames across studies (Table 14). Again, small trial sizes and substantial crossover from medical therapy to RFA should be considered; these factors, along with the variety of measures used across studies make it difficult to draw firm conclusions.

In patients with paroxysmal AF, no differences between treatment groups in EQ-5D were observed at 12 months in one trial.<sup>42</sup> In patients with persistent AF (and heart failure), one trial found no differences between treatment groups in Kansas City Cardiomyopathy (KCCQ) scores,<sup>40</sup> while a difference favoring RFA in the New York Heart Association (NYHA) score at 6 months was seen in another.<sup>37</sup> An additional analysis of the Mont SARA trial reported and found that there were significant improvements at 12 months in the Atrial Fibrillation Quality of Life Questionnaire (AFQOL) scores in the RFA but not medical therapy group, however their methods don't allow for direct comparisons between treatment groups, precluding firm conclusions.<sup>41, 85</sup>

Two nonrandomized comparative studies, one fair- and the other poor-quality, assessed the Self-Rating Depression Scale (SDS) and the Self-Rating Anxiety Scale (SAS) at 12 months in patients with paroxysmal AF.<sup>52, 54</sup> Both studies reported a significant improvement compared with baseline in mean SDS and SAS scores following RFA (Table 13), although limitations in the way the outcomes limit the ability to draw conclusions.

There were insufficient data to formally compare HRQOL for those receiving RFA as a first-line versus second-line therapy, however no consistent patterns of improvement in QOL are seen across studies. For RFA as first-line treatment, two trials in those with paroxysmal AF employed the SF-36.<sup>35, 46</sup> At 6 months, one reported significant improvement in individual domains (physical function, role physical, bodily pain, general health and social function).<sup>46</sup> The other found that the PCS was significantly improved favoring RFA at 12 months, but not at 24 months and MCS was not significant at either time. Two other trials of RFA as a first-line treatment reported no difference in EQ5D assessments in those with paroxysmal AF<sup>42</sup> or in AF-QOL domains in those with persistent AF.<sup>41</sup> For RFA as a second-line treatment, SF-36 there were no significant differences in SF-36 domains or in MCS or PCS at 48 months in one trial of paroxysmal AF patients<sup>83</sup> and another in heart failure patients with persistent AF reported no difference at 6 months in MCS, but PCS favored RFA (Table 10).<sup>40</sup> Another trial reported that six of the eight SF-36 domains favored RFA but didn't provide data or information on measurement timing (Table 12).<sup>38</sup>

**Symptom improvement.** Across the two trials (both in paroxysmal AF) using the Symptom Checklist, one reported no difference between treatment groups at 3 months in the Frequency Scale or the Severity Scale,<sup>38</sup> while the other study reported a significant decrease in both scales in the RFA group compared with the medical group (Table 14).<sup>47</sup> At 12 months, there was no difference in the Frequency Scale but a difference favoring RFA in the Severity Scale in the only study reporting this length of followup.<sup>38</sup>

**Table 10. SF-36 MCS and PCS scores from RCTs comparing RFA with medical therapy\***

META-ANALYSIS – SF-36 (see Table 11)					
Outcome <sup>†</sup>	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>SF-36 MCS, mean ± SD (95% CI)</b> [score range 0 (worst) to 100 (best)]	Paroxysmal (1 <sup>st</sup> line), Cosedis Nielsen 2012 <sup>35</sup>	Baseline	45.2 ± 11.7 (n=146)	46.1 ± 11.2 (n=148)	0.50 <sup>‡</sup>
		12 months	50.8 ± 9.3 (n=146)	50.1 ± 8.5 (n=148)	0.70 <sup>‡</sup>
		24 months	51.1 ± 9.2 (n=146)	50.9 ± 8.0 (n=148)	0.93 <sup>§</sup>
	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	46.1 (n=53)	44.0 (n=59)	NS
		12 months	56.6 ± 7.8 (n=53)	51.9 ± 9.7 (n=59)	.01
	Paroxysmal (2 <sup>nd</sup> line), Wilber 2010 <sup>47</sup>	Baseline	44.5 (42.2–46.7) (n=97)	44.0 (40.7–47.3) (n=53)	0.79
		3 month change	+8.5 (5.9–11.1) (n=90)	+1.6 (–1.1 to 4.3) (n=39)	<0.001
	Paroxysmal (2 <sup>nd</sup> line), Pappone 2011 <sup>83</sup>	Baseline	43.7 ± 11 (n=99)	44.4 ± 10 (n=99)	0.64 <sup>‡</sup>
		48 months	52.9 ± 9 (n=99)	51.9 ± 9 (n=99)	0.44 <sup>‡</sup>
	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	40.7 ± 10.2 (n=20)	37.1 ± 14.0 (n=18)	0.37 <sup>‡</sup>
		6 month change	+0.4 ± 9.5 (n=20)	+5.9 ± 8.5 (n=18)	0.07

META-ANALYSIS – SF-36 (see Table 11)					
Outcome <sup>†</sup>	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>SF-36 PCS, mean ± SD (95% CI)</b> [score range 0 (worst) to 100 (best)]	Paroxysmal (1 <sup>st</sup> line), Cosedis Nielsen 2012 <sup>35</sup>	Baseline	44.3 ± 8.9 (n=146)	45.2 ± 8.9 (n=148)	0.39
		12 months	50.2 ± 8.5 (n=146)	47.5 ± 9.7 (n=148)	0.01 <sup>‡</sup>
		24 months	50.0 ± 8.8 (n=146)	47.9 ± 8.9 (n=148)	0.23 <sup>§</sup>
	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	44.8 (n=53)	43.0 (n=59)	NS
		12 months	52.0 ± 7.6 (n=53)	48.9 ± 7.2 (n=59)	.01
	Paroxysmal (2 <sup>nd</sup> line), Wilber 2010 <sup>47</sup>	Baseline	46.1 (44.4–47.8) (n=97)	47.6 (45.3–50.0) (n=53)	0.29
		3 month change	+6.9 (5.2–8.6) (n=90)	+0.4 (-1.7 to 2.6) (n=39)	<0.001
	11 Paroxysmal (2 <sup>nd</sup> line), Pappone 2011 <sup>83</sup>	Baseline	44.4 ± 9 (n=99)	45.7 ± 9 (n=99)	0.31 <sup>‡</sup>
		48 months	52.3 ± 9 (n=99)	52.6 ± 8 (n=99)	0.80 <sup>‡</sup>
	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	30.3 ± 9.2 (n=20)	30.3 ± 7.1 (n=18)	1.00 <sup>‡</sup>
		6 month change	+4.0 ± 9.5 (n=20)	-1.0 ± 4.4 (n=18)	0.04

AF = atrial fibrillation; CI = confidence interval; MCS = Mental Component Score; PCS = Physical Component Score; NR = not reported; NS = not significant; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation; SD = standard deviation; SF-36 = Short Form-36 Questionnaire.

\*A meta-analysis was performed for the SF-36 MCS and PCS from RCTs of paroxysmal AF patients with followup of ≤12 months (see Table 11).

<sup>†</sup>A higher score reflects better health status.

<sup>‡</sup>Based on t-test calculated by the EPC.

<sup>§</sup>p-value for the effect of group, time, and interaction between time and group from a repeated-measures analysis of variance as reported by authors.

**Table 11. Meta-analysis results for the SF-36 MCS and PCS at 12-months followup from RCTs comparing RFA with medical therapy in patients with paroxysmal AF**

Outcome	RFA (N)	Medical (N)	Effect Size (95% CI)*	Weight	Heterogeneity (I <sup>2</sup> )	
<b>SF-36 MCS</b>	Difference in change scores: Cosedis Nielsen 2012 <sup>35</sup> (1 <sup>st</sup> line)	146	148	1.60 (-0.78, 3.98)	71.72%	
	Difference in change scores: Jais 2008 <sup>38</sup> (2 <sup>nd</sup> line)	53	59	2.60 (-1.19, 6.39)	28.28%	
	<b>Pooled difference in change scores</b>	<b>199</b>	<b>207</b>	<b>1.88 (-0.47, 4.50)</b>	<b>100.00%</b>	<b>0.00%</b>
	<i>Difference in mean scores at followup: Cosedis Nielsen 2012<sup>35</sup> (1<sup>st</sup> line)</i>	146	148	0.70 (-1.34, 2.74)	60.91%	
	<i>Difference in mean scores at followup : Jais 2008<sup>38</sup> (2<sup>nd</sup> line)</i>	53	59	4.70 (1.45, 7.95)	39.09%	
	<b>Pooled difference in mean scores</b>	<b>199</b>	<b>207</b>	<b>2.26 (-2.12, 7.40)</b>	<b>100.00%</b>	<b>49.82%</b>
<b>SF-36 PCS</b>	<i>Difference in change scores : Cosedis Nielsen 2012<sup>35</sup> (1<sup>st</sup> line)</i>	146	148	3.60 (1.54, 5.66)	68.82%	
	<i>Difference in change scores : Jais 2008<sup>38</sup> (2<sup>nd</sup> line)</i>	53	59	1.30 (-1.76, 4.36)	31.18%	
	<b>Pooled difference in change scores</b>	<b>199</b>	<b>207</b>	<b>2.88 (-0.18, 5.25)</b>	<b>100.00%</b>	<b>32.89%</b>
	<i>Difference in mean scores at followup : Cosedis Nielsen 2012<sup>35</sup> (1<sup>st</sup> line)</i>	146	148	2.70 (0.62, 4.78)	63.52%	
	<i>Difference in mean scores at followup : Jais 2008<sup>38</sup> (2<sup>nd</sup> line)</i>	53	59	3.10 (0.35, 5.85)	36.48%	
	<b>Pooled difference in mean scores</b>	<b>199</b>	<b>207</b>	<b>2.85 (0.93, 4.82)</b>	<b>100.00%</b>	<b>0.00%</b>

AF = atrial fibrillation; CI = confidence interval; MCS = Mental Component Score; PCS = Physical Component Score; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation; SF-36 = Short-Form 36 questionnaire.

\*Profiled Likelihood method.

**Table 12. Individual SF-36 domain scores from RCTs comparing RFA with medical therapy**

<b>SF-36 Domain</b>	<b>Wazni 2005 (N=67)<sup>46</sup></b> Paroxysmal AF First line 6 months RFA vs. Med; p-value (means)	<b>Pappone 2011 (n=198)<sup>83</sup></b> Paroxysmal Second line 48 months RFA vs. Med; p-value (means)	<b>Forleo 2009 (n=70)<sup>36</sup></b> Mixed population Diabetic patients Second line 12 months RFA vs. Med; p-value (difference in mean change between groups)	<b>Hunter 2014 (n=50)<sup>37</sup></b> Persistent AF Heart failure patients First/second line 6 months RFA vs. Med; p-value (score reported as %)
Physical Functioning	97 vs. 75; p=0.001	85 vs. 82; p=0.122 <sup>†</sup>	8.4 <sup>‡</sup> ; p<0.05	71% vs. 49.1%; p=0.007
Role Physical	71 vs. 53; p=0.047	82 vs. 80; p=0.333 <sup>†</sup>	NR; NS	67.5% vs. 42.4%; p=0.004
Bodily Pain	97 vs. 90; p=0.004	80 vs. 77; p=0.271 <sup>†</sup>	5.9 <sup>‡</sup> ; p<0.05	78.8% vs. 57.1%; p=0.005
General Health	NR <sup>†</sup> vs. 68; p<0.001	79 vs. 77; p=0.365 <sup>†</sup>	8.9 <sup>‡</sup> ; p<0.05	NR; NS
Vitality	65 vs. 60; p=0.21	71 vs. 68; p=0.339 <sup>†</sup>	NR; NS	54.3% vs. 36.4%; p=0.009
Social Functioning	93 vs. 82; p=0.004	87 vs. 86; p=0.616 <sup>†</sup>	7.7 <sup>‡</sup> ; p<0.05	NR; NS
Role Emotional	76 vs. 75; p=0.90	86 vs. 84; p=0.448 <sup>†</sup>	6.8 <sup>‡</sup> ; p<0.05	NR; NS
Mental Health	65 vs. 68; p=0.62	81 vs. 78; p=0.216 <sup>†</sup>	NR; NS	NR; NS

AF = atrial fibrillation; Med = medical therapy; NR = not reported; NS = not statistically significant; RCT = randomized controlled trial; RFA = radiofrequency ablation; SF-36 = Short Form 36 Questionnaire.

\*Authors report this value as  $9 \pm 1$ ; however, this appears to be a typo in the article and the correct value cannot be ascertained. The authors report that the improvement in quality of life of patients in the ablation group was significantly better than the improvement in quality of life in the medical group.

<sup>†</sup>Based on t-test calculated by EPC (authors did not report p-values).

<sup>‡</sup>Difference in mean change of quality of life scores between groups. Favored RFA.



**Table 13. Quality of life outcomes for comparative observational studies comparing RFA with medical therapy**

Outcome	AF Type* and Study	Followup	RFA	Medical Therapy	p-value
<b>SF-36 MCS</b> [score range 0 (worst) to 100 (best)]	Paroxysmal, Sang 2013 <sup>52</sup>	Baseline	42.2 ± 7.2 (n=82)	43.2 ± 7.2 (n=84)	0.36
		12 months	54.6 (n=82)	43.9 (n=84)	<0.001
<b>SF-36 PCS</b> [score range 0 (worst) to 100 (best)]	Paroxysmal, Sang 2013 <sup>52</sup>	Baseline	42.6 ± 6.4 (n=82)	43.0 ± 6.2 (n=84)	.68
		12 months	52.9 (n=82)	43.4 (n=84)	<0.001
<b>Total SF-36 Score</b>	Paroxysmal, Yu 2012 <sup>54</sup>	Baseline	565.29 ± 143.37 (n=97)	525.24 ± 143.60 (n=102)	NR
		12 months	606.84 ± 102.84 (n=97)	545.25 ± 103.68 (n=102)	NR
<b>Zung Self-Rating Anxiety Scale</b> [score range 20 (best) to 80 (worst)]	Paroxysmal, Sang 2013 <sup>52</sup>	Baseline	48.6 ± 11.1 (n=82)	47.7 ± 10.3 (n=84)	.59
		12 months	NR (n=84)	NR (n=84)	<0.001 <sup>‡</sup>
	Paroxysmal, Yu 2012 <sup>54</sup>	Baseline	41.69 ± 8.32 <sup>§</sup> (n=97)	44.88 ± 6.98 <sup>§</sup> (n=102)	NR
		12 months	37.66 ± 4.82 <sup>§</sup> (n=97)	43.89 ± 5.64 <sup>§</sup> (n=102)	<0.001
<b>Zung Self-Rating Depression Scale</b> [score range 20 (best) to 80 (worst)]	Paroxysmal, Sang 2013 <sup>52</sup>	Baseline	49.4 ± 10.6 (n=82)	48.7 ± 10.8 (n=84)	.71
		12 months	NR (n=84)	NR (n=84)	<0.001 <sup>‡</sup>
	Paroxysmal, Yu 2012 <sup>54</sup>	Baseline	45.01 ± 9.71 <sup>§</sup> (n=97)	50.18 ± 9.07 <sup>§</sup> (n=102)	NR
		12 months	40.05 ± 8.56 <sup>§</sup> (n=97)	49.63 ± 9.12 <sup>§</sup> (n=102)	<0.001

AF = atrial fibrillation; MCS = Mental Component Score; NR = not reported; PCS = Physical Component Score; RFA = radiofrequency catheter ablation; SF-36: Short-Form-36.

\*All treatments were a second-line therapy for AF.

†Blandino et al. 2013 is a Medicare population (age ≥75 years). All other studies represent the general adult population.

‡12 months after ablation, mean SAS and SDS scores were significantly decreased compared with baseline scores in the ablation but not the medical group; catheter ablation achieved a better intervention effect than AAD therapy (F = 35.60, p<0.001 for SAS; F = 31.56, p<0.001 for SDS).

§Normalized scores (total score multiplied by 1.25).

**Table 14. Other health-related quality of life and symptom checklist outcomes from RCTs comparing RFA with medical therapy**

<b>Outcome*</b>	<b>AF Type (1<sup>st</sup>/2<sup>nd</sup> line therapy) and Study</b>	<b>Followup</b>	<b>RFA</b>	<b>Medical Therapy</b>	<b>p-value</b>
<b>MLHFQ, mean ± SD (95% CI)</b> [Score range: 0 (best) to 105 (worst)]	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Jones <sup>39</sup> (heart failure)	Baseline	42 ± 23 (n=26)	49 ± 21 (n=26)	0.23
		3 months	NR (n=26)	NR (n=26)	0.20
		6 months	NR (n=26)	NR (n=26)	0.02
		12 months	21 ± 19 (n=26)	41 ± 21 (n=26)	0.02
	Persistent (2nd line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	55.8 ± 19.8 (n=22)	59.2 ± 22.4 (n=19)	NR
		6 month change	-5.7 ± 19.7 (n=22)	-2.8 ± 17.9 (n=19)	0.65
	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Hunter 2014 <sup>37</sup> (heart failure)	Baseline	42 <sup>‡</sup> (n=26)	47 <sup>‡</sup> (n=24)	NR
		6 months	23.7 (14.6 to 32.8) (n=25)	47.0 (36.5 to 57.6) (n=23)	0.001
		12 months	26.5 (16.9 to 36.2) (n=25)	NR	NA
<b>AF-QOL Global Score, † mean</b> [Score range: 0 (worst) to 100 (best)]	Persistent (1 <sup>st</sup> line), Mont 2014 <sup>41</sup>	Baseline	42.0 (n=98)	49.3 (n=48)	NR
		6 months	53.7 (n=98)	48.2 (n=48)	0.16
		12 months	56.8 (n=98)	53.0 (n=48)	0.41
<b>AF-QOL Psychological Domain, † mean</b> [Score range: 0 (worst) to 100 (best)]	Persistent (1 <sup>st</sup> line), Mont 2014 <sup>41</sup>	Baseline	34.8 (n=98)	45.7 (n=48)	NR
		6 months	51.8 (n=98)	44.2 (n=48)	0.08
		12 months	54.8 (n=98)	48.9 (n=48)	0.25
<b>AF-QOL Physical Domain, † mean</b> [Score range: 0 (worst) to 100 (best)]	Persistent (1 <sup>st</sup> line), Mont 2014 <sup>41</sup>	Baseline	44.1 (n=98)	48.7 (n=48)	NR
		6 months	54.1 (n=98)	49.7 (n=48)	0.34
		12 months	56.2 (n=98)	55.6 (n=48)	0.91

Outcome*	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>AF-QOL Sexual Domain, † mean</b> [Score range: 0 (worst) to 100 (best)]	Persistent (1 <sup>st</sup> line), Mont 2014 <sup>41</sup>	Baseline	53.9 (n=98)	60.8 (n=48)	NR
		6 months	57.0 (n=98)	51.9 (n=48)	0.34
		12 months	63.7 (n=98)	55.4 (n=48)	0.12
<b>EQ5D Tariff Score, median (IQR)</b> [Score range: 0 (death) to 1 (optimal health)]	Paroxysmal (1 <sup>st</sup> line), Morillo 2014 <sup>42</sup>	Baseline	0.86 (0.82–1) (n=66)	0.84 (0.83–1) (n=61)	>0.99
		12 months	1 (0.84–1) (n=66)	1 (0.83–1) (n=61)	0.25
<b>EQ5D Anxiety/Depression (%)</b> [Score range: 0 (death) to 1 (optimal health)]	Paroxysmal (1 <sup>st</sup> line), Morillo 2014 <sup>42</sup>	Baseline	31.8% (n=66)	26.2% (n=61)	0.70
		12 months	13.6% (n=66)	23% (n=61)	0.25
<b>EQ5D VAS, median (IQR)</b> [Score range: 0 (worst) to 100 (best)]	Paroxysmal (1 <sup>st</sup> line), Morillo 2014 <sup>42</sup>	Baseline	75 (70–83) (n=66)	80 (70–85) (n=61)	0.53
		12 months	85 (85–90) (n=66)	80 (75–90) (n=61)	0.26
<b>KCCQ, mean ± SD</b> [Score range: 0 (worst) to 100 (best)]	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	42.1 ± 16.5 (n=22)	37.1 ± 19.5 (n=19)	NR
		6 month change	+7.1 ± 21.1 (n=22)	+5.6 ± 14.0 (n=19)	0.81
<b>NYHA Score, mean (95% CI)</b> [Score range: 1 (best) to 4 (worst)]	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Hunter 2014 <sup>37</sup> (heart failure)	Baseline	2.6 <sup>‡</sup> (n=26)	2.5 <sup>‡</sup> (n=24)	NR
		6 months	1.6 (1.4 to 1.9) (n=25)	2.4 (2.1 to 2.6) (n=23)	<0.001
		12 months	1.7 (1.4 to 2.0) (n=25)	NR	NA
<b>Symptom Checklist Frequency Scale, mean (95% CI)</b> [Score range: 0 (worst) to 64 (best)]	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	37.1 (n=53)	35.9 (n=59)	NS
		3 months	29.7 (n=53)	33.0 (n=59)	NR
		12 months	26.8 (n=53)	31.1 (n=59)	0.10
	Paroxysmal (2 <sup>nd</sup> line), Wilber 2010 <sup>47</sup>	Baseline	20.7 (18.9–22.6) (n=94)	18.6 (16.2–21.1) (n=51)	0.18
		3 month change	-11.1 (-12.9 to -9.3) (n=94)	0.7 (-2.4 to 3.9) (n=51)	<0.001

Outcome*	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>Symptom Checklist Severity Scale, mean (95% CI)</b> [Score range: 0 (worst) to 48 (best)]	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	22.1 (n=53)	21.5 (n=59)	NS
		3 months	12.0 (n=53)	18.7 (n=59)	NR
		12 months	10.4 (n=53)	13.3 (n=59)	0.001
	Paroxysmal (2 <sup>nd</sup> line), Wilber 2010 <sup>47</sup>	Baseline	17.1 (15.5–18.7) (n=76)	16.0 (13.7–18.4) (n=44)	0.44
		3 month change	-9.4 (-10.9 to -7.9) (n=76)	0 (-3.3 to 3.4) (n=44)	<0.001

AF = atrial fibrillation; AF-QOL = Atrial Fibrillation Quality of Life Questionnaire; CI = confidence interval; EQ5D = European Quality of Life-5 Dimensions; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NR = not reported; NS = not significant; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation; SD = standard deviation.

\*For all outcomes except the Minnesota Living with Heart Failure Questionnaire, a higher score reflects better health status.

†6 and 12 month results reported as baseline-adjusted (least-squares) means.

‡Baseline scores were estimated from the graphs provided.

## Functional Outcomes

Three fair-quality trials evaluated the influence of treatment on aspects of exercise, one of which was in patients with paroxysmal AF which used RFA as a second-line therapy<sup>38</sup> and two were in patients with heart failure who had persistent AF.<sup>39, 40</sup>

In the small trial in patients with paroxysmal AF,<sup>38</sup> at 12 months maximum heart rate, maximum workload and total metabolic equivalents achieved were significantly higher in those receiving RFA, but there was no difference in exercise duration between treatments (Table 13).

Two small trials in patients who had heart failure in addition to persistent AF reported no differences in change from baseline on the 6-minute walk test between treatment groups at 6 months<sup>40</sup> (mean  $+20.1 \pm 76.5$  for RFA vs.  $+21.4 \pm 77.4$  for medical therapy) at 12 months<sup>39</sup> (median  $+21$  [-51 to +89] vs.  $10$  [-73 to +15]) (Table 15). Mean peak VO<sub>2</sub> consumption was statistically higher in the RFA group as reported by two trials, one at 6 months ( $22.4$ , 95% CI  $19.7$  to  $25.1$  vs.  $17.7$ , 95% CI  $15.0$  to  $20.4$ )<sup>37</sup> and one at 12 months ( $18.7 \pm 7.5$  vs.  $17.3 \pm 5.4$ )<sup>39</sup>; both studies were in people with persistent AF and concomitant heart failure.

Of the seven included observational studies, none assessed functional outcomes.

**Table 15. Exercise capacity and related outcomes from randomized controlled trials comparing radiofrequency ablation with medical therapy**

Outcome	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>6-minute walk test (meters),</b> mean ± SD, median (IQR)	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Jones 2013 <sup>39</sup> (heart failure)	Baseline	416 ± 78 (n=26)	411 ± 109 (n=26)	0.84
		12 month change	+21 (-51 to +89) (n=26)	-10 (-73 to +15) (n=26)	0.095
	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	317.5 ± 125.8 (n=17)	351.8 ± 117.1 (n=15)	NR
		6 month change	+20.1 ± 76.5 (n=17)	+21.4 ± 77.4 (n=15)	0.96
<b>Stress tests, mean ± SD</b> Exercise duration (minutes)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	9.5 ± 4.0 (n=53)	9.1 ± 4.1 (n=59)	NS
		12 months	12.4 ± 5.3 (n=53)	10.3 ± 4.6 (n=59)	0.17
<b>Stress tests, mean ± SD</b> Heart rate at rest (bpm)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	81.0 ± 26.4 (n=53)	73.1 ± 21.4 (n=59)	NS
		12 months	82.0 ± 20.5 (n=53)	74.0 ± 13.9 (n=59)	0.002
<b>Stress tests, mean ± SD</b> Maximum heart rate (bpm)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	150.2 ± 25.9 (n=53)	140.1 ± 28.3 (n=59)	NS
		12 months	154.8 ± 18.3 (n=53)	139.2 ± 23.9 (n=59)	0.01
<b>Stress tests, mean ± SD</b> Maximum workload (W)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	157.8 ± 56.3 (n=53)	176.1 ± 61.8 (n=59)	NS
		12 months	187.6 ± 54.4 (n=53)	163.2 ± 49.9 (n=59)	0.02
<b>Stress tests, mean ± SD</b> METS	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	8.4 ± 2.6 (n=53)	8.0 ± 2.7 (n=59)	NS
		12 months	9.5 ± 2.3 (n=53)	8.1 ± 2.6 (n=59)	0.002

Outcome	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>Peak VO<sub>2</sub> consumption</b> (ml/kg/min), mean ± SD (95% CI)	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Jones 2013 <sup>39</sup> (heart failure)	Baseline	16.3 ± 5.3 (n=26)	18.2 ± 4.8 (n=26)	0.19
		3 months	17.1 ± 5.4 (n=26)	18.0 ± 4.6 (n=26)	0.38
		12 months	18.7 ± 7.5 (n=26)	17.3 ± 5.4 (n=26)	0.02
	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Hunter 2014 <sup>37</sup> (heart failure)	Baseline	21.5*	19.5*	NR
		6 months	22.4 (19.7 to 25.1) (n=25)	17.7 (15.0 to 20.4) (n=23)	0.01
		12 months	21.5 (18.8 to 24.3) (n=25)	NR	NA

AF = atrial fibrillation; bpm = beats per minute; IQR = interquartile range; METS = metabolic equivalents; ml/kg/min=milliliters per kilogram per minute; NR = not reported; NS = not significant; RF = radiofrequency; SD = standard deviation; VO<sub>2</sub> = volume of oxygen (measure of oxygen consumption); W = watts.

\*Baseline scores were estimated from the graph provided.

## Intermediate Outcomes

### Freedom from Recurrence of Atrial Arrhythmias

Ten RCTs comparing RFA with medical therapy reported sufficient data on short-term freedom from recurrence of any atrial arrhythmia (including AF, atrial flutter, and atrial tachycardia) following the blanking period, which ranged from 1 to 3 months.<sup>36-39, 41, 43-47</sup> The quality of all but one trial was considered fair, with one trial being considered good.<sup>45</sup> Freedom from recurrence was variably defined across trials, with some trials defining it based on the presence of symptoms and others defining it based on duration and frequency of recurrent episodes. Of the 10 trials, 4 evaluated patients with paroxysmal AF,<sup>38, 44, 46, 47</sup> 4 evaluated patients with persistent AF,<sup>37, 39, 41, 43</sup> and 2 included both paroxysmal and persistent AF patients.<sup>36, 45</sup> There was substantial crossover from medical therapy to RFA, which exceeded 50 percent in six trials.<sup>38, 43-47</sup> One trial provided comparative data up to 6 months only and thus was not included in the meta-analysis; 80.8 percent of patients who underwent RFA were free from arrhythmia recurrence compared to 0 percent who received medical therapy (Table 16). At 12 months, 73.1 percent of RFA patients were still free from recurrence. The pooled estimate across the remaining nine trials (N=1082) favored RFA (RR 2.62; 95% CI 1.90 to 3.96), however there was substantial heterogeneity across these trials ( $I^2 = 84.2\%$ ;  $p=0.0001$ ) (Figure 4). The pooled estimate from the four fair-quality trials of paroxysmal AF patients also favored RFA (RR 3.06; 95% CI 2.35 to 3.90) (531 patients).<sup>38, 44, 46, 47</sup> There was not significant heterogeneity across these trials ( $I^2 = 2.2\%$ ;  $p=0.381$ ). Individual trials in patients with persistent AF or those with mixed populations also favored RFA.<sup>36, 39, 41, 43, 45</sup> However, the pooled estimates for the persistent AF group and the mixed AF group were not statistically significant. Therefore, because results from individual trials were significant and because the pooled estimates were associated with substantial heterogeneity, the pooled estimates were considered to be misleading. Among the four studies that included only patients with persistent AF,<sup>37, 39, 41, 43</sup> one was limited to patients with heart failure and an LVEF less than or equal to 35 percent<sup>39</sup> and another was limited to patients with symptomatic heart failure and LVEF less than 50 percent.<sup>37</sup> The other two studies excluded patients with LVEF less than 30 percent.<sup>41, 43</sup> Further, the mean duration of AF prior to enrollment in the trials was quite different. One of the two studies that allowed both paroxysmal and persistent AF patients included only patients with diabetes mellitus.<sup>35</sup> These differences in the patient characteristics might contribute to the substantial heterogeneity observed in the pooled estimates.

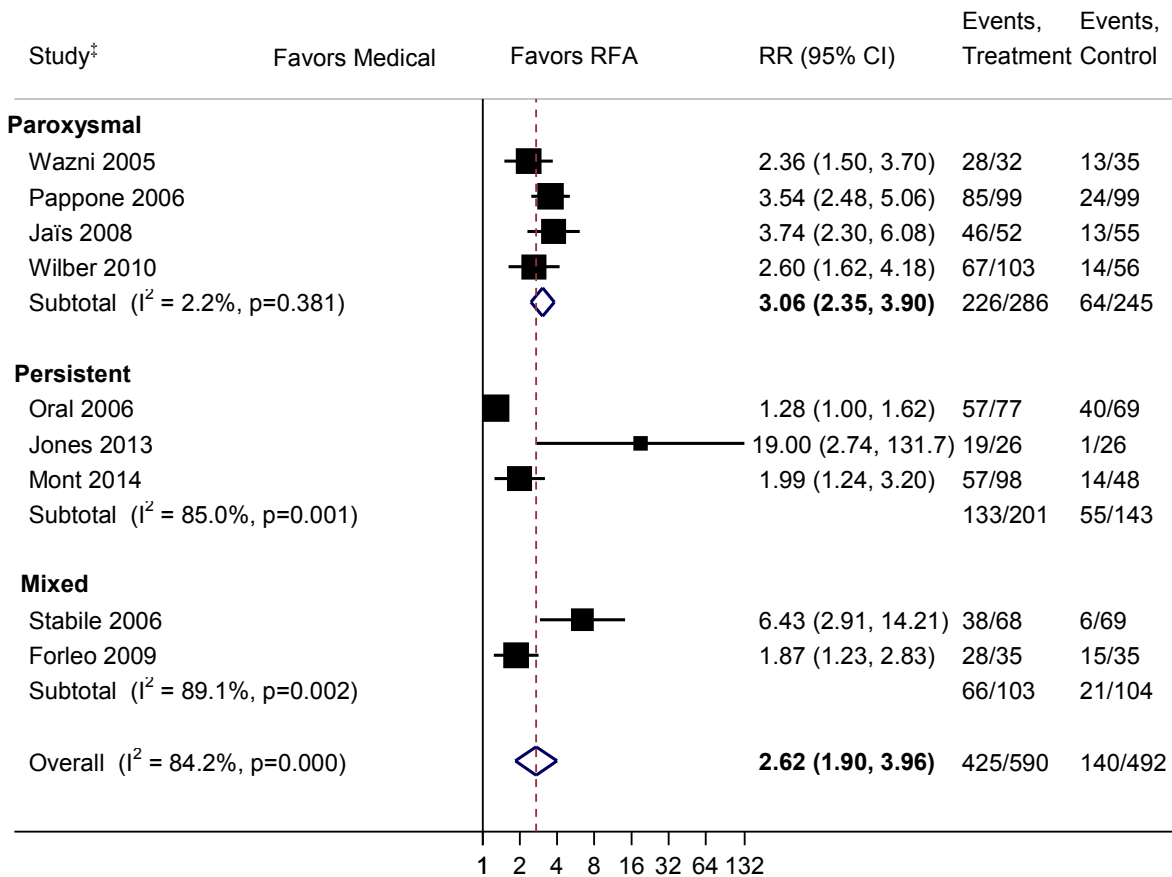
Three fair-quality RCTs comparing RFA with medical therapy reported on long-term ( $\geq 24$  months) freedom from recurrence of any atrial arrhythmias among patients with paroxysmal AF.<sup>35, 42, 83</sup> Mean followup was 24 months in two of the studies<sup>35, 42</sup> and 48 months in the third.<sup>83</sup> The pooled estimate across three trials of 619 patients favored RFA (RR 1.24; 95% CI 1.11 to 1.47) (Figure 5). There was not significant heterogeneity across these trials ( $I^2 = 0\%$ ;  $p=0.388$ ), potentially resulting from the very similar inclusion and exclusion criteria employed in these trials: all enrolled patients with at least two episodes of AF in the past 6 months and all excluded patients with appreciable left atrial enlargement, LVEF  $<35$  or 40 percent or heart failure symptoms.<sup>35, 42, 83</sup>

The comparative observational studies provided limited information on freedom from recurrence of AF (Table 17). One fair-quality prospective cohort study of paroxysmal AF patients reported similar proportions of RFA and medical therapy patients with freedom from recurrence of AF at 12 months (65% vs. 68%, respectively).<sup>49</sup> The other two studies reporting



this outcome reported that 72 to 74 percent of RFA patients achieved freedom from recurrence but did not provide data for the medical therapy group.<sup>51, 52</sup>

**Figure 4. Profile likelihood model meta-analysis of freedom from any arrhythmia recurrence within 12 months\* of followup in RCTs comparing RFA with medical therapy†**



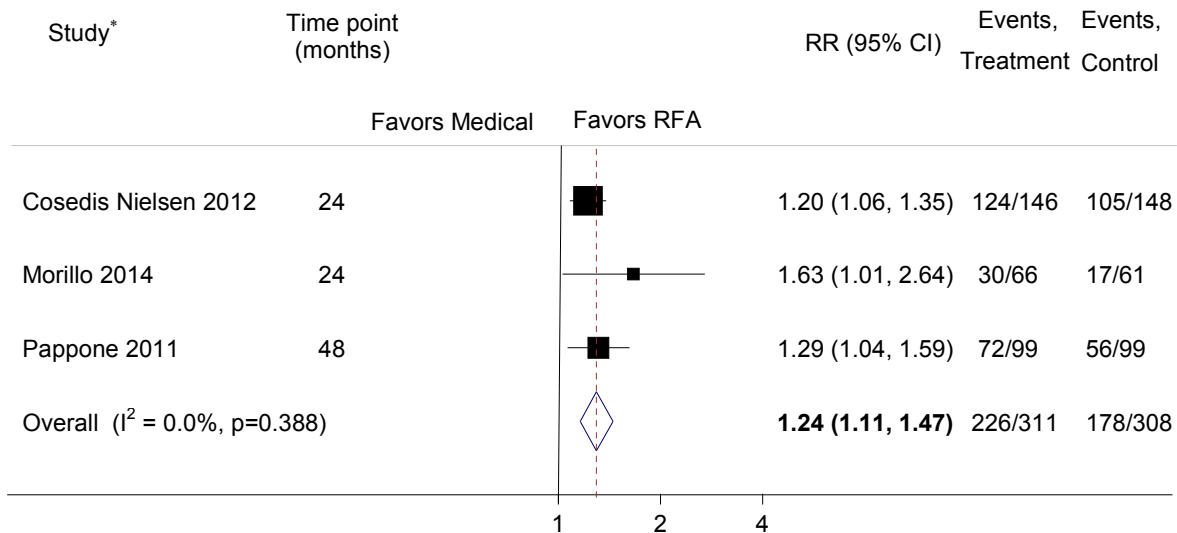
RCT = randomized controlled trial; RFA = radiofrequency catheter ablation; RR = relative risk.

\*For Stabile 2006, followup time included a 1-month blanking period, for a total of 13 months followup.

†The combined estimates for the persistent and mixed groups are not significant while each individual study provides significant results. Thus, the combined estimates are misleading and only combined estimates were reported for the paroxysmal group and all groups combined (overall).

‡All studies were in patients undergoing treatment as a second-line therapy (i.e., had failed prior medical therapy) with the exception of Wazni 2005 which was in patients treated as a first-line therapy.

**Figure 5. Profile likelihood model meta-analysis of freedom from any arrhythmia recurrence at followup times greater than 12 months in RCTs comparing RFA with medical therapy in patients with paroxysmal AF**



AF = atrial fibrillation; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation; RR = relative risk.  
 \*Cosedis Nielsen 2012 and Morillo 2014 were in patients treated as a first-line therapy; Pappone 2011 was in patients undergoing treatment as a second-line therapy (i.e., had failed prior medical therapy).

## Reablation of Atrial Arrhythmias

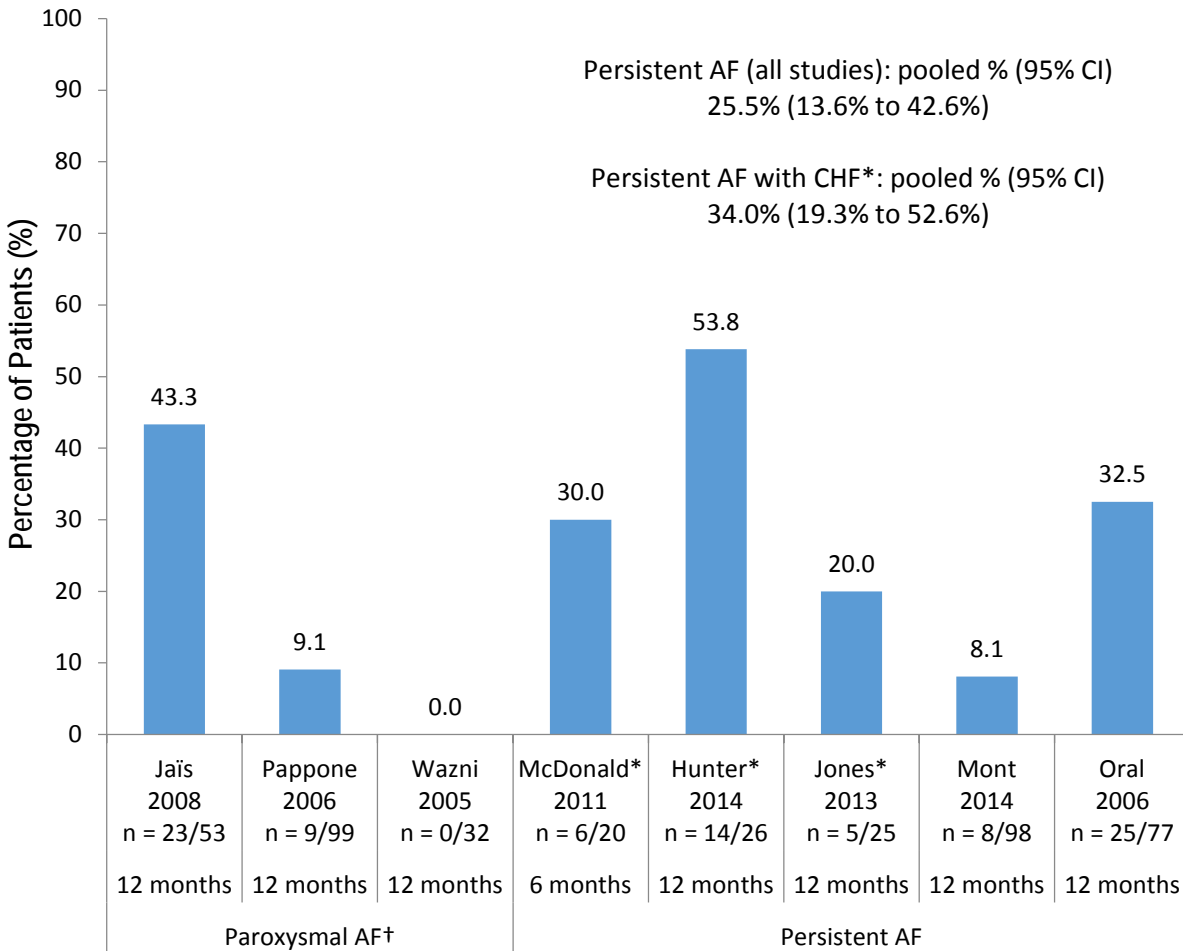
Eight RCTs examined reablation of any arrhythmia within 12 months of followup,<sup>37-41, 43, 44, 46</sup> three in patients with paroxysmal AF (n=184)<sup>38, 44, 46</sup> and five in patients with persistent AF (n=246).<sup>37, 39-41, 43</sup> All trials were fair-quality. The percentage of patients with paroxysmal AF who underwent reablation ranged from 0 to 43.3 percent. In the trials that only included persistent AF, the rate of reablation ranged from 8.1 to 53.8 percent with a pooled estimate of 25.5 percent (95% CI 13.6 to 42.6) (Figure 6).

One comparative observational study in paroxysmal AF patients reported reablation for AF recurrence within 12 months with a rate of 12.2 percent (n=82)<sup>52</sup> (Table 17).

Four RCTs examined reablation of any arrhythmia at long-term followup, two through 24 months,<sup>35, 42</sup> one through 48 months<sup>83</sup> and one trial that primarily reported short-term outcomes but provided information on reablation beyond 12 months.<sup>46</sup> All trials included only patients with paroxysmal AF (n=619). The quality of all trials was considered fair. The rate of reablation in that trial was 12.5 percent. The rate of reablation ranged from 13.6 to 49.2 percent during 24 months of followup.<sup>35, 42</sup> The trial that examined outcomes over 48 months showed a reablation rate of 27.3 percent.<sup>83</sup> The pooled estimate for the four trials was 24.2 percent (95% CI 12.6 to 41.5%) (Figure 7).

One comparative observational study in a Medicare-relevant population of persistent AF patients examined reablation of any arrhythmia within a mean followup period of 60 months and reported a rate of 18.3 percent (n=153)<sup>48</sup> (Table 17).

**Figure 6. Reablation for any arrhythmia within 12 months following RFA in patients with paroxysmal and persistent AF**

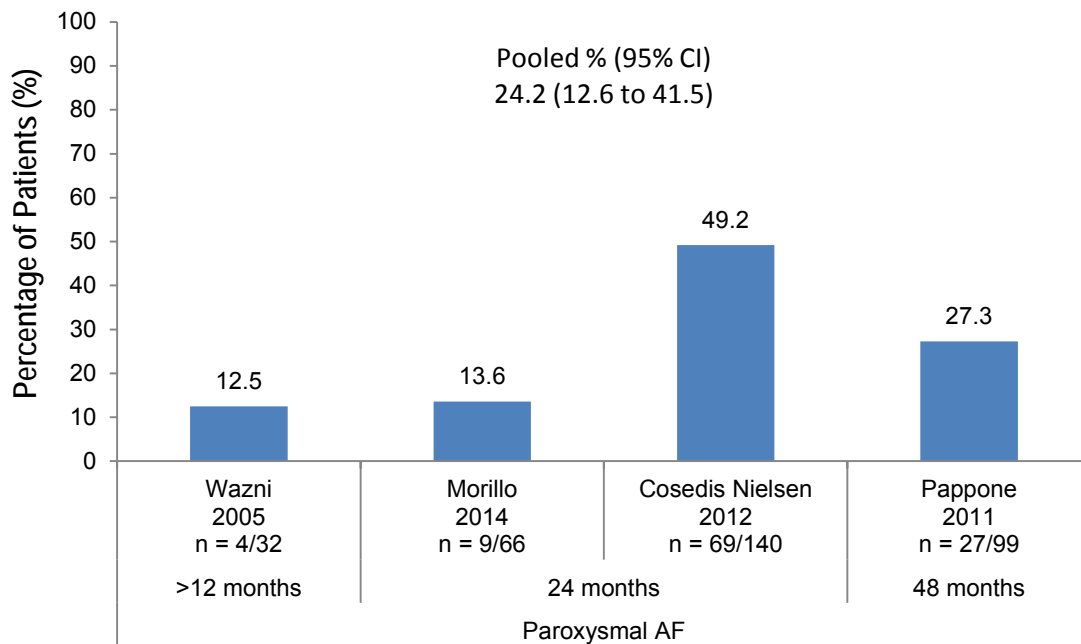


AF = atrial fibrillation; CHF = congestive heart failure; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation.

\*Patients with heart failure (MacDonald 2011, Hunter 2014, and Jones 2013).

†The range of frequency for reablation was large and data were considered too sparse to provide a meaningful pooled estimate.

**Figure 7. Reablation for any arrhythmia at long-term followup (>12 months) after RFA from RCTs of patients with paroxysmal AF**



AF = atrial fibrillation; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation.

## Maintenance of Sinus Rhythm

Four RCTs examined maintenance of sinus rhythm; two included patients with paroxysmal AF<sup>38, 44</sup> and two included patients with persistent AF.<sup>39, 40</sup> The latter two studies were also limited to patients with heart failure. Except for one trial that had a followup period of 6 months,<sup>40</sup> these studies had a followup period of 12 months. The quality of all four trials was considered fair. None of the long-term studies reported on maintenance of sinus rhythm.

Of the two RCTs that examined maintenance of sinus rhythm in patients with paroxysmal AF,<sup>38, 44</sup> one showed no difference between medical therapy and RFA (87% vs. 88% during 12 months of followup)<sup>38</sup> and the other showed a significant improvement in maintenance of sinus rhythm with RFA (92.9% vs. 35.4% during 12 months of followup).<sup>44</sup> Both trials that examined maintenance of sinus rhythm in patients with persistent AF and heart failure showed a significant difference in this outcome with RFA (88% vs. 7.7% during 12 months of followup in one study<sup>39</sup> and 50% vs. 0% during 6 months in another<sup>40</sup>) (Table 16).

Four comparative observational studies reported on maintenance of sinus rhythm; two included patients with paroxysmal AF,<sup>52, 54</sup> one included patients with persistent AF<sup>48</sup> and one included patients with paroxysmal or persistent AF.<sup>51</sup> Followup was 12 months in two studies,<sup>52, 54</sup> 15 months in one study,<sup>51</sup> and 60 months in one study.<sup>48</sup> The quality of the four studies was considered fair<sup>48, 49, 52, 53</sup> and of the other two was poor.<sup>51, 54</sup>

The rate of maintenance of sinus rhythm during 12 months of followup in patients with paroxysmal AF included in one comparative observational study was 71.1 percent in the RFA arm and 47.1 percent in the medical therapy.<sup>54</sup> In another study of patients with paroxysmal AF the rate of maintenance of sinus rhythm was 72 percent in the RFA arm vs. 20.2 percent in the medical therapy arm.<sup>52</sup> In a study of Medicare-relevant (age  $\geq 75$  years) patients with persistent AF, the rate of maintenance of sinus rhythm was 58 percent in the RFA arm vs. 43 percent in the medical therapy arm during a mean followup period of 60 months.<sup>48</sup> In a study that followed patients with paroxysmal or persistent AF for a mean of 15 months, the rate of maintenance of sinus rhythm was 82 percent in the RFA arm and 40 percent in the medical therapy arm (Table 17).<sup>51</sup>

## **Rehospitalization for Cardiovascular Causes**

Four trials provided information on rehospitalization for cardiovascular causes (Table 16). One trial in patients with paroxysmal AF provided information on rehospitalizations up to 12 months<sup>44</sup> and then at 48 months in a separate publication.<sup>83</sup> RFA was used as a second-line treatment in this trial. Two additional trials in those with paroxysmal AF reported on rehospitalization at 12 months<sup>46</sup> and 24 months respectively.<sup>35</sup> Both of these studies used RFA as a first-line treatment. One trial in patients with persistent AF reported on rehospitalization up to 12 months.<sup>41</sup> All trials were considered to be of fair quality. Overall, studies did not provide detail regarding reasons for hospitalization and the extent to which hospitalization for reablation procedures or crossover from medical therapy to ablation were included. This may at least partially explain discrepancies in rehospitalization frequency across studies and time frames.

Overall, hospitalization was more frequent in patients who received medical therapy. In those with paroxysmal AF, rehospitalization was more common in the medical treatment groups by 12 months across two trials.<sup>44,46</sup> This was also evident in the trial population followed to 48 months.<sup>83</sup> In this trial, the 12 months results do not include the hospitalization for crossover to ablation;<sup>44</sup> at 48 months, however, results do include repeat procedures and crossover to ablation.<sup>83</sup> The other trial in patients with paroxysmal AF reported no hospitalizations in those with AF and only two in the medical treatment group.

In patients with persistent AF, rehospitalization was more common among those receiving medical therapy in one study.<sup>41</sup> Recurrent arrhythmia was cited as the reason.

Of the six comparative observational studies, one fair-quality administrative database study in the general population reported a lower annualized rate of hospitalization for heart failure (1.5%) following RFA versus the medical treatment arm (2.2%) (Table 17). The Cox regression unadjusted hazard ratio for heart failure hospitalization in the ablation versus medical treatment cohorts was 0.69 (95% CI 0.42 to 1.15,  $p=0.158$ ). In multivariable models, there was no association between age  $\geq 65$  years and rates of hospitalization for heart failure at 27 months.

## **Atrial Fibrillation Burden**

One RCT reported on AF burden in patients with paroxysmal AF defined as percentage of time in AF on each Holter recording (obtained at each clinic visit) and as percentage of time in AF on all the Holter recordings obtained during the 24-month followup (cumulative burden).<sup>35</sup> The per-visit burden was significantly lower in the RFA arm (9%) versus the medical therapy arm (18%) ( $p=0.007$ ) and the cumulative burden was 13 percent versus 19 percent, respectively ( $p=0.10$ ). In second study of paroxysmal AF patients, the median reduction in AF over 24 hours

for each Holter recordings was significantly higher in the RFA arm than the medical therapy arm (10 vs. 3.2 minutes,  $p=0.0001$ ) (Table 16).<sup>38</sup>

### **Reduction in Use of Antiarrhythmic Medications**

Only one study reported on reduction in use of antiarrhythmic medications. This fair-quality study was a retrospective propensity matched analysis of the MarketScan Research Database between 2005 and 2009 of catheter ablation ( $n=801$ ) versus medical therapy ( $n=801$ ).<sup>50</sup> A significant reduction in the use of antiarrhythmic medications in the ablation arm compared with the medical therapy arm at 12 months (49% vs. 80%,  $p<0.001$ ), 24 months (40% vs. 72%,  $p<0.001$ ) and 36 months of followup (39% vs. 63%,  $p<0.001$ ) was seen (Table 17).

### **Change in Cardiac Chamber Size and Function**

*Left Atrial Size:* A total of four RCTs assessed the effect of RFA on left atrial size.<sup>38-40, 44</sup> Two examined left atrial dimension on echocardiography in patients with paroxysmal AF ( $n=310$ ),<sup>38, 44</sup> one assessed left atrial area on echocardiography in patients with persistent AF ( $n=52$ )<sup>39</sup> and one assessed left atrial end-diastolic area using cardiac MRI in patients with persistent AF ( $n=41$ ) (Table 18).<sup>40</sup> There was no significant difference in the left atrial size between RFA and medical therapy arm in the two studies that examined patients with paroxysmal AF.<sup>38, 44</sup> There was a significant reduction in the left atrial size at 6 and 12 months in the RFA arm compared with the medical therapy arm in the study by Jones and colleagues and a trend toward a reduction in left atrial size at 6 months with RFA compared with medical therapy in the study by MacDonald and colleagues.<sup>39, 40</sup>

Only one comparative observational study examined the association between RFA and left atrial size and showed no significant difference between RFA and medical therapy (Table 17).<sup>49</sup>

*Left Ventricular Size:* Three RCTs examined the effect of RFA on left ventricular size.<sup>37, 38, 40</sup> two using echocardiography, one in patients with paroxysmal AF<sup>38</sup> and other in patients with persistent AF,<sup>37</sup> and the third using cardiac MRI in patients with persistent AF.<sup>40</sup> Except for one study, they showed no significant difference in left ventricular size between RFA and medical therapy at 6 months in one study<sup>40</sup> and 12 months in the other (Table 18).<sup>38</sup> The study by Hunter et al showed a significant reduction in left ventricular size with ablation at 6 months.<sup>37</sup>

*Left Ventricular Ejection Fraction:* Four RCTs<sup>37-40</sup> examined the effect of RFA on the left ventricular ejection fraction, using echocardiography in one study in patients with paroxysmal AF<sup>38</sup> and another study in patients with persistent AF,<sup>37</sup> and radionuclide ventriculography in the other two that included patients with persistent AF (Table 18).<sup>39, 40</sup> In the study by Jais et al.,<sup>38</sup> there was no significant difference in change of left ventricular ejection fraction between RFA and medical therapy at 12 months. In the study by MacDonald and colleagues, there was a significant difference in the magnitude of improvement in the left ventricular ejection fraction with RFA vs. medical therapy at 6 months.<sup>40</sup> In the study by Jones and colleagues, there was a trend toward greater improvement in left ventricular ejection fraction at 12 months ( $p=0.06$ ).<sup>39</sup> In the study by Hunter et al, there was a significant improvement (mean increase of 8.1%) in the LVEF within 6 months of followup in the ablation group.<sup>37</sup>

### **Change in Biomarkers**

Three RCTs compared RFA with medical therapy with regard to their effect on brain natriuretic peptide (BNP) in patients with persistent AF (Table 18).<sup>37, 39, 40</sup> In one study, there

was no significant difference between the two arms at 6 months.<sup>40</sup> In another study, the reduction in BNP was significantly greater in the RFA arm than in the medical therapy arm at 6 months and 12 months.<sup>39</sup> In the study by Hunter et al., at 6 months, BNP was 126 pg/ml in the ablation group and 327 pg/ml in the medical therapy group ( $p=0.014$ ).<sup>37</sup>

**Table 16. Intermediate efficacy outcomes for RCTs comparing RFA with medical therapy\***

Outcome	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)	p-value
<b>Freedom From Recurrence (Any Arrhythmia)</b>	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line)	Hunter 2014 <sup>37</sup> (heart failure)	6 months	80.8% (21/26) <sup>†</sup>	0% (24/24) <sup>†</sup>	NR
			12 months	73.1% (19/26) <sup>†</sup>	NR	NR
<b>Maintenance of Sinus Rhythm</b>	Paroxysmal (2 <sup>nd</sup> line)	Jais 2008 <sup>38</sup>	12 months	88% (46/52) <sup>‡</sup>	87% (48/55) <sup>‡</sup>	NR
		Pappone 2006 <sup>44</sup>	12 months	92.9% (92/99)	35.4% (35/99)	NR
	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line)	Jones 2013 <sup>39</sup> (Heart failure)	12 months	88.0% (22/25)	7.7% (2/26)	NR
		MacDonald 2011 <sup>40</sup> (Heart failure)	6 months	50.0% (10/20)	0% (0/18)	NR
<b>Rehospitalization For Cardiovascular Causes</b>	Paroxysmal (1 <sup>st</sup> line)	Wazni 2005 <sup>46</sup>	12 months	9.4% (3/32)	54.3% (19/35)	NR
		Cosedis Nielsen 2012 <sup>35</sup>	24 months	0% (0/146)	1.4% (2/148) <sup>§</sup>	NR
	Paroxysmal (2 <sup>nd</sup> line)	Pappone 2006 <sup>44</sup>	12 months	9.1% (9/99) (24 admissions)**	NR (NR/99) (167 admissions) <sup>††</sup>	NR
		Pappone 2011 <sup>83</sup>	48 months	NR (61 admissions)**	NR (325 admissions) <sup>††</sup>	NR
	Persistent (2 <sup>nd</sup> line)	Mont 2014 <sup>41</sup>	12 months	2.0% (2/98) <sup>‡‡</sup>	6.3% (3/48) <sup>‡‡</sup>	NR
<b>AF Burden</b> % of time in AF on each Holter recording (per-visit burden)	Paroxysmal (1 <sup>st</sup> line)	Cosedis Nielsen 2012 <sup>35</sup>	24 months	$\frac{n=146}{9\%}$ <sup>§§</sup>	$\frac{n=148}{18\%}$ <sup>§§</sup>	0.007
<b>AF Burden</b> % of time in AF on all the Holter recordings obtained during followup (cumulative burden)	Paroxysmal (1 <sup>st</sup> line)	Cosedis Nielsen 2012 <sup>35</sup>	24 months	$\frac{n=146}{13\%}$ <sup>§§</sup>	$\frac{n=148}{19\%}$ <sup>§§</sup>	0.10
<b>AF Burden</b> Median (IQR) reduction in AF over 24 hours for each Holder recording (minutes)	Paroxysmal (2 <sup>nd</sup> line)	Jais 2008 <sup>38</sup>	Baseline 12 months	$\frac{n=53}{14 (0-578)}$ $\frac{10.0 (0-588)}$	$\frac{n=59}{14 (0-215)}$ $\frac{3.2 (0-155)}$	0.69 0.0001

AF = atrial fibrillation; IQR = interquartile range; NR = not reported; RFA = radiofrequency ablation.

\*A meta-analysis was performed for the outcomes freedom from recurrence (any arrhythmia) (see Figures 4 and 5) and reablation (see Figures 6 and 7)

†According to the methods, freedom recurrence was defined as freedom from documented AF/atrial tachycardia lasting ≥30 secondary after the 3-month blanking period. As reported in the results, it appears that 4 patients with early AF recurrences (<3 months) were included in this estimate (for the purposes of this report, this is considered an adverse event). None of these patients received further treatment for the recurrence, however, so we are making the assumption that they remained in AF through the 6 and 12 months followup. Therefore, these patients are counted under both efficacy and adverse events in this report.

‡Only percent provided. Back calculated using ITT to get “n’s”.

§Hospitalization for congestive heart failure.

\*\*Including repeat procedures. Pappone 2006 and Pappone 2011 represent the same population with different followup.

††At 12 months, results do not include the hospitalization for crossover to ablation; at 48 months, however, results do include repeat procedures and crossover to ablation. Pappone 2006 and Pappone 2011 represent the same population with different followup.

‡‡Due to arrhythmia recurrences.

§§90<sup>th</sup> percentile of arrhythmia burden



**Table 17. Intermediate effectiveness outcomes for comparative observational studies comparing RFA with medical therapy**

Outcome	AF Type*	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)	p-value
Freedom from recurrence (any arrhythmia)	Mixed	Rossillo 2008 <sup>51</sup>	Mean 15 months	74% (63/85)	NR	NA
Freedom from recurrence (AF only) <sup>†</sup>	Paroxysmal	Lan 2009 <sup>‡49</sup>	12 months	65% (78/120)	68.3% (82/120)	NR
		Sang 2013 <sup>§2</sup>	12 months	72% (53/82)	NR	NA
Reablation for any arrhythmia	Persistent	Blandino 2013 <sup>§48</sup>	Mean 60 months	18.3% (28/153)	NR	NA
Reablation for AF	Paroxysmal	Sang 2013 <sup>§2</sup>	12 months	12.2% (10/82)	NR	NA
Maintenance of sinus rhythm <sup>†</sup>	Paroxysmal	Yu 2012 <sup>§4</sup>	12 months	71.1% (69/97)	47.1% (48/102)	NR
		Sang 2013 <sup>§2</sup>	12 months	72% (59/82)	20.2% (17/84)	<0.001
	Persistent	Blandino 2013 <sup>§48</sup>	Mean 60 months	58% (88/153)	43% (111/259)	0.003
	Mixed	Rossillo 2008 <sup>51</sup>	Mean 15 months	82% (70/85)	40% (34/85)	NR
Reduction in antiarrhythmic medication**	Mixed	Reynolds 2012 <sup>50</sup>		<u>N=801</u>	<u>N=801</u>	
			Baseline	79%	79%	NS
			6 months	70%	90%	<0.001
			12 months	49%	80%	<0.001
			18 months	42%	75%	<0.001
			24 months	40%	72%	<0.001
			30 months	37%	69%	<0.001
			36 months	39%	63%	<0.001
Left atrial size (mm), mean [anteroposterior diameter at end-systole, transthoracic echocardiography]	Paroxysmal	Lan 2009 <sup>‡49</sup>		<u>n=120</u>	<u>n=120</u>	
			Baseline	34.66	34.69	NR
			3 months	33.82	34.66	NR
			6 months	33.91	34.90	NR
			9 months	34.15	35.26	NR
			12 months	34.49	35.80	NR

AF = atrial fibrillation; mm = millimeter; NA = not applicable; NR = not reported; RFA = radiofrequency ablation.

\*All treatments were a second-line therapy for AF.

†Yu et al. 2012 and Rossillo et al. 2008 seem to be using maintenance of sinus rhythm and freedom from AF recurrence interchangeably. Only maintenance of sinus rhythm was reported for these studies.

‡Data from the circumferential pulmonary vein ablation (CPVA; 32/60) and the segmental pulmonary vein isolation (SPVI; 46/60) groups were combined to form one radiofrequency ablation group; similarly data were combined from the amiodarone only (AMIO; 35/60) and the amiodarone + losartan (AMIO+LO) groups to form one medical therapy group. Standard deviations were provided for all 4 groups.

§Represents the Medicare population (age ≥75 years). All other studies represent the general adult population.

\*\*These values are estimated from Figure 2 in the report. Authors also report patterns of rate control medication usage and Warfarin usage over the study period which were nearly identical between the cohorts over the entire timeframe (75% to 70% and 70% to 50%, respectively) with the exception of day 8 to 6 months, during which they were used more often in the ablation patients (p=0.019, and p<0.001, respectively).

**Table 18. Cardiac chamber size/function and biomarkers reported by RCTs comparing RFA with medical therapy**

Outcome (mode of measurement)	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
<b>Left atrial size, mean ± SD</b> Left atrial dimension (parasternal long axis, mm) (Echo)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	39.5 ± 5.6 (n=53)	40.0 ± 5.7 (n=59)	NR
		12 months	38.7 ± 7.0 (n=53)	38.9 ± 6.2 (n=59)	0.92
	Paroxysmal (2 <sup>nd</sup> line), Pappone 2006 <sup>44</sup>	Baseline	40 ± 6 (n=99)	38 ± 6 (n=99)	0.25
		12 months	36 ± 6 (n=99)	NR (n=99)	NA
<b>Left atrial size, mean (95% CI)</b> Left atrial area (cm <sup>2</sup> ) (Echo)	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Jones 2013 <sup>39</sup> (heart failure)	Baseline	NR	NR	NR
		Mean difference between groups at: 6 months	-4.96 (-7.23 to -2.68)*	—	0.001
		Mean difference between groups at: 12 months	-6.22 (-9.17 to -3.27)*	—	0.001
<b>Left atrial size, mean ± SD</b> Left atrial end-diastolic area (mm <sup>2</sup> ) (CMR)	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	3291.1 ± 766.1 (n=19)	3214.5 ± 594.1 (n=18)	NR
		6 month change	-237.0 ± 490.4 (n=19)	+35.5 ± 364.0 (n=18)	0.06
<b>Left ventricular size, mean ± SD</b> End-diastolic dimension (mm) (Echo)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	51.9 ± 4.2 (n=53)	50.5 ± 7.7 (n=59)	NR
		12 months	50.0 ± 5.2 (n=53)	51.0 ± 4.5 (n=59)	0.35
<b>Left ventricular size, mean ± SD</b> End-diastolic volume (ml) (CMR)	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	244.1 ± 94.0 (n=19)	215.0 ± 74.7 (n=18)	NR
		6 month change	-12.6 ± 51.7 (n=19)	-9.4 ± 35.7 (n=18)	0.80
<b>Left ventricular size, mean ± SD</b> End-systolic volume (ml) (CMR)	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	163.8 ± 83.2 (n=19)	126.3 ± 58.4 (n=18)	NR
		6 month change	-20 ± 50.2 (n=19)	-10.6 ± 32.2 (n=18)	0.50
<b>Left ventricular size, mean (95% CI)</b> End-systolic volume (ml) (Echo)	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Hunter 2014 <sup>37</sup> (heart failure)	Baseline	NR	NR	NA
		6 month change	-14.2% (-26.2% to -2.2%) (n=25)	+4.7% (-7.9% to 17.2%) (n=23)	0.030

Outcome (mode of measurement)	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy) and Study	Followup	RFA	Medical Therapy	p-value
LVEF (%), mean ± SD (Echo)	Paroxysmal (2 <sup>nd</sup> line), Jais 2008 <sup>38</sup>	Baseline	63.1% ± 11.0% (n=53)	65.6% ± 7.2% (n=59)	NR
		12 months	65.4% ± 8.9% (n=53)	65.4% ± 5.9% (n=59)	0.99
	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Hunter 2014 <sup>37</sup> (heart failure)	Baseline	31.8% ± 7.7% (n=26)	33.7% ± 12.1% (n=24)	NR
		6 month change <sup>†</sup>	+8.1% (95% CI 3.0 to 13.1) (n=25)	-3.6% (95% CI -7.7 to 0.5) (n=23)	<0.001
LVEF (%), mean ± SD (RNVG)	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Jones 2013 <sup>39</sup> (heart failure)	Baseline	21.5% ± 8.3% (n=26)	24.9% ± 7.2% (n=26)	.13
		12 month change	+10.9% ± 11.5% (n=26)	+5.4% ± 8.5% (n=26)	0.06
	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	15.1% ± 6.5% (n=20)	19.6% ± 5.9% (n=17)	NR
		6 month change	+8.2% ± 12.0% (n=20)	+1.4% ± 5.9% (n=17)	0.03
LVEF (%), mean ± SD (CMR)	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	36.1% ± 11.9% (n=19)	42.9% ± 9.6% (n=18)	NR
		6 month change	+4.5% ± 11.1% (n=19)	+2.8% ± 6.7% (n=18)	0.60
Brain natriuretic peptide (pg/ml) mean ± SD (95% CI), median (IQR)	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Jones 2013 <sup>39</sup> (heart failure)	Baseline	412 ± 324 (n=26)	283 ± 285 (n=26)	.13
		6 months change	NR (n=26)	NR (n=26)	0.04 <sup>‡</sup>
		12 month change	-124 (-284 to 0) (n=26)	-18 (-86 to +31) (n=26)	0.04
	Persistent (2 <sup>nd</sup> line), MacDonald 2011 <sup>40</sup> (heart failure)	Baseline	2550 ± 2150 (n=20)	1846 ± 1687 (n=18)	NR
		6 month change	-196 ± 1469 (n=20)	+85 ± 648 (n=28)	0.45
	Persistent (1 <sup>st</sup> /2 <sup>nd</sup> line), Hunter 2014 <sup>37</sup> (heart failure)	Baseline	400 <sup>§</sup>	650 <sup>§</sup>	NA
6 months <sup>†</sup>		126 (95% CI 63 to 189) (n=25)	327 (95% CI 172 to 481) (n=23)	0.01	

AF = atrial fibrillation; CI = confidence interval; cm = centimeter; CMR = cardiovascular magnetic resonance; Echo = transthoracic echocardiography; IQR = interquartile range; LVEF = left ventricular ejection fraction; pg/ml = picograms per milliliter; mm = millimeter; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RFA = radiofrequency ablation; RNVG = radionuclide ventriculography; SD = standard deviation.

\*Mean difference (95% CI) in the ablation compared with medical therapy group at 6 and 12 months.

<sup>†</sup>The improvement in the ablation group was sustained at 1 year; no comparison data available for the medical therapy group.

<sup>‡</sup>There was a significant reduction in brain natriuretic peptide at 6 months in the ablation group compared with the medical therapy group.

<sup>§</sup>Baseline scores were estimated from the graph provided.

## Cryoablation Versus Medical Therapy

### Description of Included Studies

One multi-center RCT (26 centers within North America) compared cryoballoon ablation (n=163) with medical therapy (n=82) over 12 months of followup, which included a 3 month blanking period.<sup>86</sup> Patients had highly symptomatic paroxysmal (78%) or persistent (22%) AF. The trial was funded by Medtronic Inc. Conflicts of interests were reported and were in the form of research funding, consultant fees, and honoraria.

The study population was predominantly male (77.1%) and had a mean age of 57 years (Table 19). All patients had previously failed medical therapy. Almost all patients (93.5%) had either no or Class I heart failure. Patients in the cryoballoon ablation arm were allowed to be treated with AADs during the blanking period, after which the drug was discontinued. Within the drug therapy arm, patients received flecainide, propafenone, or sotalol; AF drugs such as amiodarone and dofetilide were not permitted since they did not have FDA approval for treatment of paroxysmal AF. Patients were only allowed to crossover to cryoballoon ablation after meeting protocol-defined effectiveness failure endpoints. Over the course of the study 65 of the 82 drug-treated patients (79%) crossed over to ablative therapy. The median time to crossover was 186 days (range 29 to 364 days).

The cryoballoon ablation therapy had as a goal electrical PVI of the four major pulmonary veins as confirmed by entrance and/or exit block, with additional focal cryoballoon ablation deliveries allowed at investigator discretion (e.g., for focal triggers, cavotricuspid isthmus-dependent atrial flutter). One repeat cryoballoon ablation procedure was allowed during the blanking period and 31 (19%) patients had a second ablation during this time. No reablation occurred after the blanking period. A substudy of this trial examining the significance of early recurrence of AF in those randomized to cryoballoon ablation is also included; however it contributed limited evidence since it did not provided comparative data.<sup>73</sup>

There were no observational studies of cryoballoon or focal cryoablation versus medical therapy.

**Table 19. Patient characteristics and overview of study characteristics for the STOP AF Pivotal RCT comparing cryoballoon ablation with medical therapy in patients with paroxysmal/early persistent AF**

Author (Year) Therapy Sample Size		Packer 2013 <sup>72</sup> Cryoballoon ablation (n=163)	Packer 2013 <sup>72</sup> Medical (n=82)
<b>Patient Demographics</b>	Male, % (n)	76.7 (125)	78.0 (64)
	Age (years); mean ± SD	57 ± 9	56 ± 9
	AF duration (years)	NR	NR
	AF episodes (past 2 months); mean ± SD	24 ± 42	21 ± 32
	Left atrial size (mm); mean ± SD	40 ± 5	41 ± 6
	LVEF (%), mean ± SD	60 ± 6	61 ± 6
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	None	None
<b>Comorbidities, % (n)</b>	Hypertension	41.1 (67)	45.1 (37)
	Coronary artery disease	8.0 (13)	9.8 (8)
	NYHA class II	6.7 (11)	6.1 (5)
	History of atrial flutter	46.0 (75)	43.9 (36)
	Prior cardioversion	22.7 (37)	20.7 (17)
	Diabetes	6.7 (11)	8.5 (7)
	CHADS2 score, mean ± SD	0.6 ± 0.7	0.6 ± 0.7
<b>Study Characteristics</b>	Followup period	12 months	12 months
	Completed followup, % (n)	100 (163)	96.3 (7)
	Blanking period	3 months	3 months
	Crossover, % (n)	None	79.3 (65)
	Use of AADs in ablation group	Flecainide, propafenone, or sotalol during the blanking period only; after blanking period, previously ineffective drugs permitted	

AAD = antiarrhythmic drug; AF = atrial fibrillation; CHADS2 = Congestive heart failure, Hypertension, Age, Diabetes, Stroke System; IQR = interquartile range; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association; RCT = randomized controlled trial; SD = standard deviation; STOP AF = Sustained Treatment of Paroxysmal Atrial Fibrillation.

## Detailed Synthesis

### Primary Outcomes

#### All-Cause and Cardiovascular Mortality >30 days

Within the included RCT,<sup>86</sup> there was one unrelated death from a myocardial infarction in the cryoballoon ablation strategy at 10 months (Table 20). Patients were only followed for 12 months after treatment initiation and so longer-term all-cause or cardiovascular mortality evidence was not available.

#### Stroke >30 Days

Within the included RCT,<sup>86</sup> there were three strokes in patients who either received cryoballoon ablation initially or who crossed over to ablation following medical therapy (Table 20). An additional four patients had nonprocedural-related cerebral vascular events over the 12 months of followup; all recovered without residual neurological deficits. Patients were only followed for 12 months after treatment initiation and so longer-term evidence regarding stroke events was not available. It is not clear that anticoagulation prior to ablation was adequate but

appeared to be adequate during the procedure. Anticoagulation was required for the first 3 months after ablation and was discontinued at the investigators discretion.

### **Transient Ischemic Attacks >30 Days**

There were no patients who experienced a TIA after 30 days (Table 20); no data provided on longer-term TIA outcomes.

### **Myocardial Infarction >30 Days**

Within the included RCT,<sup>86</sup> there was one myocardial infarction within the cryoballoon ablation patients with one being fatal (10 months following treatment) (Table 20). There was no evidence on longer-term myocardial infarction outcomes given the 12-month followup limitation.

### **Congestive Heart Failure**

Within the included RCT,<sup>86</sup> one patient was hospitalized for AF-related CHF (Table 20). There was no evidence in longer-term CHF outcomes given the 12-month followup limitation.

### **Health-Related Quality of Life**

Within the included RCT,<sup>86</sup> patients' overall SF-36 was assessed at baseline and then during followup. The study notes that improvements in SF-36 quality-of-life scores were seen in the cryoballoon ablation group; however, the scores were not reported. Similar data regarding the quality-of-life findings in the medical therapy patients were not reported.

## **Intermediate Outcomes**

### **Freedom from Protocol Defined Treatment Failure**

The primary efficacy outcome for this trial was freedom from chronic treatment failure defined as any detectable AF after the blanking period, use of a nonstudy antiarrhythmic drug, or any nonprotocol intervention for AF (i.e., RF ablation). After 12 months of followup a significantly greater number of patients in the cryoballoon ablation group were free from protocol defined treatment failure (69.9%) compared with the medical therapy group (69.9% vs. 7.3%;  $p<0.001$ ) (Table 20).<sup>86</sup> At the end of the 12 months, 26 percent of the cryoballoon ablation patients were taking AADs. During a follow up of 12 months (after the blanking period), 41 patients experienced AF recurrence resulting in 74.8 percent of patients experiencing freedom from AF in the ablation group; no data were reported for the medical therapy group.<sup>73</sup>

### **Atrial Flutter**

Within the included RCT,<sup>86</sup> six patients (3.7%) reported atrial flutter during 12-month followup. In comparison, 12 (14.6%) of the drug-treatment patients reported atrial flutter during this same time period ( $p=NR$ ) (Table 20).

### **Reduction in Arrhythmia-Related Symptoms**

Symptomatic AF occurrence fell from 100 percent at baseline to 19 percent at 12 months in the cryoballoon ablation group. Similarly, compared with baseline, arrhythmia-related symptoms were reduced in cryoballoon ablation patients by 12 months with any AF symptoms reduced from 100 percent to 20 percent, dizziness from 48 percent to 9 percent, palpitations from 86 percent to 25 percent, and fatigue from 76 percent to 13 percent (Table 20).<sup>86</sup> The authors note

that these symptomatic improvements were confirmed by improvements in the SF-36 quality-of-life subscores (no data provided). Similar data regarding the symptom improvement in the drug treated patients were not reported.

**Table 20. Efficacy outcomes from the STOP AF pivotal RCT comparing cryoballoon ablation with medical therapy in patients with paroxysmal/early persistent AF<sup>72</sup>**

Type of Outcome	Outcome	Followup	Cryoballoon ablation* % (n/N)	Medical Therapy* % (n/N)	p-value
Primary Outcomes	Mortality (all-cause) >30 days	12 months	0.6% (1/163) <sup>†</sup>	0% (0/79)	NR
	Mortality (cardiovascular) >30 days	12 months	0.6% (1/163) <sup>†</sup>	0% (0/79)	NR
	Stroke (any type) >30 days	12 months	1.8% (3/163) <sup>‡</sup>	0% (0/79)	NR
	Myocardial infarction >30 days	12 months	0.6% (1/163) <sup>†</sup>	0% (0/79)	NR
	Transient ischemic attack >30 days	12 months	0% (0/163)	0% (0/79)	NR
	Congestive heart failure (requiring hospitalization, timing NR)	12 months	0.6% (1/163)	0% (0/79)	NR
Intermediate Outcomes	Freedom from protocol defined treatment failure <sup>§</sup>	12 months	69.9% (114/163)	7.3% (6/82)	<0.001
	Reduction in arrhythmia-related AF symptoms <sup>††</sup>	Baseline	100% (163/163)	NR	NA
		12 months	20% (33/163)	NR	NA
	Reduction in arrhythmia-related dizziness symptoms <sup>††</sup>	Baseline	48% (78/163)	NR	NA
		12 months	9% (15/163)	NR	NA
	Reduction in arrhythmia-related palpitation symptoms <sup>††</sup>	Baseline	86% (140/163)	NR	NA
		12 months	25% (41/163)	NR	NA
	Reduction in arrhythmia-related fatigue symptoms <sup>††</sup>	Baseline	76% (124/163)	NR	NA
		12 months	13% (21/163)	NR	NA
	Atrial Flutter	12 months	3.7% (6/163)	14.6% (12/82)	NR

AF = atrial fibrillation; MI = myocardial infarction; NA = not applicable; NR = not reported; RCT = randomized controlled trial; STOP AF = Sustained Treatment of Paroxysmal Atrial Fibrillation; TIA = transient ischemic attack.

\*No patient was lost to followup in the cryoballoon group; 3 patients were lost to followup in the medical group and, over the course of the study, 79% (65/82) crossed over to ablative intervention.

<sup>†</sup>Fatal MI deemed unrelated to procedure (same patient).

<sup>‡</sup>Nonprocedural-related as determined by authors. Include: 1 small hemorrhagic stroke on day 183, 1 lacunar infarct of indeterminate age on CT examination on day 51, and 1 subarachnoid hemorrhage on day 260 in a patient on aspirin.

<sup>§</sup>Defined by the absence of: 1) any detectable AF after the blanking period; 2) use of a nonstudy, antiarrhythmic drug; or 3) any nonprotocol intervention for AF (i.e., RF ablation).

\*\*As treated analysis only. This outcome is comparing the patients who underwent ablation as intended (randomized ablation group) to those patients who underwent ablation after crossing over from medical therapy (65 patients from the medical group crossed over to ablation during the study period).

<sup>††</sup>Authors only report %'s at baseline and 12 months. However, these results are from the intention-to-treat analysis so back-calculations were done to get the number of patients.

Key Question 1b. What is the comparative efficacy and effectiveness of AF catheter ablation versus different energy sources on short- (6-12 months) and long- (>12 months) term outcomes in the general adult and Medicare populations?

## Key Points

### Cryoablation Versus Radiofrequency Ablation

#### Primary Outcomes

- Neither of the two RCTs identified reported on the primary clinical outcomes. One poor-quality observational study in patients with paroxysmal AF reported no statistical differences between treatments for all-cause mortality or TIA (>30 days) at 23 months (insufficient strength of evidence).

#### Intermediate Outcomes

##### Freedom From Recurrence and Reablation (>30 days)

- Short term ( $\leq 12$  months):
  - Freedom from AF recurrence was less common following cryoballoon ablation compared with RFA across two trials, one in paroxysmal AF patients and one in a population that included those with different AF types, but differences failed to reach statistical significance in either. (insufficient strength of evidence).
  - Reablation was more common following cryoballoon ablation versus RFA in both trials but was statistically significant in only in the trial in those with paroxysmal AF (insufficient strength of evidence).
- Long term (>12 months)
  - No data from RCTs were identified
  - The proportions of patients in each group experiencing freedom from recurrence were similar in the cryoballoon ablation and RFA groups across two observational studies in those with paroxysmal AF (insufficient strength of evidence).

## Description of Included Studies

### Randomized Controlled Trials

Two RCTs compared cryoballoon ablation with RFA reported outcome up to 12 months (range 3–29 months).<sup>74,75</sup> One trial included only patients with paroxysmal AF and the other included patient with both paroxysmal and persistent AF (mixed population). (Table 21) For both treatment arms of both studies, ablation was a second-line treatment, both studies reported a 3 month blanking period and no attrition was reported in either study. Study funding from National Institute of Health Carlos III, Madrid, Spain supported one study<sup>75</sup> and the other was supported by CryoCath<sup>74</sup> and authors in both trials reported receiving consulting and speaking fees from various industry groups.

Study sample sizes were small (50 and 60) and populations were predominantly male (80% and 78%) with similar mean ages (57 years). Hypertension was common in both trials (45% and



28%). Cryoballoon ablation was supplemented with focal cryoablation in one trial (which did not report on cross-over) if PV conduction persisted,<sup>75</sup> but not in the other trial (which didn't allow cross-over) which monitored cardiac electrical activity via an implantable cardiac monitor.

One trial was considered fair quality<sup>75</sup> and the other poor quality.<sup>74</sup> Neither study reported concealed treatment allocation and patients were not blinded. Information on randomization, and intention to treat analysis was not evident in the poor-quality trial.

**Table 21. Patient characteristics and overview of study characteristics for RCTs comparing cryoballoon ablation with RFA in patients with AF**

Author (Year) Therapy Sample Size	Herrera Siklody (2012) <sup>74</sup> Cryoballoon ablation (n=30)	Herrera Siklody (2012) <sup>74</sup> RFA (n=30)	Perez-Castellano (2014) <sup>75</sup> Cryoballoon ablation (n=25)	Perez-Castellano (2014) <sup>75</sup> RFA (n=25)	
<b>Patient Demographics</b>	Male, % (n)	83.3 (25)	76.7 (23)	68 (17)	88 (22)
	Age (years); mean ± SD	57 ± 8	56 ± 10	58 (range, 54–62)	56 (range, 40–61)
	Paroxysmal AF, % (n)	70 (21)	56.7 (17)	100 (25)	100 (25)
	Persistent AF, % (n)	30 (9)	43.3 (13)	0 (0)	0 (0)
	Mixed*, % (n)	0 (0)	0 (0)	0 (0)	0 (0)
	AF duration (years); median (IQR)	4.2 ± 2.7	5.6 ± 4.2	NR	NR
	Left atrial size (mm); mean ± SD	41.4 ± 4.3	40 ± 5.5	42 (range, 39-47)	42 (range, 38–45)
	LVEF (%), mean ± SD	NR	NR	NR	NR
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	None	None	None	None
<b>Comorbidities, % (n)</b>	Heart failure	NR	NR	NR	NR
	Hypertension	43.3 (13)	46.7 (17)	24 (6)	32 (8)
	Coronary artery disease	10.0 (3)	13.3 (4)	16 (4)	16 (4)
	Cardiomyopathy	6.7 (2)	3.3 (1)	NR	NR
	History of prior stroke	NR	NR	NR	NR
	CHADS2 score, median (IQR)	NR	NR	NR	NR
	Diabetes	NR	NR	16 (4)	8 (2)
<b>Study Characteristics</b>	Followup period (months)	12 months (range, 3–29 months)	12 months (range, 3–29 months)	12 months	12 months
	Completed followup, % (n)	NR	NR	100 (25)	100 (25)
	Blanking period (months)	3 months	3 months	3 months	3 months
	Crossover, % (n)	NR	NR	0 (0)	0 (0)

AF = atrial fibrillation; BMI = body mass index; CHADS2 = Cardiac failure, Hypertension, Age, Diabetes, Stroke system; IQR = interquartile range; LVEF = left ventricular ejection fraction; NR = not reported; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation; SD = standard deviation.

\*Mixed pattern was a combination of both types of AF (paroxysmal and persistent).

## Comparative Observational Studies

Six comparative observational studies were also identified comparing cryoballoon ablation with RFA.<sup>76-81</sup> Three studies reported outcomes during the periprocedural period only, with complete followup achieved in all patients,<sup>76, 79, 81</sup> The remaining three studies reported longer-term outcomes with followup periods ranging from 14 to 28 months;<sup>77, 78, 80</sup> and none of them reported attrition. Four studies only included patients with paroxysmal AF for whom ablation was a second-line therapy<sup>76, 77, 80, 81</sup> (Table 22) and two studies included patients with either paroxysmal, persistent, or permanent AF who were treated as a second-line therapy in one study<sup>78</sup> and as either a first and second-line therapy in the other (Table 23).<sup>79</sup> Funding was reported by two of the four studies; one study received grant support from Basel University<sup>77</sup> and several authors disclosed having received grants, speaking, and/or consulting fees from various industry groups and the other was funded by the British Heart Foundation and reported no conflicts of interest.<sup>78</sup>

The study sample sizes ranged from 124 to 3775. The cryoballoon ablation and RFA treatment groups were predominantly male and mean patient ages ranged from 57 to 63 years. All studies reported enrolling patients with comorbidities, particularly hypertension, but do not stratify results by population characteristics.

Patients received PVI either alone<sup>76, 77, 80, 81</sup> or in combination with ablation at other sites (e.g., cavotricuspid isthmus, superior vena cava, linear lines and/or CFAE).<sup>78, 79</sup> In one study, touchup ablation using RF energy was performed in 28 percent of cryoballoon ablation patients; only results for the subgroup of patients who received cryoballoon ablation only compared with RFA are included in this report. In all other studies, touchup ablation if necessary was performed with the same energy type or with RF energy in less than 20 percent of the cryoballoon ablation arm. Details of ablation and mapping techniques for each study are outline in Table H6 of the Appendix. Percent of patients who underwent touch-up ablation with the other energy source was reported in all studies, ranging from 0 to 28.2 percent in patients with paroxysmal AF,<sup>76, 77, 80, 81</sup> and 11 to 23 percent in patients with paroxysmal, persistent, or permanent AF.<sup>78, 79</sup>

Two studies were considered to be fair quality,<sup>76, 77</sup> and the other four poor quality.<sup>78-81</sup> Five studies are of moderate sample size<sup>76-80</sup> and one is a large study.<sup>81</sup> Assessor blinding for primary clinical outcomes was not described in any of the studies, only three studies had acceptable attrition,<sup>76, 79, 81</sup> three studies controlled for confounding,<sup>76, 77, 80</sup> and four reported fully on prespecified outcomes.<sup>76-79</sup> There were no studies in the Medicare population.

**Table 22. Patient characteristics and overview of study characteristics for comparative observational studies comparing cryoballoon ablation with RFA in patients with paroxysmal atrial fibrillation**

Author (Year) Therapy Sample Size		Schmidt (2013) Retrospective <sup>81</sup> Cryoballoon ablation (n=905)	Schmidt (2013) Retrospective <sup>81</sup> RFA (n=2,870)	Mugnai (2014) Retrospective <sup>80</sup> Cryoballoon ablation (n=136)	Mugnai (2014) Retrospective <sup>80</sup> RFA (n=260)	Chierchia (2010) Prospective <sup>76</sup> Cryoballoon ablation (n=46)	Chierchia (2010) Prospective <sup>76</sup> RFA (n=87)	Knecht (2014) Prospective <sup>77</sup> Cryoballoon ablation (n=71)*	Knecht (2014) Prospective <sup>77</sup> RFA (n=71)*
<b>Patient Demographics</b>	Male, % (n)	64.3 (582)	62.7 (1,800)	72.1 (98)	69.6 (181)	78 (36)	79 (69)	74.7 (53)	77.5 (55)
	Age (years); mean ± SD	63 (53–69)	63 (54–69)	57 ± 13.3	58.3 ± 8.7	56 ± 11	56 ± 9	58.6 ± 10.6	57.8 ± 11.2
	Paroxysmal AF, % (n)	100 (905)	100 (2,870)	100 (136)	100 (260)	100 (46)	100 (87)	100 (71)	100 (71)
	Persistent AF, % (n)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Permanent AF, % (n)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	AF duration (years); mean ± SD	NR	NR	25.1 ± 24	25.4 ± 37.1	3.3 ± 1.9	3.2 ± 1.7	67 ± 70	62 ± 70
	Left atrial size (mm); mean ± SD	NR	NR	41.6 ± 6.8	42.8 ± 6.7	41 ± 5	42 ± 5	39.5 ± 6.0	39.2 ± 5.3
	LVEF (%), mean ± SD	≤40%: 1.2 (11)	≤40%: 2.4 (69)	≤40%: 1.5 (2)	≤40%: 2.3 (6)	64 ± 6	64 ± 6	58.9 ± 6.6	58.8 ± 6.5
	1st/2nd line therapy	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	None	None	None	None	None	None	None	None
<b>Comorbidities, % (n)</b>	Hypertension	57.8 (523)	55.8 (1,601)	25.7 (35)	34.9 (90)	24 (11)	23 (20)	43.7 (31)	47.9 (34)
	Coronary artery disease	16.4 (149)	16.4 (471)	5.1 (7)	9.6 (25)	NR	NR	7.0 (5)	9.9 (7)
	Underlying heart disease	32.5 (294)	31.0 (890)	NR	NR	NR	NR	NR	NR
	Kidney disease	1.8 (16)	2.7 (77)	NR	NR	NR	NR	NR	NR
	Cardiomyopathy	1.7 (15)	2.2 (63)	4.4 (6)	5.0 (13)	NR	NR	NR	NR
	Valvular disease (moderate/severe)	3.0 (27)	8.1 (232)	1.5 (2)	1.5 (4)	NR	NR	NR	NR
	Prior stroke	3.8 (34)	5.5 (158)	5.1 (7)	7.6 (20)	NR	NR	NR	NR
	Diabetes	8.2 (74)	7.2 (207)	2.9 (4)	6.9 (18)	NR	NR	0 (0)	0 (0)
	BMI (kg/m <sup>2</sup> ); mean ± SD	NR	NR	26.2 ± 3.8	27.4 ± 4.8	NR	NR	NR	NR
	Dyslipidemia	NR	NR	33.1 (45)	24.4 (64)	NR	NR	NR	NR
	Prior pacemaker or ICD implant	5.0 (45)	5.8 (167)	NR	NR	NR	NR	NR	NR
	Previous ablation†	NR	NR	9.6 (13)	18.1 (47)	NR	NR	NR	NR
	Hypercholesterolemia	NR	NR	NR	NR	NR	NR	38.0 (27)	35.2 (25)
	Smoking	NR	NR	NR	NR	NR	NR	9.9 (7)	9/9 (7)

<b>Author (Year)</b> Therapy Sample Size		<b>Schmidt (2013)</b> <b>Retrospective</b> <sup>81</sup> Cryoballoon ablation (n=905)	<b>Schmidt (2013)</b> <b>Retrospective</b> <sup>81</sup> RFA (n=2,870)	<b>Mugnai (2014)</b> <b>Retrospective</b> <sup>80</sup> Cryoballoon ablation (n=136)	<b>Mugnai (2014)</b> <b>Retrospective</b> <sup>80</sup> RFA (n=260)	<b>Chierchia</b> <b>(2010)</b> <b>Prospective</b> <sup>76</sup> Cryoballoon ablation (n=46)	<b>Chierchia</b> <b>(2010)</b> <b>Prospective</b> <sup>76</sup> RFA (n=87)	<b>Knecht</b> <b>(2014)</b> <b>Prospective</b> <sup>77</sup> Cryoballoon ablation (n=71) <sup>*</sup>	<b>Knecht</b> <b>(2014)</b> <b>Prospective</b> <sup>77</sup> RFA (n=71) <sup>*</sup>
<b>Study Characteristics</b>	Followup period	Periprocedural	Periprocedural	22.1 ± 14	24.0 ± 13.4	Periprocedural	Periprocedural	28 ± 15	28 ± 15
	Completed followup, % (n)	100 (905)	100 (2,870)	NR	NR	100 (46)	100 (87)	NR	NR
	Blanking period (months)	NR	NR	3 months	3 months	NR	NR	3 months	3 months
	Touch-up with other energy source	10.6 (96)	0 (0)	3.7 (5)	0 (0)	0 (0)	0 (0)	28.2 (20)	0 (0)

AF = atrial fibrillation; BMI = body mass index; CHADS2 = Cardiac failure, Hypertension, Age, Diabetes, Stroke system; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; NR = not reported; RFA = radiofrequency catheter ablation; SD = standard deviation.

\*In the cryoballoon ablation group, 28% (20/71) of patients received touchup ablation using a focal RF catheter. Authors report a propensity score-matched subgroup analysis in those patients who received cryoballoon only (n=51) vs. RFA (n=51); outcomes are reported in these subgroups only.

†Reported as previous cavotricuspid isthmus ablation or accessory pathway ablation.

**Table 23. Patient characteristics and overview of study characteristics for comparative observational studies comparing cryoballoon ablation with RFA in patients with paroxysmal, persistent, or permanent atrial fibrillation**

<b>Author (Year)</b> Therapy Sample Size		<b>Mandell (2013) Retrospective<sup>79</sup></b> Cryoballoon ablation (n=62)	<b>Mandell (2013) Retrospective<sup>79</sup></b> RFA (n=62)	<b>Kojodjojo (2010) Retrospective<sup>78</sup></b> Cryoballoon ablation (n=124)	<b>Kojodjojo (2010) Retrospective<sup>78</sup></b> RFA (n=53)
<b>Patient Demographics</b>	Male, % (n)	58.1 (36)	74.2 (46)	77 (96)	77 (41)
	Age (years); mean ± SD	61 ± 8.8	60.4 ± 8.4	58.5 ± 9.4	59.3 ± 9.7
	Paroxysmal AF, % (n)	67.7 (42)	54.8 (34)	72.6 (90)	100 (53)
	Persistent AF, % (n)	29.0 (18)	43.5 (27)	27.4 (34)	0 (0)
	Permanent AF, % (n)	3.3 (2)	1.6 (1)	0 (0)	0 (0)
	AF duration (years); mean ± SD	NR	NR	5.7 years	6.0 ± 4.8
	Left atrial size (mm); mean ± SD	NR (23.4% dilated)	NR (25.0% dilated)	40.6	41.6 ± 6.5
	LVEF (%), mean ± SD	NR	NR	64.7	60.3 ± 7.3
	1st/2nd line therapy	Both (85.5% 1 <sup>st</sup> line)	Both (53.2% 1 <sup>st</sup> line)	2 <sup>nd</sup> line	2 <sup>nd</sup> line
	Special population	None	None	None	None
<b>Comorbidities, % (n)</b>	Heart failure	8.8 (5)	12.9 (8)	NR	NR
	Hypertension	52.5 (33)	64.5 (40)	106 (62)	26 (14)
	Coronary artery disease	16.1 (10/62)	16.1 (10)	6 (5)	6 (3)
	Obstructive sleep apnea	9.7 (6)	20.9 (13)	NR	NR
	Valvular disease (moderate/severe)	Mitral: 14.5 (9) Aortic: 3.2 (2) Other: 0 (0)	Mitral: 4.8 (3) Aortic: 0 (0) Other: 3.2 (2)	NR	NR
	LV hypertrophy	1.7 (1)	9.7 (6)	NR	NR
	BMI (kg/m <sup>2</sup> ); mean ± SD	30.5 ± 7.2	31.3 ± 7.2	NR	NR
<b>Study Characteristics</b>	Followup period	Periprocedural	Periprocedural	13.3 ± 7.4 months	15.6 ± 7.4 months
	Completed followup, % (n)	100 (62)	100 (62)	NR	NR
	Blanking period (months)	None used	None used	3 months	3 months
	Touch-up with other energy source	11 (7)	0 (0)	23 (28)	0 (0)

AF = atrial fibrillation; BMI = body mass index; CHADS2 = Cardiac failure, Hypertension, Age, Diabetes, Stroke system; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; NR = not reported; RFA = radiofrequency catheter ablation; SD = standard deviation.

## Detailed Synthesis

### Primary Outcomes

None of the primary outcomes of interest (mortality, stroke, congestive heart failure, health-related quality of life, etc.) were reported by any of the RCTs. One poor-quality observational study<sup>80</sup> in people with paroxysmal AF reported all-cause mortality greater than 30 days of 1.2 percent (3/260) in the RFA arm versus none (0/136) in the cryoballoon ablation arm and TIA of 0.4 percent (1/260) and 0.7 percent (1/136) in the RFA and cryoballoon ablation patients, respectively (Table 24).

### Intermediate Outcomes

#### Freedom From Recurrence of Atrial Arrhythmia

Freedom from AF recurrence was reported in both RCTs and was less common in those receiving cryoballoon ablation (48% and 68%) versus RFA (66.7% and 86.7%) but differences between treatments failed to reach statistical significance in either trial (Table 25).<sup>74, 75</sup> In those with paroxysmal AF 48 percent of the cryoballoon group versus 68 percent of the RFA group were free from recurrence at 12 months.<sup>75</sup> The trial that included patients with any AF type reported 66.7 percent of cryoballoon ablation versus 86.7 percent RFA recipients were free from recurrence.<sup>74</sup>

Across three observational studies (one fair-, two poor-quality), in paroxysmal AF patients, no statistical differences between cryoballoon ablation and RFA for freedom from recurrence were seen at 12 months,<sup>78</sup> 23<sup>80</sup> or 28 months<sup>77</sup>; the proportions of patients in each group experiencing freedom from recurrence were similar (Table 24). One poor-quality study reported no significant differences between treatment groups based on survival analysis at any time point up to 18 months.<sup>78</sup>

#### Reablation

Reablation for AF only was more common following cryoballoon ablation in both RCTs at 12 months. In the fair-quality trial of paroxysmal AF, a significant difference was seen between cryoballoon ablation (24%) and RFA (0%) (RR 0.22, 95% CI 0.07 to 0.37, p=0.01).<sup>75</sup> In the second poor-quality trial in people with any AF type, the difference between groups failed to reach statistical significance (cryoballoon ablation 30% vs. RFA 13.3%; RR 2.25, 95% CI 0.78 to 6.51; p=0.12)<sup>74</sup> as did reablation for any arrhythmia as reported by this same trial (cryoballoon ablation 30% vs. RFA 20%; RR 1.5, 0.61 to 3.7, p=0.37)<sup>74</sup> (Table 25).

Conversely, repeat ablation was more common in the RFA arm (23%) as compared to the cryoballoon ablation arm (14%) after an overall mean followup period of 14 months in one poor-quality observational study of a mixed AF population but was not statistically significant.<sup>78</sup> Of note, the patients who received RFA were followed for a longer period of time than those who received cryoballoon ablation, 15.6 ± 7.4 months versus 13.3 ± 7.4 months (Table 24).

#### Atrial Flutter

There were no statistical differences between cryoballoon and RFA in either trial, however, the trial of paroxysmal AF (fair quality) reported a higher frequency after cryoballoon ablation versus RFA (16% versus 4%)<sup>75</sup> than the other poor-quality trial in a mixed AF population (0% versus 6.7%)<sup>74</sup> (Table 25).

## **AF burden**

AF burden in patients who experienced AF recurrence after ablation (n=21) was reported in one fair-quality trial of paroxysmal AF.<sup>75</sup> Although there was no statistical difference between cryoballoon and RFA in the median number of AF episodes per month (7.3 for cryoballoon versus 0.7 for RFA) or in the maximum duration of AF episodes (12 versus 4.4 hours), the number of hours per month and percent of time spent in AF were significantly different (Table 25).

## **Complete Isolation of Pulmonary Veins**

One poor-quality retrospective comparative observational study of a mixed AF population reported no difference between cryoballoon ablation and RFA treatment groups in terms of the percentage of patients who had treatment failure (96.2% vs. 93.4%) (N=124), which was defined as complete isolation of all pulmonary veins as evidenced by complete entrance and exit block.<sup>79</sup>

## **Effect on Coagulation and Inflammatory Biomarkers**

One poor-quality RCT focused on comparing cryoballoon ablation with RFA with respect to procoagulant microparticles, platelet activation and inflammatory biomarkers.<sup>74</sup> Both treatments were similar with respect to the release of high-sensitivity troponin T, shedding of procoagulant microparticles, and platelet activation at 24 and 48 hours. High sensitivity C-reactive protein tended toward a higher peak value after 48 hours post RFA ( $28.6 \pm 22.7$  mg/L vs. cryoablation  $20.5 \pm 23.3$  mg/L,  $p=0.175$ ), with no statistically significant differences after correction for repeated measurements.



**Table 24. Primary and intermediate effectiveness outcomes for comparative observational studies comparing cryoballoon ablation with RFA**

Outcome		AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	Cryoballoon ablation % (n/N)	RFA % (n/N)	p-value
Primary Outcomes *	Mortality (all-cause) >30 days	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Mean 23 ± 13.4 months	0% (0/136)	1.2% (3/260) <sup>†</sup>	NR
	TIA >30 days	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Mean 23 ± 13.4 months	0.7% (1/136) <sup>‡</sup>	0.4% (1/260) <sup>‡</sup>	NR
Intermediate Outcomes	Freedom from recurrence (any arrhythmia)	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Mean 23 ± 13.4 months	63.2% (86/136)	57.3% (149/260)	0.25
			Knecht 2014 <sup>77</sup>	Mean 28 ± 15 months	54.9% (28/51) <sup>§</sup>	54.9% (28/51) <sup>§</sup>	0.81
			Kojodjojo 2010 <sup>78</sup> **	12 months	76.7% (79/90)**	71.7% (38/53)**	NS
	Repeat ablation for recurrent AF	Mixed (2 <sup>nd</sup> line)	Kojodjojo 2010 <sup>78</sup>	Mean 14 months	13.7% (17/124)	22.6% (12/53)	NR

AF = atrial fibrillation; NA = not applicable; NR = not reported; NS = not significant; RFA = radiofrequency ablation; TIA = transient ischemic attack.

\*Mortality and TIA had to occur at a time point >30 days (or timing NR) to be considered an effectiveness outcome. TIA was not defined further in the study.

<sup>†</sup>Spontaneous massive intracerebral hemorrhage (after 3 months); cardiogenic shock and sepsis in hypertrophic cardiomyopathy with severely reduced ejection fraction (33%) (at 7 months); and severe endocranial hypertension secondary to cerebral glioblastoma (at 9 months).

<sup>‡</sup>TIAs occurred at 5 months (RFA) and 6 months (Cryoablation). One patient receiving RFA had 2 TIAs.

<sup>§</sup>Reported in a subset of 51 patient subset of propensity score-matched dataset comparing patients who underwent pulmonary vein isolation using cryoballoon ablation only and RFA.

\*\*Kojodjojo 2010 included both paroxysmal (n=90) and persistent (n=34) patients in the cryoballoon ablation group. However, for the outcome freedom from recurrence, authors compared only the 90 paroxysmal patients with the RFA group (all 53 paroxysmal); therefore, for this outcome only, Kojodjojo 2010 is listed as “AF Type” paroxysmal (versus mixed for repeat ablation).

**Table 25. Intermediate efficacy outcomes for RCTs comparing cryoballoon ablation with RFA**

Outcome	AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	Cryoablation % (n/N)	RFA % (n/N)	Effect size RR (95% CI)*
Freedom From Recurrence (AF only)	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	48.0% (12/25)	68.0% (17/25)	RR 0.71 (0.43, 1.14) p=0.15
	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	12 months	66.7% (20/30)*	86.7% (26/30)	RR 1.1 (0.76, 1.5) p=0.68
Reablation (AF only)	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	24.0% (6/25)	0% (0/25)	RR 0.22 (0.07, 0.37) p=0.01
	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	12 months	30.0% (9/30)	13.3% (4/30)	RR 2.25 (0.78, 6.51) p=0.12
Reablation (any arrhythmia)	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	12 months	30.0% (9/30)	20.0% (6/30) <sup>†</sup>	RR 1.5 (0.61, 3.7) p=0.37
Atrial Flutter	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	16.0% (4/25) <sup>‡</sup>	4.0% (1/25) <sup>‡</sup>	RR 4.0 (0.48, 33.3) p=0.17
	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	12 months	0% (0/30)	6.7% (2/30)	RR incalculable p=0.49
AF Burden (median IQR): Number of AF episodes per month	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	$\frac{n=13^{\S}}{7.3 (0.2-381)}$	$\frac{n=8^{\S}}{0.7 (0.1-2.2)}$	p=0.07
AF Burden (median IQR): Time in AF (hours/month)	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	$\frac{n=13^{\S}}{44.6 (1.4-197.5)}$	$\frac{n=8^{\S}}{1.4 (0.2-5.4)}$	p=0.02
AF Burden (median IQR): Time in AF (%)	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	$\frac{n=13^{\S}}{0.06 (0.002-0.27)}$	$\frac{n=8^{\S}}{0.002 (0.001-0.01)}$	p=0.02
AF Burden (median IQR): Maximum duration of AF episodes (hours)	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	12 months	$\frac{n=13^{\S}}{12 (4.8-23.6)}$	$\frac{n=8^{\S}}{4.4 (1.4-23.2)}$	p=0.38

AADs = antiarrhythmic drugs; AF = atrial fibrillation; IQR = interquartile range; NR = not reported; RFA = radiofrequency ablation; RR = risk ratio.

\*Risk ratios, 95% CI and p-values (except for AF burden) were calculated using Stata. Risk ratio was chosen (as opposed to odds ratio) because it may be a more appropriate measure of effect size given that this is a frequent event.

\*Of the 11 patients reported to have an AF recurrence in the cryoablation group, one experienced AV nodal reentrant tachycardia and underwent reablation 2 months after the index procedure. For the purposes of this report, any recurrence or reablation occurring with 3 months is considered an adverse event; thus, this patient was not counted for either freedom from recurrence or reablation as a secondary efficacy outcome.

<sup>†</sup>Two patients underwent reablation for atrial flutter.

<sup>‡</sup>All patients with atrial flutter recurrence also had AF recurrence.

<sup>§</sup>AF burden in patients with AF recurrences after ablation.

Key Question 2a. What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation versus medical therapy in the general adult and Medicare populations?

## Key Points

### Radiofrequency Ablation Versus Medical Therapy

#### Mortality (all-cause) (within 30 days)

- **Overall:** The 30-day mortality risk was similarly low following RFA versus medical therapy based on data from five RCTs of patients with paroxysmal or persistent AF.
- **Paroxysmal AF:** There was low risk of this event in both treatment groups based on three RCTs (RFA: 0% to 0.7%; medical therapy: 0%) (low strength of evidence).
- **Persistent AF:** There was low risk of all-cause mortality following RFA and medical therapy based on data from two RCTs (RFA: 0%; medical therapy: 0% to 4.2% [1/24]) (low strength of evidence). One prospective cohort study of the subpopulation of patients 65 years and older (Medicare population) reported low risk in both treatment groups (insufficient strength of evidence).

#### Stroke (any type) (within 30 days)

- **Overall:** The 30-day stroke risk was low following RFA and medical therapy based on data from eight RCTs (RFA: 0% to 4.8%; medical therapy: 0%).
- **Paroxysmal AF:** There was low risk in both groups as reported by three RCTs (RFA: 0% to 0.7%; medical therapy: 0%) (low strength of evidence).
- **Persistent AF:** The risk was low in both groups based on data from three RCTs (RFA: 0% to 4.8%; medical therapy: 0%) (low strength of evidence). In the subpopulation of patients 65 years and older (Medicare population) a single observational prospective cohort study reported higher risk following RFA versus medical therapy (insufficient strength of evidence).
- **Mixed:** There was low risk in both groups based on data from two RCTs (RFA: 0% to 1.5%; medical therapy: 0%) (low strength of evidence). One observational retrospective cohort study also reported low risk in both treatment groups (insufficient strength of evidence).

#### Atrial Fibrillation (within 3 months)

- **Paroxysmal AF:** The 3-month AF risk was similarly low across RFA and medical therapy groups based on data from two RCTs (pooled RR 0.67, 95% CI 0.40 to 1.11) (low strength of evidence).
- **Persistent AF:** The 2- to 3-month risk of AF recurrence was lower following RFA versus medical therapy based on data from three RCTs (pooled RR, 0.18, 95% CI 0.11 to 0.30).
- **Mixed:** Comparative data not reported (insufficient strength of evidence).

## Cardiac Tamponade

- **Paroxysmal AF:** The incidence of cardiac tamponade following RFA was low based on data from four RCTs (512 patients total) (pooled risk 1.7%; 95% CI 0.8 to 2.6) (low strength of evidence).
- **Persistent AF:** Pooled data from three small RCTs of 73 patients total suggested the incidence of cardiac tamponade following RFA was 5.5 percent (95% CI 2.1 to 13.7), while one observational comparative study on the subset of patients aged 65 years and older (Medicare population) reported no events (insufficient strength of evidence).

## Pericardial Effusion

- **Overall:** The incidence of pericardial effusion following RFA was low based on data from five RCTs (range, 0.5% to 0.9 %).
- **Paroxysmal AF:** The incidence of pericardial effusion following RFA was low based on data from four RCTs (pooled risk 0.6%, 95% CI 0.2 to 1.8) (low strength of evidence).
- **Persistent AF; Mixed AF:** One RCT each reported a low risk following RFA (insufficient strength of evidence).

## Pulmonary Vein Stenosis

- **Paroxysmal AF:** The incidence of pulmonary vein stenosis following RFA was low based on data from five RCTs (range, 0% to 3.1%) (low strength of evidence). One nonrandomized comparative study reported zero cases (insufficient strength of evidence).
- **Persistent AF:** The incidence of pulmonary vein stenosis following RFA was low based on data from two RCTs (range, 0% to 0.9%) (low strength of evidence). For the subset of patients aged 65 years and older (Medicare population), one nonrandomized comparative study reported no cases (insufficient strength of evidence).
- **Mixed:** There were no cases following RFA as reported by one RCT (low strength of evidence). The risk of pulmonary vein stenosis was higher in one nonrandomized comparative study (insufficient strength of evidence).

## Drug Intolerance Leading to Discontinuation

- **Paroxysmal AF:** Overall, 5 to 23 percent of patients randomized to medical therapy discontinued antiarrhythmic drugs due to adverse events or intolerance (2 RCTs) (low strength of evidence). Due to limited duration and/or usage of medical therapy in the RFA group it was difficult to make comparative conclusions.
- **Persistent AF:** There was no evidence from RCTs. One nonrandomized comparative study of Medicare-aged patients reported this event in fewer patients in the RFA versus the medical therapy groups (insufficient strength of evidence).
- **Mixed:** One RCT reported similar risk between groups (insufficient strength of evidence).

## Cryoablation Versus Medical Therapy

### Mortality (all-cause), Stroke (any type) (within 30 days)

- **Mixed:** No deaths occurred in either treatment group, and the 30-day stroke risk was low in both treatment groups (cryoballoon ablation: 0.6%; medical therapy: 1.2%) based on data from one RCT (insufficient strength of evidence).

### AF recurrence (within 3 months)

- **Mixed:** Over half of cryoablation patients (51.5%) experienced recurrence of AF within 3 months of treatment based on data from one RCT; no data were reported for the control group (insufficient strength of evidence).

### Cardiac Tamponade

- **Mixed:** One RCT reported low incidence of cardiac tamponade following cryoballoon ablation (0.9% for both) (insufficient strength of evidence).

### Pulmonary Vein Stenosis

- **Mixed:** One RCT reported low incidence of pulmonary vein stenosis following cryoablation (0.9%) (insufficient strength of evidence).

### Atrial Fibrillation (within 3 months), Pericardial Effusion, Drug Intolerance Leading to Discontinuation

- **Mixed:** No data reported.

## Radiofrequency Ablation Versus Medical Therapy

### Description of Included Studies

#### Randomized Controlled Trials

All thirteen RCTs comparing RFA with medical therapy that were included in Key Question 1a reported adverse events.<sup>35-47, 83</sup> See Key Question 1a as well as the detailed demographics tables for general study characteristics (Appendix E, Tables E1–E3, E7–E9). There was substantial crossover (37.0%–87.9%) from medical therapy to RFA in six trials<sup>35, 42-45, 47, 83</sup> and two trials reported lower crossover rates of 9.4 percent<sup>38</sup> and 3.8 percent.<sup>39</sup> There was also crossover from RFA to medical therapy in seven RCTs (0%–9.4%).<sup>35, 38, 41, 42, 44, 46, 47, 83</sup> Adverse events attributable to either ablation or medical therapy were reported on an as-treated basis and thus data includes crossover patients.

#### Comparative Observational Studies

Seven comparative observational studies comparing RFA with medical therapy reported adverse events. See Key Question 1a as well as the detailed demographics tables for general study characteristics (Appendix E, Table E4–E6, E10–E12). Four of the studies were fair-quality,<sup>48-50, 52</sup> and three were poor quality.<sup>51, 53, 54</sup> Three included only paroxysmal AF patients,<sup>49, 52, 54</sup> one included only persistent AF patients,<sup>48</sup> two included a mix of AF types,<sup>51, 53</sup> and one did not specify AF type.<sup>50</sup> The study of persistent AF patients reported that 1.9 percent (5/259)

medical therapy patients crossed over to RFA due to AF/AT recurrence, while 9.2 percent (14/153) of RFA patients experienced recurrence and were treated with medical therapy.<sup>48</sup> Two studies were applicable to the Medicare population: one only included elderly patients (mean age, 75.6 years),<sup>48</sup> while another included patients with a mean age of 67 years.<sup>53</sup>

## Case Series

Sixteen case series and one meta-analysis of case series specifically designed to evaluate the incidence of adverse events following catheter ablation were included: four prospective<sup>57, 58, 64, 68</sup> and two retrospective<sup>63, 71</sup> case-series; two prospective, multicenter registries;<sup>55, 60</sup> two prospective database studies (one single-center,<sup>59</sup> one multicenter<sup>56</sup>); one survey of eighteen electrophysiological centers;<sup>69</sup> five administrative database studies,<sup>61, 62, 65, 67, 70</sup> one of which was in Medicare beneficiaries<sup>65</sup> and one meta-analysis of case series reporting on AF recurrence.<sup>66</sup> Seven studies included paroxysmal, persistent and permanent AF patients,<sup>55-59, 66, 71</sup> two included only paroxysmal and persistent,<sup>60, 64</sup> and six did (or could) not report the type of AF in their populations.<sup>61-63, 65, 67-70</sup> Sample sizes ranged from 1000 to 15,423 patients, with two studies reporting events per the number of procedures only (1190 and 93,801).<sup>59, 62</sup> Followup periods varied across studies and included inpatient,<sup>61, 62, 66</sup> periprocedural,<sup>57, 58, 63</sup> 7 days or less,<sup>67, 69</sup> 30 days or less,<sup>55, 59, 60, 65</sup> and 3 months or less.<sup>56, 64</sup> Ablation was performed using RF energy exclusively in twelve studies,<sup>55-59, 62-64, 66-68, 71</sup> and a mix of energy sources (i.e., RF, cryoballoon) in two,<sup>60, 61</sup> three studies did not report the type of energy used.<sup>65, 69, 70</sup>

## Detailed Synthesis

### Major Adverse Events

#### Mortality (cardiovascular) (within 30 days)

Five fair-quality small RCTs (range, 50–286 patients) comparing RFA with medical therapy reported mortality caused by cardiovascular events that occurred within 30 days of treatment.<sup>35, 37, 41, 42, 47</sup> Three trials included only paroxysmal AF patients,<sup>35, 42, 47</sup> while two included only persistent AF patients.<sup>37, 41</sup> Overall, the risk of mortality from cardiovascular causes following RFA versus medical therapy was low (range, 0%–0.7% vs. 0%–4.2% of patients). Specifically only one death occurred in each treatment group: one paroxysmal AF patient in the ablation group died of a procedure-related cerebral stroke<sup>35</sup> and one persistent AF patient with heart failure treated with medical therapy experienced sudden cardiac death<sup>37</sup> (Table 26).

No comparative observational studies comparing RFA with medical therapy reported cardiovascular mortality within 30 days of treatment.

Mortality due to cardiovascular causes within 30 days of ablation was not reported in any of the case series.

#### Mortality (all-cause) (within 30 days)

Five fair-quality RCTs comparing RFA with medical therapy reported all-cause mortality occurring within 30 days of treatment.<sup>35, 37, 41, 42, 47</sup> These trials were small, enrolling between 50 and 286 patients. Three trials included only paroxysmal AF patients,<sup>35, 42, 47</sup> and two included only persistent AF patients.<sup>37, 41</sup> Overall, the risk of mortality following RFA versus medical therapy was low (range, 0%–0.7% vs. 0%–4.5% of patients), with only one death occurring in each treatment group (Table 26). Details on the causes of death are noted in the previous section (cardiovascular mortality).

One fair-quality prospective comparative observational study of 412 persistent AF patients with a mean age of 75 (i.e., Medicare population) treated with RFA versus medical therapy similarly reported low rates of all-cause mortality (0% vs. 0.4%, respectively) (Table 27).<sup>48</sup> The cause of death was not reported.

Across eleven case series, all-cause mortality within 30 days of ablation was reported in: 0 to 0.4 percent of RFA patients (N=1000–5947),<sup>55-57, 64, 67</sup> 0.4 percent of RFA procedures (1190–93,801 procedures),<sup>59, 62</sup> and 0.1 to 0.8 percent of patients who underwent procedures using a variety of energy sources (N=1273–15,423) (Appendix H, Table H4).<sup>60, 61, 65, 70</sup>

### **Stroke (any type) (within 30 days)**

Eight RCTs reported stroke within 30 days following RFA versus the initiation of medical therapy.<sup>35-37, 40-42, 45, 46</sup> One trial was considered good quality,<sup>45</sup> and the remaining seven were fair quality.<sup>35-37, 40-42, 46</sup> Each trial enrolled between 40 and 286 patients. Overall, there was no difference in 30-day stroke risk between treatment groups in any study, with stroke reported in 0 to 4.8 percent of RFA patients per study and in 0 percent of medical therapy patients (Table 26). In total, four RFA patients experienced a stroke: one paroxysmal AF patient had a peri-procedural cerebral stroke (that resulted in death),<sup>35</sup> one patient in another study of heart failure patients experienced a procedural stroke and withdrew from the study,<sup>37</sup> and one person in a study of patients with advanced heart failure and persistent AF had a stroke 6 days post-ablation and withdrew from the study,<sup>40</sup> and one patient in a mixed AF population study had a stroke during left atrium ablation.<sup>45</sup>

Two comparative observational studies<sup>48, 51</sup> reported on this outcome: one fair-quality prospective of 412 persistent AF patients with a mean age of 75 years (i.e., Medicare population),<sup>48</sup> and one poor-quality retrospective study of a mixed AF population.<sup>51</sup> While the fair-quality Medicare population study found a higher risk of 30-day stroke following RFA versus medical therapy (2.6% vs. 0.4%,  $p=0.0462$ ) (N=411),<sup>48</sup> there was no difference in the occurrence of stroke within the first 30 days of treatment initiation between treatment groups in the low-quality study (1.2% vs. 1.2%; N=170) (Table 27).<sup>51</sup>

Across eight case series and one meta-analysis of case series, stroke within 30 days of ablation was reported in: 0.08 percent to 0.71 percent of RFA patients (N=1000–7217),<sup>55, 57, 64, 66-68</sup> 0.8 percent of 1190 RFA procedures,<sup>59</sup> and in 0.2 percent to 0.6 percent of patients who underwent procedures using a variety of energy sources (N=4156–6207) (Appendix H, Table H4).<sup>61, 70</sup>

### **Myocardial Infarction (within 30 days)**

One RCT of 159 paroxysmal AF patients reported no cases of myocardial infarction within 30 days of treatment initiation in either group (Table 26).<sup>47</sup>

One prospective fair-quality cohort study of 412 persistent AF patients with a mean age of 75 years (i.e., Medicare population) reported no difference in 30-day myocardial infarction between the RFA and medical therapy groups (1.3% vs. 0%; N=412 patients total) (Table 27).<sup>48</sup>

Across three case series, myocardial infarction within 30 days of ablation was reported in: 0.30 percent of 5947 RFA patients,<sup>67</sup> 0.37 percent of 93,801 RFA procedures,<sup>62</sup> and in 0.31 percent of patients who underwent procedures using a variety of energy sources (N=15,423) (Appendix H, Table H4).<sup>65</sup>

### **Transient Ischemic Attack (within 30 days)**

Six fair-quality RCTs reported TIA within 30 days of treatment (Table 26).<sup>36, 41, 42, 44, 46, 47</sup> Across the four RCTs of paroxysmal AF patients (range, 70–198 patients), TIA occurred in 0 to 1 percent of patients in the RFA group and in 0 percent of medical therapy patients.<sup>42, 44, 46, 47</sup> One small study of persistent AF patients<sup>41</sup> and one small study of a mixed population of patients<sup>36</sup> each reported no instances of 30-day TIA in either treatment group.

One prospective fair-quality cohort study of 412 persistent AF patients with a mean age of 75 (i.e., Medicare population) reported similar risk of 30-day TIA following RFA versus medical therapy (1.3% vs. 0.4%) (Table 27).<sup>48</sup>

Across eight case series, TIA within 30 days of ablation was reported in: 0.1 percent to 0.6 percent of RFA patients (N=1000–5947),<sup>55-57, 64, 67, 68</sup> 0.3 percent of 1190 RFA procedures,<sup>59</sup> and in 0.07 percent of patients who underwent procedures using a variety of energy sources (N=4156) (Appendix H, Table H4).<sup>61</sup>

Across four case series, stroke or TIA within 30 days of ablation was reported in: 0.4 percent to 1.0 percent of 1506 to 93,801 RFA procedures<sup>62, 71</sup> and in 0.7 to 0.8 percent of patients who underwent procedures using a variety of energy sources (N=1273–15,423) (Appendix H, Table H4).<sup>60, 65</sup>

### **Other Embolic Events (within 30 days)**

One fair-quality RCT of 159 paroxysmal AF patients reported no cases of thromboembolic events within 30 days of treatment in either group (Table 26).<sup>47</sup>

Two fair-quality prospective cohort studies also reported on this outcome. While one study of 412 elderly patients (mean age, 75 years, Medicare population) with persistent AF reported no other instances of 30-day embolic events following either RFA or initiation of medical therapy,<sup>48</sup> one study of 166 paroxysmal AF patients reported that no RFA patients and three AAD patients experienced thromboembolic events (0% vs. 3.6%, respectively) (Table 27).<sup>52</sup> This difference was not statistically meaningful.

Two case series reported other embolic events within 30 days of ablation in 0.08 percent to 0.70 percent of RFA patients (N=1294–5947); specifically, there was one case of mesenteric embolism (Appendix H, Table H4).<sup>64, 67</sup>

### **Major Bleeding, Hemorrhage, or Transfusion (within 30 days)**

There was no difference in the risk of 30-day major bleeding, hemorrhage, or transfusion between treatment groups as reported by two fair-quality RCTs (range, 5.7%–6.4% vs. 1.9%–5.7%; N=137 total) (Table 26).<sup>46, 47</sup> One study enrolled paroxysmal AF patients<sup>46</sup> and the other enrolled a mix of paroxysmal and persistent AF patients.<sup>47</sup>

One fair-quality prospective observational study of 412 persistent AF patients with a mean age of 75 (i.e., Medicare population) reported no cases of this outcome following RFA versus medical therapy (N=412 patients) (Table 27).<sup>48</sup>

Across five case series, major bleeding, hemorrhage, or transfusion within 30 days of ablation was reported in: 3.7 percent of 5947 RFA patients,<sup>67</sup> 0.07 to 4.0 percent of 1190 to 93,801 RFA procedures,<sup>59, 62, 71</sup> and 2.1 percent of 6207 patients undergoing ablation using a variety of energy sources<sup>70</sup> (Appendix H, Table H4).

### **Heart Failure (within 30 days)**

Two fair-quality RCTs reported heart failure within 30 days of treatment initiation.<sup>40, 47</sup> There was no difference between treatment groups in the risk of heart failure in one trial of 159



paroxysmal AF patients (1.0 % vs. 0%)<sup>47</sup> or in the development of worsening heart failure in one trial of 40 persistent AF patients with advanced heart failure (14.3% vs. 0%) (Table 26).<sup>40</sup> In the latter trial, two patients were treated with intravenous diuretic before discharge, and one patient required readmission for treatment.

One fair-quality prospective observational study of 412 persistent AF patients with a mean age of 75 (i.e., Medicare population) reported no instances of 30-day heart failure (Table 27).<sup>48</sup>

Heart failure within 30 days of ablation was not reported in any of the case series.

## **Arrhythmia (within 3 months)**

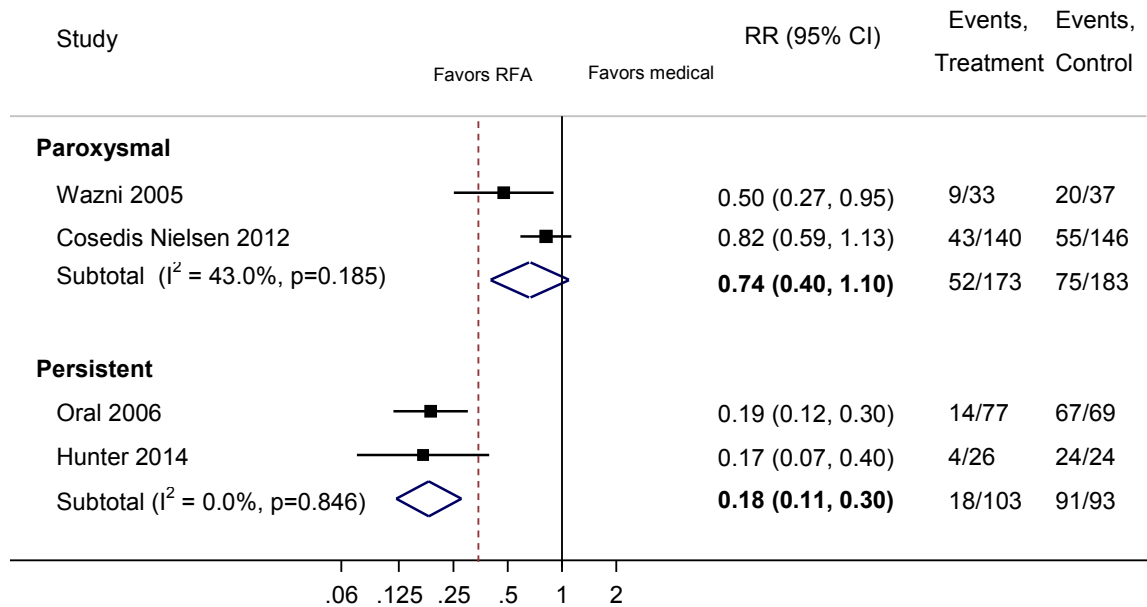
### **Atrial Fibrillation**

Atrial fibrillation was reported to recur within the first 3 months following initiation of treatment in 11.1 to 47.6 percent of RFA patients (6 RCTs)<sup>35, 37, 40, 43, 44, 46</sup> and in 37.7 to 100 percent of medical therapy patients (4 RCTs) (Table 26).<sup>35, 37, 43, 46</sup> Although the trend suggests that 3-month AF recurrence was more frequent in the medical therapy group, only four of the six RCTs reported comparative data for the RFA versus medical therapy groups, all of which were fair quality.<sup>35, 37, 43, 46</sup> Of the two studies of paroxysmal AF patients reporting data for both groups, the pooled estimate suggests no difference between treatment groups (pooled RR 0.74, 95% CI 0.40 to 1.10) (Figure 8). While one found a significantly lower risk of 2-month AF recurrence in RFA patients (RR 0.50, 95% CI 0.27 to 0.95; N=70),<sup>46</sup> the other found no difference between treatment groups in AF recurrence within the first 3 months (RR 0.82, 95% CI 0.59 to 1.13; N=286).<sup>35</sup> Both of these studies were treating patients with a first-line therapy for paroxysmal AF, and in neither study administered medical therapy to RFA patients (unless crossover occurred). One trial did not allow crossover until much later ( $\geq 12$  months),<sup>46</sup> and the other did not restrict the timing of crossover.<sup>35</sup> In the latter RCT, 9 percent of RFA and 37 percent of medical therapy patients crossed over. In contrast, pooled data from the two trials of persistent AF patients reporting for both groups found that the risk of 2- to 3-month AF recurrence was significantly lower in RFA patients (pooled RR 0.18, 95% CI 0.11 to 0.30; N=146) (Figure 8).<sup>37, 43</sup> Of note, both of these trials were in heart failure patients.

One poor-quality observational retrospective cohort study of a mixed population of AF patients reported that 46 percent (39/85) of RFA patients had recurrence of AF within the first 2 months, however, no data were reported for the medical therapy group (Table 27).<sup>51</sup>

AF within 3 months of ablation was not reported in any of the included case series.

**Figure 8. Profile likelihood model meta-analysis of AF recurrence within the first 3 months of followup in RCTs comparing RFA with medical therapy in patients with paroxysmal AF**



AF = atrial fibrillation; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation; RR = relative risk.

### Other Types of Arrhythmia (within 3 months)

Data from three fair-quality RCTs suggested that atrial flutter within the first 3 months of treatment initiation occurred in a small percentage of patients, with no difference between RFA and medical therapy treatment groups in any trial (0%–5.2% vs. 0%–1.5%) (125 to 198 patients per study) (Table 26).<sup>42-44</sup>

Two fair-quality RCTs reported that, compared to those in the RFA groups, nearly twice as many patients in the medical therapy experienced atrial fibrillation or atrial flutter within the first 5 weeks to 3 months.<sup>36, 41</sup> In the trial of 141 persistent AF patients the difference between groups was significant (29.6% vs. 54.2%),<sup>41</sup> while the difference between groups in the smaller study of 70 mixed AF patients did not (8.6% vs. 14.3%) (Table 26).<sup>36</sup>

Regarding bradycardia, one fair-quality RCT of 125 paroxysmal patients reported no difference between RFA and medical therapy groups (1.5% vs. 0%),<sup>42</sup> while another fair-quality RCT of 198 paroxysmal AF patients reported significantly lower risk of bradycardia following RFA versus medical therapy (0% vs. 15.2%,  $p<0.001$ ) (Table 26).<sup>83</sup> This latter RCT also reported lower rates of tachycardia following RFA versus medical therapy (9.1% vs. 36.4%; RR 0.25, 95% CI 0.13 to 0.49).<sup>44</sup>

Arrhythmias not clearly defined that occurred within the first 3 months as reported by RCTs are listed in Table 26.

One comparative observational study reported no cases of torsade de points in either treatment group (Table 27).<sup>49</sup>

Arrhythmias within 3 months of ablation were not reported in any of the included case series.

## Ablation-Related Adverse Events

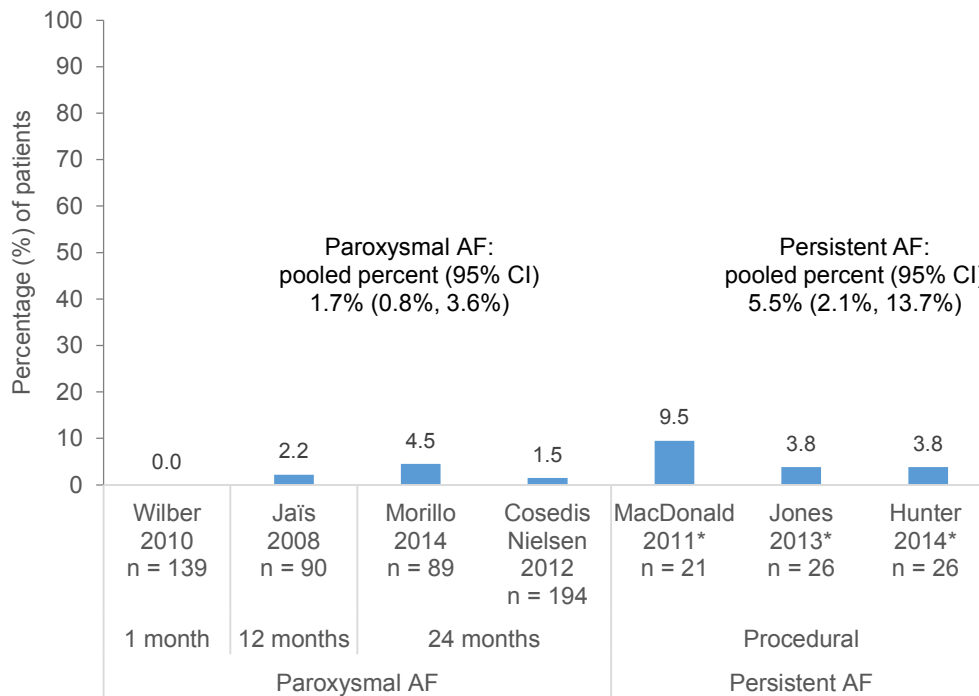
### Cardiac Tamponade

Seven fair-quality RCTs assessed the risk of cardiac tamponade in patients who were randomized to RFA or who received RFA after crossover from the medical therapy group.<sup>35, 37-40, 42, 47</sup> Overall, the risk of cardiac tamponade ranged from 0 to 9.5 percent (2/21) (range, 21–194 patients per study) (Figure 9, Table 26). In the four trials of paroxysmal AF patients, cardiac tamponade occurred in 0 to 4.5 percent (4/89) of patients (range, 89–194 patients per study), with a pooled estimate of 1.7 percent (95% CI 0.8 to 3.6).<sup>35, 38, 42, 47</sup> In the three small trials of persistent AF patients, procedural cardiac tamponade occurred in 4 percent (1/26) to 10 percent (2/21 in both trials reporting) of patients, with a pooled estimate of 5.4 percent (95% CI 2.1 to 13.7).<sup>37, 39, 40</sup> In total, 13 patients from these RCTs developed cardiac tamponade, and no long-term sequelae were attributed to this complication.

Two fair-quality prospective observational studies reported no instances of cardiac tamponade following RFA (Table 27).<sup>48, 52</sup> One trial enrolled paroxysmal AF patients (N=85),<sup>52</sup> and the other enrolled elderly (mean age 75 years, Medicare population) patients with persistent AF (N=158).<sup>48</sup>

Across eight case series and one meta-analysis of case series, cardiac tamponade was reported in: 0.6 to 1.3 percent of RFA patients (N=1000–7217),<sup>55-57, 66</sup> 1.1 percent of 1190 RFA procedures,<sup>59</sup> 2.5 to 6.7 percent of patients who underwent procedures using a variety of energy sources (N=1273–6207),<sup>60, 61, 70</sup> and 0.8 percent of 34,943 procedures performed with a variety of energy sources (Appendix H, Table H4).<sup>69</sup>

**Figure 9. Risk of cardiac tamponade following RFA from RCTs in patients with paroxysmal or persistent AF**



AF = atrial fibrillation; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation.

\*Patients with heart failure.

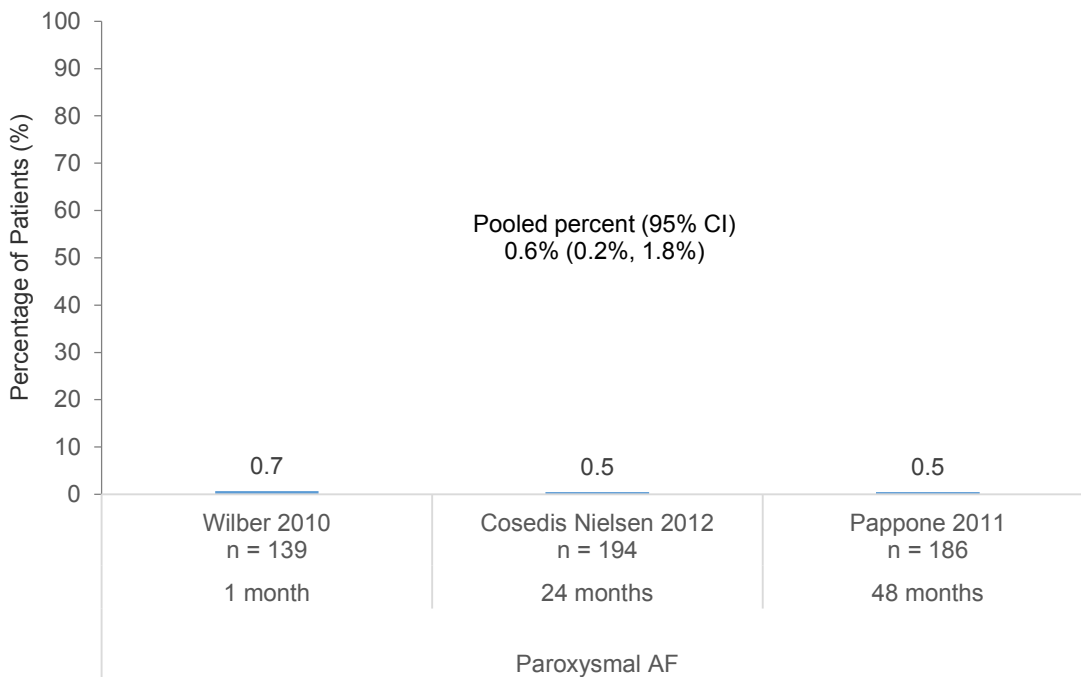
## Pericardial Effusion

Five RCTs (one good and four fair quality) reported an overall risk of pericardial effusion (not leading to tamponade) following RFA that ranged from 0.5 to 0.9 percent (Figure 10, Table 26).<sup>35, 41, 45, 47, 83</sup> These trials enrolled between 116 and 194 patients each. Across the three RCTs of paroxysmal AF patients, pericardial effusion occurred in 0.5 to 0.7 percent of RFA patients (range, 139–194 patients per study), with a pooled estimate of 0.6 percent (95% CI 0.2 to 1.8).<sup>35, 42, 47, 83</sup> One RCT reported pericardial effusion in 0.9 percent of 116 persistent AF patients,<sup>41</sup> and another RCT reported a similar risk in a mixed AF population of patients (0.7% of 139 patients).<sup>47</sup>

One fair-quality prospective observational study reported pericardial effusion in 1.9 percent (3/158) elderly patients (mean age 75 years, Medicare population) with persistent AF who received RFA (Table 27).<sup>48</sup>

Across four case series, pericardial effusion was reported in 0.1 to 6.0 percent of RFA patients (N=1011–59470).<sup>55, 58, 64, 67</sup> Three case series reported cardiac tamponade or pericardial effusion requiring pericardiocentesis occurred in 0.4 percent of 5947 RFA patients,<sup>67</sup> 0.8 percent of 1506 RFA procedures,<sup>71</sup> and 1.7 percent of 15,423 patients who underwent ablation using a variety of energy sources (Appendix H, Table H4).<sup>65</sup>

**Figure 10. Risk of pericardial effusion following RFA from RCTs in patients with paroxysmal AF**



AF = atrial fibrillation; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation.

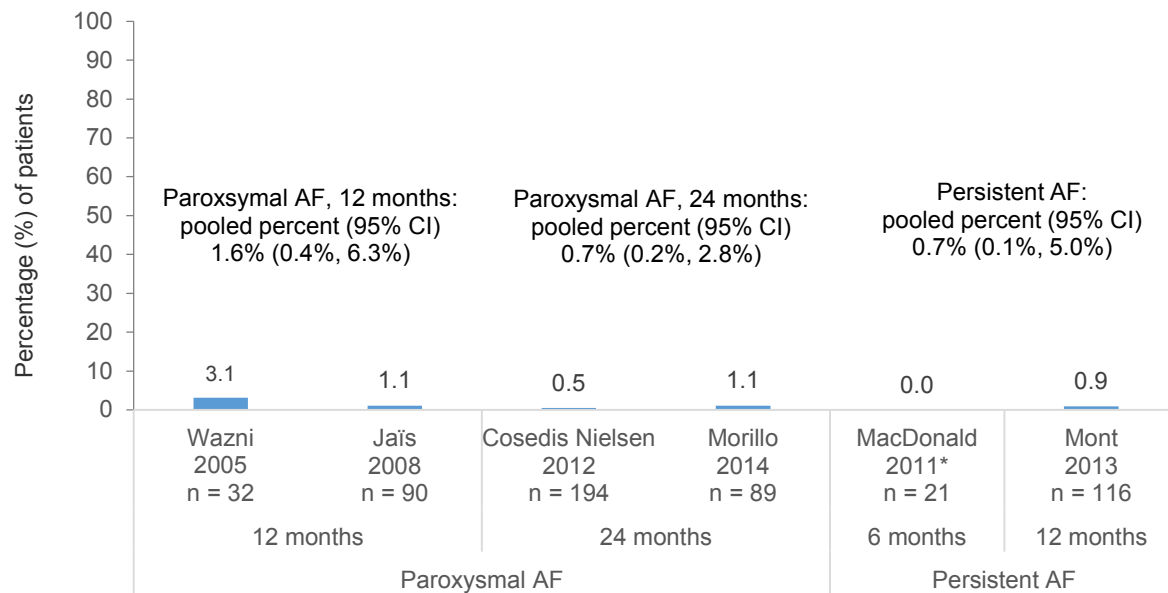
### Pulmonary Vein Stenosis

Pulmonary vein stenosis was reported in 0 to 3.1 percent of patients following RFA by eight RCTs, of which one was good quality and seven were fair quality (Figure 11, Table 26).<sup>35, 38, 40-42, 45-47</sup> In the five trials of paroxysmal AF patients, pulmonary vein stenosis occurred in 0 to 3.1 percent of patients, with 32 to 194 RFA patients per study.<sup>35, 38, 42, 46, 47</sup> Of the two trials with 12 months followup, the pooled estimate indicated that pulmonary vein stenosis occurred in 1.6 percent (95% CI 0.4 to 6.3) of patients.<sup>38, 46</sup> For the two trials with 24 months followup, the pooled estimate was 0.7 percent (95% CI 0.2 to 2.8).<sup>35, 42</sup> Two RCTs of persistent AF patients (N=21–116) reported pulmonary vein stenosis in 0 to 0.9 percent following RFA, with a pooled estimate of 0.7 percent (95% CI 0.1 to 5.0).<sup>40, 41</sup> One study of a mixed population of paroxysmal and persistent AF patients reported no cases of this complication in 137 RFA patients.<sup>45</sup>

Three comparative observational studies reported pulmonary vein stenosis in 0 to 7.1 percent of patients, with 85 to 158 RFA patients per study (Table 27).<sup>48, 51, 52</sup> Two of these studies were fair quality<sup>48, 52</sup> and one was poor quality.<sup>51</sup> Of note, study of 158 Medicare population patients (mean age, 75 years) with persistent AF reported no cases of pulmonary vein stenosis.<sup>48</sup>

Across seven case series, pulmonary vein stenosis was reported in: 0 to 1.4 percent of RFA patients (N=1000–1380),<sup>55, 57, 58, 64</sup> 0.08 to 0.4 percent of 1190 to 1506 RFA procedures,<sup>59, 71</sup> and 0.2 percent of patients who underwent procedures using a variety of energy sources (N=1273) (Appendix H, Table H4).<sup>60</sup>

**Figure 11. Risk of pulmonary vein stenosis following RFA from RCTs in patients with paroxysmal or persistent AF**



AF = atrial fibrillation; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.  
 \*Patients with heart failure.

### Other Ablation-Related Complications

Atrioesophageal fistula occurred in no RFA patients as reported from two fair-quality RCTs of 89 to 139 paroxysmal AF patients<sup>42, 47</sup> as well as from one study of 158 elderly Medicare population patients with persistent AF (Table 26).<sup>48</sup> Across five case series, atrioesophageal fistula was reported in: 0 to 0.2 percent of RFA patients (N=1000–1380)<sup>57, 58, 64</sup> and in 0 to 0.07 percent of 1190 to 1506 RFA procedures (Appendix H, Table H4).<sup>59, 71</sup>

Other ablation-related harms reported in the RCTs included chest infection (1 RCT, 3.8%),<sup>39</sup> phrenic nerve paralysis (1 RCT, 0.7%),<sup>45</sup> perforation at the trans-septal puncture (1 RCT, 0.5%),<sup>35</sup> and perimyocarditis (3 RCTs, 0% to 1.7%).<sup>35, 41, 47</sup> There were no instances of diaphragmatic paralysis, heart block, or pneumothorax as reported by one RCT of 139 patients (Table 26).<sup>47</sup>

One poor-quality comparative observational study reported iatrogenic left atrial flutter/tachycardia in 8.2 percent (7/85) of ablation patients treated for paroxysmal, persistent or permanent AF over a mean followup period of 15 months (timing not reported) (Table 27).<sup>51</sup>

Two case series reported that hematoma occurred in 2.1 to 3.7 percent of patients who underwent ablation using a variety of energy sources (N=1273–6207) (Appendix H, Table H4).<sup>60, 70</sup>

Across the case series, other ablation harms were reported to occur in 0 to 0.7 percent of patients or procedures, including: pericardial complications,<sup>62</sup> arteriovenous fistula,<sup>55, 57, 59, 71</sup> atrioventricular fistula,<sup>56</sup> persistent postoperative fistula,<sup>67</sup> phrenic nerve paralysis,<sup>55, 58, 59, 63, 64, 67</sup> phrenic nerve injury,<sup>71</sup> heart block,<sup>55, 59, 87</sup> perforation at trans-septal puncture,<sup>55</sup> esophageal perforation,<sup>56</sup> endocarditis,<sup>57</sup> pneumothorax,<sup>55, 61, 62, 67</sup> hemothorax,<sup>59, 61, 55</sup> mitral valve injury,<sup>59</sup> or

iatrogenic respiratory complications (Appendix H, Table H4).<sup>62</sup> One case series reported iatrogenic cardiac complications in 1.2 percent of 93,801 RFA procedures.<sup>62</sup>

## **Drug Therapy-Related Adverse Events**

### **Drug Intolerance Leading To Discontinuation**

Three RCTs reported drug intolerance (Table 26).<sup>36, 44, 47</sup> Two fair-quality small RCTs of paroxysmal AF patients reported disabling or serious drug intolerance requiring discontinuation of therapy in 5.4 to 23.2 percent of medical therapy patients.<sup>44, 47</sup> Wilber et al. did not describe the symptoms that led to the withdrawal,<sup>47</sup> but Pappone et al. listed reasons for discontinuation as pro-arrhythmia, thyroid dysfunction, and sexual impairment.<sup>44</sup> One fair-quality RCT of a mixed AF population indicated one (2.9%) RFA patient developed bradycardia post-ablation and discontinued medical therapy; no cases were reported for the medical therapy group.<sup>45</sup>

One fair-quality prospective comparative observational study of 412 persistent AF patients with a mean age of 75 (i.e., Medicare population) reported discontinuation of antiarrhythmic therapy due to intolerance or side effects in significantly fewer RFA (2.6%) versus medical therapy patients (12.7%) ( $p=0.0005$ ) (Table 27).<sup>48</sup> The primary reasons for discontinuation included worsening sick sinus syndrome (1.3% vs. 5.8%, respectively;  $p=0.037$ ) and dysthyroidism (0.7% vs. 5.4%, respectively;  $p=0.013$ ).

### **Toxicity**

Two RCTs described drug-related toxicity (Table 26). Thyrotoxicosis, which was defined as transient and subclinical suppressed thyroid levels, developed in 0 percent RFA patients versus 19.2 percent medical therapy patients in one fair-quality trial of 198 paroxysmal patients.<sup>83</sup> Another fair-quality RCT of paroxysmal patients reported hyperthyroidism in 1.7 percent of 59 medical therapy patients.<sup>38</sup> Other reports of drug-related toxicity were confined to one fair-quality RCT of paroxysmal AF patients, and included hepatotoxicity (1.0%), dermatological toxicity (2.0%), and ophthalmological toxicity (2.0%) in the medical therapy group (with no cases in the RFA group).<sup>83</sup>

### **Sexual Impairment**

One fair-quality RCT of 198 paroxysmal AF patients reported sexual impairment in 0 percent of RFA and 11.1 percent of medical therapy patients (Table 26).<sup>83</sup>

### **Other Drug Therapy-Related Adverse Events**

Other drug therapy-related adverse events included atrial flutter attributed to flecainide (1 RCT),<sup>36</sup> symptomatic bradycardia attributed to medical therapy (within 12 months followup) (1 RCT),<sup>36</sup> symptomatic sinus node dysfunction requiring pacemaker implantation (1 RCT),<sup>36</sup> weakness/tiredness (1 RCT),<sup>35</sup> flecainide intoxication (1 RCT),<sup>41</sup> hematoma related to anticoagulation (2 RCTs),<sup>35, 41</sup> and occurred in less than 2 percent of patients (Table 26).

### **Peripheral Vascular Complications**

Hematomas developed at the catheter insertion site in 1.6 to 3.8 percent of RFA patients as reported by four RCTs (range, 26–186 patients per study) (Table 26).<sup>36, 38, 39, 83</sup> None of the comparative observational studies reported this complication.

Two RCTs reported vascular injury due to access occurred in 0.7 percent patients to 3.4 percent procedures (range, 116 patients to 139 procedures) (Table 26),<sup>41, 47</sup> while one prospective

observational study of 412 persistent AF patients with a mean age of 75 (i.e., Medicare population) reported this complication in 0.7 percent of 153 RFA patients (Table 27).<sup>48</sup>

Across the case series, peripheral vascular complications were reported to occur in 0.1 to 2.6 percent of patients or procedures, including: hematoma at catheter insertion site,<sup>58</sup> vascular injury due to access,<sup>60, 64</sup> vascular complications requiring surgical repair,<sup>61, 62, 65</sup> retroperitoneal hematoma,<sup>57</sup> and pseudoaneurysm (Appendix H, Table H4).<sup>55, 57, 59</sup>

### **Other Adverse Events**

Adverse events not attributable to either treatment were reported following RFA versus medical therapy, and included deep vein thrombosis (0% vs. 0%, 2 RCTs),<sup>36, 46</sup> pulmonary embolism (0% vs. 0%, 2 RCTs),<sup>36, 46</sup> and pneumonia (1.0% vs. 0%, 1 RCT).<sup>47</sup> Pulmonary edema risk was similar in the RFA versus medical therapy treatment groups as reported by four RCTs (0%–3.8% vs. 0%–4.0% of patients) (52 to 198 patients per trial) (Table 26).<sup>36, 39, 47, 83</sup>

One prospective cohort study of elderly (mean age 75 years, Medicare population) persistent AF patients reported no cases of minor bleeding (Table 27).<sup>48</sup> Another retrospective comparative observational study of a Medicare-relevant patient population (mean age, 67 years) reported several events that led to death during the  $69 \pm 27$  month followup: respiratory failure (0% vs. 1.5%), infection (0% vs. 1.0%), and cancer (0% vs. 1.5%).<sup>53</sup> Finally, one administrative database study of the MarketScan database reported no difference in three-year pneumonia-related hospitalization rate estimates between ablation and no ablation groups (2.6% versus 2.4%).<sup>50</sup> Otherwise, no other adverse events were reported in the comparative observational studies.

One administrative database study reported that 9.4 percent of patients required rehospitalization for any cause (N=4156).<sup>61</sup> One case series reported pulmonary hypertension in 1.4 percent of 1380 RFA patients.<sup>58</sup> Otherwise, across the case series, other harms were reported to occur in 0.08 to 0.8 percent of patients or procedures, including: postoperative infections,<sup>62</sup> deep vein thrombosis,<sup>57, 64</sup> respiratory compromise or failure,<sup>59, 62</sup> aspiration with or without pneumonia,<sup>57</sup> and the need for open heart surgery (Appendix H, Table H4).<sup>62</sup>



**Table 26. Adverse events for RCTs comparing RFA with medical therapy**

Adverse Event		AF Type (1st/2nd line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)
Major Events	Mortality (cardiovascular) <30 days	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	Periprocedural	0.7% (1/140) <sup>*</sup>	0% (0/146)
			Morillo 2014 <sup>42</sup>	1 month	0% (0/65)	0% (0/60)
		Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	0% (0/56)
		Persistent (2nd line)	Mont 2013 <sup>41</sup>	1 month	0% (0/93)	0% (0/48)
		Persistent (1st/2nd line)	Hunter 2014 <sup>37</sup>	Periprocedural	0% (0/26)	4.2% (1/24)
	Mortality (all cause) <30 days	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	Periprocedural	0.7% (1/140) <sup>*</sup>	0% (0/146)
			Morillo 2014 <sup>42</sup>	1 month	0% (0/65)	0% (0/60)
		Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	0% (0/56)
		Persistent (2nd line)	Mont 2013 <sup>41</sup>	1 month	0% (0/93)	0% (0/48)
		Persistent (1st/2nd line)	Hunter 2014 <sup>37</sup>	Periprocedural	0% (0/26)	4.2% (1/24)
	Stroke (any type) <30 days	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	Periprocedural	0.7% (1/140) <sup>*</sup>	0% (0/146)
			Morillo 2014 <sup>42</sup>	1 month	0% (0/65)	0% (0/60)
			Wazni 2005 <sup>46</sup>	1 month	0% (0/33)	0% (0/37)
		Persistent (2nd line)	MacDonald 2011 <sup>40</sup>	Periprocedural	4.8% (1/21)	0% (0/19)
			Mont 2013 <sup>41</sup>	1 month	0% (0/93)	0% (0/48)
		Persistent (1st/2nd line)	Hunter 2014 <sup>37</sup>	Periprocedural	3.8% (1/26)	0% (0/24)
	Mixed (2nd line)	Forleo 2009 <sup>36</sup>	1 month	0% (0/35)	0% (0/35)	
		Stabile 2006 <sup>45</sup>	Periprocedural	1.5% (1/68) <sup>†</sup>	0% (0/69)	
	Myocardial infarction <30 days	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	0% (0/56)
	Transient ischemic attack <30 days	Paroxysmal (1st line)	Morillo 2014 <sup>42</sup>	1 month	0% (0/65)	0% (0/60)
Wazni 2005 <sup>46</sup>			1 month	0% (0/33)	0% (0/37)	
Paroxysmal (2nd line)		Pappone 2006	Periprocedural	1.0% (1/99)	0% (0/99)	
		Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	0% (0/56)	
Persistent (2nd line)		Mont 2013 <sup>41</sup>	1 month	0% (0/93)	0% (0/48)	
Mixed (2nd line)	Forleo 2009 <sup>36</sup>	1 month	0% (0/35)	0% (0/35)		
Other embolic events <30 days	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	0% (0/56)	
Bleeding (major)/ hemorrhage/ transfusion (<30 days)	Paroxysmal (1st line)	Wazni 2005 <sup>46</sup>	1 month	6.3% (2/32)	1.9% (1/35)	
	Mixed (2nd line)	Forleo 2009 <sup>36</sup>	1 month	5.7% (2/35) <sup>‡</sup>	5.7% (2/35) <sup>‡</sup>	
Heart failure <30 days	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	1.0% (1/103)	0% (0/56)	
	Persistent (2nd line)	MacDonald 2011 <sup>40</sup>	Periprocedural	14.3% (3/21)	0% (0/19)	
“Major complications” (overall)	Persistent (2nd line)	MacDonald 2011 <sup>40</sup>	Periprocedural	14.8% (4/27 procedures) <sup>§</sup>	NR	

Adverse Event		AF Type (1st/2nd line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)
Arrhythmia (<3 months)**	Atrial fibrillation	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	3 months	30.7% (43/140)	37.7% (55/146)
			Wazni 2005 <sup>46</sup>	2 months	27.3% (9/33)	54.1% (20/37)
		Paroxysmal (2nd line)	Pappone 2006 <sup>44</sup>	1.5 months	11.1% (11/99)	NR
		Persistent (2nd line)	MacDonald 2011 <sup>40</sup>	3 months	47.6% (10/21)	NR
			Oral 2006 <sup>43</sup>	2 months	18.2% (14/77)	97.1% (67/69)
		Persistent (1st/2nd line)	Hunter 2014 <sup>37</sup>	3 months	15.4% (4/26)	100% (24/24)
	Atrial flutter	Paroxysmal (1st line)	Morillo 2014 <sup>42</sup>	NR (F/U to 24 mos.)	0% (0/65)	1.5% (1/60) <sup>††</sup>
		Paroxysmal (2nd line)	Pappone 2006 <sup>44</sup>	NR (F/U to 12 mos.)	0% (0/99)	0.1% (1/99) <sup>††</sup>
		Persistent (2nd line)	Oral 2006 <sup>43</sup>	2 months	5.2% (4/77)	0% (0/69)
	Atrial fibrillation or atrial flutter	Persistent (2nd line)	Mont 2013 <sup>41</sup>	3 months	29.6% (NR/93)	54.2% (NR/48)
		Mixed (2nd line)	Forleo 2009 <sup>36</sup>	5 weeks	8.6% (3/35)	14.3% (5/35)
	Arrhythmia (type NR)	Paroxysmal (1st line)	Morillo 2014 <sup>42</sup>	3 months	1.5% (1/65)	5.0% (3/60)
		Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	10.1% (10/99) <sup>††</sup>
		Persistent (1st/2nd line)	Jones 2013 <sup>39</sup>	2 months	30.8% (8/26)	NR
			Forleo 2009 <sup>36</sup>	Periprocedural	5.7% (2/35) <sup>††</sup>	NA
		Mixed (2nd line)	Stabile 2006 <sup>45</sup>	1 month (blinking)	35.3% (24/68)	71.0% (49/69)
	Bradycardia	Paroxysmal (1st line)	Morillo 2014 <sup>42</sup>	NR (F/U to 24 mos.)	1.5% (1/65) <sup>††</sup>	0% (0/60)
		Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	15.2% (15/99)
	Hospitalization for direct current cardioversion and medication adjustment	Paroxysmal (1st line)	Wazni 2005 <sup>46</sup>	2 months	0% (0/33)	54.1% (20/37)
	Tachycardia	Paroxysmal (2nd line)	Pappone 2006 <sup>44</sup>	72-102 days	9.1% (9/99)	36.4% (36/99)
Ventricular arrhythmia	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	0% (0/56)	
Ablation-Related Events <sup>§§</sup>	Cardiac tamponade	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	1.5% (3/194)	NA
			Morillo 2014 <sup>42</sup>	NR (F/U to 24 mos.)	4.5% (4/89)	NA
		Paroxysmal (2nd line)	Jais 2008 <sup>38</sup>	NR (F/U to 12 mos.)	2.2% (2/90)	NA

Adverse Event	AF Type (1st/2nd line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)	
		Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA	
	Persistent (2nd line)	MacDonald 2011 <sup>40</sup>	Periprocedural	9.5% (2/21)	NA	
	Persistent (1st/2nd line)	Hunter 2014 <sup>37</sup>	Periprocedural	3.8% (1/26)	NA	
		Jones 2013 <sup>39</sup>	Periprocedural	3.8% (1/26)	NA	
	Pericardial effusion	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.5% (1/194)	NA
		Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	Periprocedural	0.5% (1/186)	NA
			Wilber 2010 <sup>47</sup>	1 month	0.7% (1/139)	NA
		Persistent (2nd line)	Mont 2013 <sup>41</sup>	Periprocedural	0.9% (1/116)	NA
	Mixed (2nd line)	Stabile 2006 <sup>45</sup>	Periprocedural	0.7% (1/137)	NA	
	Pulmonary vein stenosis	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.5% (1/194)	NA
			Morillo 2014 <sup>42</sup>	NR (F/U to 24 mos.)	1.1% (1/89)	NA
			Wazni 2005 <sup>46</sup>	NR (F/U to 12 mos.)	3.1% (1/32)	NA
		Paroxysmal (2nd line)	Jais 2008 <sup>38</sup>	NR (F/U to 12 mos.)	1.1% (1/90)	NA
			Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA
		Persistent (2nd line)	MacDonald 2011 <sup>40</sup>	NR (F/U to 6 mos.)	0% (0/21)	NA
			Mont 2013 <sup>41</sup>	NR (F/U to 12 mos.)	0.9% (1/116)	NA
	Mixed (2nd line)	Stabile 2006 <sup>45</sup>	NR (F/U to 12 mos.)	0% (0/137)	NA	
	Atrioesophageal fistula	Paroxysmal (1st line)	Morillo 2014 <sup>42</sup>	NR (F/U to 24 mos.)	0% (0/89)	NA
		Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA
	Chest infection	Persistent (1st/2nd line)	Jones 2013 <sup>39</sup>	2 weeks	3.8% (1/26)	NA
	Phrenic nerve paralysis	Mixed (2nd line)	Stabile 2006 <sup>45</sup>	Periprocedural	0.7% (1/137)	NA
Perforation at transeptal puncture	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.5% (1/194)	NA	
Perimyocarditis	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.5% (1/194)	NA	
	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA	
	Persistent (2nd line)	Mont 2013 <sup>41</sup>	Periprocedural	1.7% (2/116)	NA	
Diaphragmatic paralysis	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA	
Heart block	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA	
Pneumothorax	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0% (0/139)	NA	

Adverse Event		AF Type (1st/2nd line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)
<b>Drug Therapy-Related Adverse Events**</b>	Drug intolerance requiring discontinuation	Paroxysmal (2nd line)	Pappone 2006 <sup>44</sup>	NR (F/U to 12 mos.)	0% (0/99)	23.2% (23/99)
			Wilber 2010 <sup>47</sup>	1 month	0% (0/103)	5.4% (3/56)
		Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	2.9% (1/35)	0% (0/35)
	Thyrotoxicosis (transient, subclinical)	Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	19.2% (19/99)
	Hyperthyroidism	Paroxysmal (2nd line)	Jais 2008 <sup>38</sup>	NR (F/U to 12 mos.)	NA	1.7% (1/59)
	Toxicity (hepatotoxicity)	Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	1.0% (1/99)
	Toxicity (dermatological toxicity)	Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	2.0% (2/99)
	Toxicity (ophthalmological toxicity)	Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	2.0% (2/99)
	Sexual impairment (severe)	Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	11.1% (11/99)
	Weakness/tiredness (attributed to drug therapy)	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0% (0/140)	1.4% (2/146)
	Hematoma related to anticoagulation	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.7% (1/140)	0% (0/146)
		Persistent (2nd line)	Mont 2013 <sup>41</sup>	NR (F/U to 12 mos.)	1.7% (1/93)	0% (0/48)
	Atrial flutter attributed to flecainide	Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	2.9% (1/35)	NR
	Symptomatic bradycardia attributed to medical therapy	Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	NR	14.3% (5/35)
	Symptomatic sinus node dysfunction attributed to medical therapy	Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	NR	2.9% (1/35) <sup>†††</sup>
	Flecainide intoxication	Persistent (2nd line)	Mont 2013 <sup>41</sup>	NR (F/U to 12 mos.)	0% (0/93)	2.1% (1/48)
<b>Peripheral Vascular Complications</b>	Hematoma at catheter insertion site	Paroxysmal (2nd line)	Jais 2008 <sup>38</sup>	NR (F/U to 12 mos.)	2.2% (2/90)	NA
			Pappone 2011 <sup>83</sup>	Periprocedural	1.6% (3/186)	NA
		Persistent (1st/2nd line)	Jones 2013 <sup>39</sup>	Periprocedural	3.8% (1/26)	NA
		Mixed (2nd line)	Forleo 2009 <sup>36</sup>	Periprocedural	2.9% (1/35)	NA
	Vascular injury due to access	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	0.7% (1/139)	NA

Adverse Event	AF Type (1st/2nd line therapy)	Study	Followup	RFA % (n/N)	Medical Therapy % (n/N)	
	Persistent (2nd line)	Mont 2013 <sup>41</sup>	Periprocedural	3.4% (4/116 procedures)	NA	
Adverse Events (not ablation dependent) <sup>†††</sup>	Deep vein thrombosis	Paroxysmal (1st line)	Wazni 2005 <sup>46</sup>	2 months	0% (0/33)	0% (0/37)
		Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	0% (0/35)	0% (0/35)
	Pulmonary embolism	Paroxysmal (1st line)	Wazni 2005 <sup>46</sup>	2 months	0% (0/33)	0% (0/37)
		Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	0% (0/35)	0% (0/35)
	Pneumonia (<30 days)	Paroxysmal (2nd line)	Wilber 2010 <sup>47</sup>	1 month	1.0% (1/103)	0% (0/56)
	Pulmonary edema	Paroxysmal (2nd line)	Pappone 2011 <sup>83</sup>	NR (F/U to 48 mos.)	0% (0/99)	4.0% (4/99)
			Wilber 2010 <sup>47</sup>	1 month	1.0% (1/103)	0% (0/56)
		Persistent (1st/2nd line)	Jones 2013 <sup>39</sup>	Periprocedural	3.8% (1/26)	0% (0/26)
		Mixed (2nd line)	Forleo 2009 <sup>36</sup>	NR (F/U to 12 mos.)	0% (0/35)	2.9% (1/35)
	Bleeding (severity NR)	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.7% (1/140)	0% (0/146)
	Chest discomfort	Paroxysmal (1st line)	Cosedis Nielsen 2012 <sup>35</sup>	NR (F/U to 24 mos.)	0.7% (1/140)	0% (0/146)
Syncope (fainting)	Paroxysmal (1st line)	Morillo 2014 <sup>42</sup>	NR (F/U to 24 mos.)	0% (0/65)	3.3% (2/60)	

AF = atrial fibrillation; F/U = followup; NA = not applicable; NR = not reported; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation.

\*Procedure-related cerebral stroke resulting in death. Any mortality due to cardiovascular causes is also included under all-cause mortality.

†During left atrium ablation. Patient died at 9 months.

‡RFA: 1 subarachnoid hemorrhage and 1 intestinal bleeding accompanying an elevated INR; Medical therapy: gastrointestinal or subdural bleeding.

§Include cerebrovascular accident, cardiac tamponade or readmission to hospital within 1 week; unclear if these are the same complications as above.

\*\*Analysis based on patients “as treated”.

††Drug therapy induced.

†††Spontaneous atrial arrhythmias; unclear if these patient overlap with those reported under atrial fibrillation or atrial flutter, but unlikely given the timing and the language used.

§§Denominator is the number of patients who underwent the procedure, and may include patients randomized to medical therapy that crossed over and underwent ablation.

\*\*\* Followup time included a 1-month blanking period, for a total of 13 months followup.

††††Required pacemaker insertion.

†††††Adverse events that could occur regardless of whether ablation was performed.

**Table 27. Adverse events from comparative observational studies comparing RFA with medical therapy**

Adverse Event		AF Type	Study*	Followup	RFA % (n/N)	Medical Therapy % (n/N)
<b>Major Events</b>	Mortality (all cause) <30 days	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/153)	0.4% (1/259)
	Stroke (any type) <30 days	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	2.6% (4/153)	0.4% (1/259)
		Mixed (1st/2nd line)	Rossillo 2008 <sup>51</sup>	Periprocedural	1.2% (1/85)	1.2% (1/85)
	Transient ischemic attack <30 days	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	1.3% (2/153)	0.4% (1/259)
	Other embolic events <30 days	Paroxysmal (2nd line)	Sang 2013 <sup>52</sup>	≤30 days	0% (0/82)	3.6% (3/84)
		Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/153)	0% (0/259)
	Myocardial infarction <30 days	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	1.3% (2/153)	0% (0/259)
	Bleeding (major)/ hemorrhage/ transfusion (>30 days)	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	>30 days	1.3% (2/153)	0.8% (2/259)
	Heart failure <30 days	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/153)	0% (0/259)
“Major complications” (overall)	Paroxysmal (2nd line)	Lan 2009 <sup>49</sup>	NR (F/U to 12 mos.)	5.8% (7/120) <sup>†</sup>	9.2% (11/120) <sup>†</sup>	
<b>Arrhythmia (&lt;3 Months)<sup>‡</sup></b>	Atrial fibrillation	Mixed (1st/2nd line)	Rossillo 2008 <sup>51</sup>	2 months	45.9% (39/85)	NR
	Torsade de points (<3 months)	Paroxysmal (2nd line)	Lan 2009 <sup>49</sup>	NR (F/U to 12 mos.)	0% (0/120)	0% (0/120)
<b>Ablation-Related Events<sup>§</sup></b>	Cardiac tamponade	Paroxysmal (2nd line)	Sang 2013 <sup>52</sup>	12 months	0% (0/85)	NA
		Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/158)	NA
	Pericardial effusion	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	1.9% (3/158)	NA
	Pulmonary vein stenosis	Paroxysmal (2nd line)	Sang 2013 <sup>52</sup>	12 months	0% (0/85)	NA
		Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/158)	NA
		Mixed (1st/2nd line)	Rossillo 2008 <sup>51</sup>	NR (F/U mean 15 ± 7 mos.)	7.1% (6/85)	NA

Adverse Event	AF Type	Study*	Followup	RFA % (n/N)	Medical Therapy % (n/N)	
	Atrioesophageal fistula	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/158)	NA
	Iatrogenic left atrial flutter/tachycardia	Mixed (1st/2nd line)	Rossillo 2008 <sup>51</sup>	NR (F/U mean 15 ± 7 mos.)	8.2% (7/85)	NA
<b>Drug Therapy-Related Adverse Events<sup>‡</sup></b>	AAD adverse events (leading to discontinuation)	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	>30 days	2.6% (4/153)	12.7% (33/259)
	Dysthyroidism**	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	>30 days	0.7% (1/153)	5.4% (14/259)
	Arrhythmia (attributed to AADs)**	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	>30 days	1.3% (2/153) <sup>††</sup>	5.8% (15/259) <sup>††</sup>
<b>Peripheral Vascular Complications</b>	Vascular injury due to access	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0.7% (1/153)	0% (0/259)
<b>Adverse Events (not ablation dependent)<sup>§§</sup></b>	Minor bleeding	Persistent (2nd line)	Blandino 2013 <sup>48</sup>	≤30 days	0% (0/153)	0% (0/259)
	Respiratory failure <sup>‡‡</sup>	Mixed (2nd line)	Sonne 2009 <sup>53</sup>	NR (F/U mean 69 ± 27 mos.)	0% (0/146)	1.5% (3/205)
	Infection (not otherwise specified) <sup>‡‡</sup>	Mixed (2nd line)	Sonne 2009 <sup>53</sup>	NR (F/U mean 69 ± 27 mos.)	0% (0/146)	1.0% (2/205)
	Cancer <sup>‡‡</sup>	Mixed (2nd line)	Sonne 2009 <sup>53</sup>	NR (F/U mean 69 ± 27 mos.)	0% (0/146)	1.5% (3/205)
	Other unspecified complications <sup>‡‡</sup>	Mixed (2nd line)	Sonne 2009 <sup>53</sup>	NR (F/U mean 69 ± 27 mos.)	0% (0/146)	1.5% (3/205)
	Pneumonia hospitalization	NR	Reynolds 2012 <sup>50</sup>	Mean 27 months	Annualized rate <sup>***</sup> : 1.0% Kaplan-Meier estimate <sup>†††</sup> : 2.6%	Annualized rate <sup>***</sup> : 0.6% Kaplan-Meier estimate <sup>†††</sup> : 2.4%

AF = atrial fibrillation; F/U = followup; NA = not applicable; NR = not reported; RFA = radiofrequency catheter ablation.

\*Blandino 2013 and Sonne 2009 represent the Medicare population (age ≥75 years and mean age 67 years, respectively); all other studies represent the general adult population.

†Authors do not report the number of patients with each complication which included pericardial tamponade which required pericardiocentesis, moderate to severe pulmonary vein stenosis and cerebral embolism leading to transient retrograde amnesia in the ablation group; sinus bradycardia, hypotension, significant QT prolongation, hyperthyroidism, hypothyroidism and hepatic deterioration in the drug therapy group.

‡Analysis based on patients “as treated”.

§Denominator is the number of patients who underwent the procedure.

\*\*The main causes for AAD discontinuation; included in AAD adverse events above.

††Worsening of sick sinus syndrome.

§§Adverse events that could occur regardless of whether ablation was performed.

‡‡All events resulted in death.

\*\*\* Annualized rate calculated as percentage (number of patients in the cohort who had an event within 3 years/average length of followup in the cohort).

†††Product-limit estimates of the 3-year event rates (percentages) and P values of the nonparametric log-rank test comparing survival functions of the 2 cohorts.

# Cryoablation Versus Medical Therapy

## Description of Included Studies

One randomized controlled trial compared AF cryoballoon ablation with medical therapy;<sup>86</sup> an article with additional data from the cryoablation arm only was also recently published.<sup>73</sup> See Key Question 1a as well as the detailed demographics tables for general study characteristics (Appendix E, Tables E13–E14). The study consisted of 78 percent paroxysmal and 22 percent persistent AF patients. There was substantial crossover from medical therapy to cryoballoon ablation, with 79 percent of patients allocated to medical therapy eventually receiving cryoballoon ablation. Crossover from cryoballoon ablation to medical therapy was not reported. Adverse events attributable to either ablation or medical therapy were reported on an as-treated basis and thus data includes crossover patients.

## Detailed Synthesis

### Major Adverse Events

#### Mortality (cardiovascular or all-cause) (within 30 days)

No deaths were reported to occur within 30 days of treatment initiation in either treatment group (Table 28).<sup>86</sup>

#### Stroke (any type) (within 30 days)

There was no difference in the incidence of stroke within a month of treatment initiation between cryoballoon ablation and medical therapy groups (0.6% vs. 0%) (Table 28). Overall, 1.3 percent of all patients who underwent cryoballoon ablation experienced a stroke within 30 days of ablation. Of the two strokes that occurred within 30 days, one occurred in a medical therapy patient who crossed over to cryoballoon ablation and was considered procedure-related, and the other manifested as a transient bilateral visual disturbance 1 month post-ablation. Both patients recovered without any negative sequelae.<sup>86</sup>

#### Myocardial Infarction (within 30 days)

There was no difference in the incidence of myocardial infarction within a month of treatment initiation between the cryoballoon ablation and medical therapy groups (0.6% vs. 0%) (Table 28). One patient experienced a periprocedural non-Q-wave myocardial infarction that was attributed to the anesthesia.<sup>86</sup>

#### Transient Ischemic Attack (within 30 days)

TIA occurred within a month of treatment initiation in 1.8 percent of patients randomized to cryoballoon ablation and 0 percent in those allocated to medical therapy (Table 28). Overall, 1.7 percent (4/228) patients who received cryoballoon ablation, including crossover patients, experienced a TIA within 30 days of ablation.<sup>86</sup>

#### Other Embolic Events (within 30 days)

No other embolic events were reported.



### **Major Bleeding, Hemorrhage, or Transfusion (within 30 days)**

There was no difference in the incidence of major bleeding complications, including subarachnoid hemorrhage (one patient), intestinal bleeding (two patients), and subdural bleeding (one patient), between the cryoballoon ablation and medical therapy groups (1.2% vs. 2.4%) (Table 28).<sup>86</sup>

### **Arrhythmia (within 3 months)**

#### **Atrial Fibrillation**

AF recurrence within 3 months of treatment initiation was reported in 51.5% (84/163) of cryoablation patients; no data were reported for the medical therapy group.<sup>73, 86</sup>

#### **Other Types of Arrhythmia (within 3 months)**

Atrial flutter within 3 months was not reported.

### **Ablation-Related Adverse Events**

#### **Cardiac Tamponade**

Cardiac tamponade occurred in 0.9 percent of all patients who received cryoballoon ablation, including crossover patients (2/228) (Table 28).<sup>86</sup>

#### **Pericardial Effusion**

Pericardial effusion was not reported.

#### **Pulmonary Vein Stenosis**

Pulmonary vein stenosis was reported in 3.1 percent of patients treated with cryoballoon ablation, including crossover patients (7/228) (Table 28).<sup>86</sup>

#### **Other Ablation-Related Complications**

Atrioesophageal fistula occurred in no patients who underwent cryoballoon ablation (n=228), although one patient developed Wegener's related hemoptysis (0.4%) (Table 24).<sup>86</sup>

Other ablation-related harms reported in the 228 patients who received cryoballoon ablation included phrenic nerve palsy (12.3%), arteriovenous fistula (0.9%), and pseudoaneurysm (0.9%) (Table 28).<sup>86</sup>

### **Drug Therapy-Related Adverse Events**

No drug therapy related adverse events were reported.

### **Peripheral Vascular Complications**

No peripheral vascular complications were reported.

### **Other Adverse Events**

Adverse events not attributable to either treatment were reported.

**Table 28. Adverse events for the RCT by Packer et al 2013 comparing cryoballoon ablation with medical therapy<sup>72</sup>**

Adverse Event		Followup	Cryoballoon Ablation* % (n/N)	Medical Therapy* % (n/N)
<b>Major Events</b>	Mortality (cardiovascular) <30 days	NR (followed to 12 months)	0% (0/163)	0% (0/82)
	Mortality (all-cause) <30 days	NR (followed to 12 months)	0% (0/163)	0% (0/82)
	Stroke (any type) <30 days	NR (followed to 12 months)	0.6% (1/163)	1.2% (1/82)
	Myocardial infarction <30 days	Periprocedural	0.6% (1/163)	0% (0/82)
	Transient ischemic attack <30 days	<20 days of ablation	1.8% (3/163)	0% (0/82)
	Bleeding (major)/hemorrhage (<30 days)	NR (followed to 12 months)	1.2% (2/163)	2.4% (2/82)
<b>Arrhythmia (&lt;3 Months)</b>	Atrial fibrillation	3 months	51.5% (84/163)	NR
<b>Ablation-Related Events<sup>†</sup></b>	Cardiac tamponade	NR (followed to 12 months)	0.9% (2/228)	NA
	Pulmonary vein stenosis	NR (followed to 12 months)	3.1% (7/228)	NA
	Atrioesophageal fistula	NR (followed to 12 months)	0% (0/228)	NA
	Wegener's related hemoptysis	NR (followed to 12 months)	0.4% (1/228)	NA
	Phrenic nerve palsy	NR (followed to 12 months)	12.3% (28/228)	NA
	Arteriovenous fistula	NR (followed to 12 months)	0.9% (2/228)	NA
	Pseudoaneurysm	NR (followed to 12 months)	0.9% (2/228)	NA

AF = atrial fibrillation; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

\*Patients had paroxysmal or persistent AF (i.e. mixed) and were undergoing treatment as a 2<sup>nd</sup> line therapy.

†Denominator is the number of patients who underwent the procedure.

**Key Question 2b. What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation versus different energy sources in the general adult and Medicare populations?**

## Key Points

### Mortality (all-cause) (within 30 days)

- **Paroxysmal:** No RCTs were reported. There were no cases reported in either the cryoablation or RFA group during the periprocedural period in two nonrandomized comparative studies (insufficient strength of evidence).
- **Persistent, Mixed AF:** No data was reported.

### Stroke (any type) (within 30 days)

- **Paroxysmal:** No RCTs were reported. There were no cases reported in either the cryoablation or RFA group during the periprocedural period as reported by one small nonrandomized comparative study (insufficient strength of evidence).

- **Persistent, Mixed AF:** No data was reported.

### **Atrial Fibrillation (within 3 months)**

- **Paroxysmal:** No RCTs were reported. One large nonrandomized comparative study reported similar AF recurrence rates in both groups during the hospitalization period (insufficient strength of evidence).
- **Persistent, Mixed AF:** No data was reported.

### **Cardiac Tamponade**

- **Paroxysmal:** No RCTs were reported. Periprocedural cardiac tamponade rates ranged from 0.7 to 2.2 percent during cryoablation and from 1.1 to 1.5 percent during RFA based on data from three nonrandomized comparative studies (insufficient strength of evidence).
- **Persistent, Mixed AF:** No data was reported.

### **Pericardial Effusion**

- **Paroxysmal:** No RCTs were reported. Pericardial effusion occurred in 7.3 to 8.7 percent of cryoablation patients and in 10 to 13.8 percent of RFA patients based on data from two nonrandomized comparative studies (insufficient strength of evidence).
- **Persistent:** No data was reported.
- **Mixed AF:** No RCTs were reported. Pericardial effusion occurred in 0 to 1.1 percent of cryoablation patients and in 1.6 to 3.8 percent of RFA patients based on data from two nonrandomized comparative studies (insufficient strength of evidence).

### **Pulmonary Vein Stenosis**

- **Paroxysmal:** No RCTs were reported. There were no cases reported in either group during the periprocedural period in two nonrandomized comparative studies (insufficient strength of evidence).
- **Persistent:** No data was reported.
- **Mixed AF:** No RCTs were reported. There were no cases reported in either group during the periprocedural period in one nonrandomized comparative study (insufficient strength of evidence).

## **Description of Included Studies**

Two RCTs<sup>74, 75</sup> and five nonrandomized comparative studies<sup>76, 78-81</sup> comparing cryoballoon ablation to RFA reported adverse events. Of the RCTs, one was considered fair quality, included only paroxysmal AF patients and reported periprocedural complications<sup>75</sup>; the other was considered poor quality, included a mix of paroxysmal and persistent AF patients, and reported complications up to 2 months followup;<sup>74</sup> both were small, enrolling 50 and 60 patients each. Of the nonrandomized comparative studies, one was a prospective fair-quality comparative observational study,<sup>76</sup> one a poor-quality prospective registry study,<sup>81</sup> and three were retrospective poor-quality comparative observational studies.<sup>78-80</sup> Of the nonrandomized comparative studies, two were prospective fair-quality comparative observational studies,<sup>76, 77</sup> one prospective study was of poor quality,<sup>81</sup> and three were retrospective poor-quality comparative observational studies.<sup>78-80</sup> Of the comparative observational studies, three included

only paroxysmal AF patients<sup>76, 80, 81</sup> and two included only paroxysmal AF patients.<sup>78, 79</sup> Three of the nonrandomized comparative studies were smaller, reporting on between 124 and 177 patients<sup>76, 78, 79</sup> and another was slightly larger, reporting on 396 patients.<sup>80</sup> One observational comparative study was registry based and large in size, reporting on 3775 patients.<sup>81</sup> The vast majority of adverse events reported in the nonrandomized studies occurred periprocedurally. See Key Question 1b as well as the detailed demographics tables for general study characteristics and additional details (Appendix E, Tables E15–E18).

## **Detailed Synthesis**

### **Major Adverse Events**

#### **Mortality (within 30 days)**

Neither RCT reported 30-day mortality rates. The two larger retrospective cohort studies both reported no deaths during the periprocedural period following cryoablation or RFA (total N=4171) (Table 29).<sup>80, 81</sup>

#### **Stroke (any type) or Transient Ischemic Attack (within 30 days)**

Neither RCT reported 30-day stroke rates. The prospective cohort study reported no strokes following cryoballoon ablation or RFA (N=133);<sup>76</sup> two retrospective cohort studies reported no difference in the risk stroke or transient ischemic attack during the periprocedural period (0-0.3% in both groups, total N=4171) (Table 29).<sup>80, 81</sup>

#### **Myocardial Infarction (within 30 days)**

Neither RCT reported 30-day myocardial infarction. One large registry-based comparative study reported no difference in periprocedural myocardial infarction occurrences between patients who received cryoablation and RFA (0.1% vs. 0%, N=3775) (Table 29).<sup>81</sup>

#### **Other Embolic Events**

None of the studies reported on any other embolic events.

#### **Major Bleeding, Hemorrhage, or Transfusion (within 30 days)**

Neither RCT reported 30-day major bleeding events. The large comparative registry study reported a statistically similar risk following cryoablation versus RFA (0.6% vs. 1.1%, p=0.1775; N=3775) (Table 29).<sup>81</sup>

#### **Arrhythmia (within 3 months)**

##### **Atrial Fibrillation (within 3 months)**

Neither RCT reported on AF recurrence within 3 months. One large comparative registry-based study found no difference in AF recurrence rates during the hospitalization period in patients who underwent cryoballoon ablation or RFA (5.9% vs. 5.6%, N=3775) (Table 29).<sup>81</sup>

##### **Other types of Arrhythmia (within 3 months)**

One RCT of paroxysmal and persistent AF patients reported that 3 percent (1/30) of cryoablation and 0 percent of RFA (0/30) patients experienced atrioventricular nodal reentrant

tachycardia within 3 months; the patient was successfully reablated within 2 months of the original ablation (Table 30).<sup>74</sup> One retrospective cohort study reported similar risk of recurrence of any arrhythmia following cryoablation and RFA (0.7% vs. 1.9%, N=396); the same study reported two cases of sinus arrest/third-degree atrioventricular block following RFA (0.8%) and no cases following cryoablation.<sup>80</sup> One large observational registry study reported one case of atrioventricular block in the cryoablation group (0.1%) and none in those who received RFA; this study also noted that 0.2 percent of patients in both groups required pacemaker implantation following ablation (Table 29).<sup>81</sup> No other arrhythmias were reported within 3 months of the ablation procedure.

## **Ablation-Related Adverse Events**

### **Cardiac Tamponade**

Neither RCT reported information on cardiac tamponade. Three nonrandomized comparative studies of paroxysmal AF patients found no difference between cryoballoon ablation and RFA groups in the risk of cardiac tamponade (0.7–2.2% vs. 1.1–1.5%, total N=4304) (Table 29).<sup>76, 80, 81</sup>

### **Pericardial Effusion**

Neither RCT reported pericardial effusion rates. Four nonrandomized comparative studies reported pericardial effusion risks.<sup>76, 79-81</sup> In the cryoballoon ablation group, rates ranged from 0 to 9 percent; in the RFA groups, rates ranged from 2 to 14 percent (Table 29). Although rates varied across studies, there was no difference in the risk of pericardial effusion between treatment groups in any study.

One RCT reported one case of pericardial pain without effusion following cryoballoon ablation (and none following RFA) (Table 30).<sup>74</sup>

### **Pulmonary Vein Stenosis**

Pulmonary vein stenosis was not reported by either RCT. Across three nonrandomized comparative studies, there were no instances of pulmonary vein stenosis in the periprocedural period following RFA versus cryoballoon ablation (total N=4295) (Table 29).<sup>79-81</sup>

### **Other Ablation-Related Complications**

The most commonly reported other ablation-related complication in studies comparing cryoballoon ablation to RFA was phrenic nerve palsy or diaphragmatic hypokinesia. In general, the data trends suggest that this periprocedural event may be more common during cryoballoon ablation than RFA (Tables 29 and 30). One RCT reported a statistically similar risk of transient phrenic nerve palsy following cryoablation and RFA (7% [2/30] vs. 0% [0/30],  $p=0.15$ );<sup>74</sup> the other RCT also found that significantly more cryoballoon ablation patients experienced periprocedural diaphragmatic hypokinesia than did RFA patients (16% [4/25] vs. 0% [0/25],  $p=0.0390$ ).<sup>75</sup> Both RCTs reported all cases to be resolved during the procedure. All five nonrandomized studies reported on phrenic nerve palsy. The three studies on paroxysmal AF patients found significantly higher risk of periprocedural phrenic nerve palsy during cryoballoon ablation versus RFA (2.1%–8.1% vs. 0%,  $p\leq 0.0164$ );<sup>76, 80, 81</sup> in contrast both observational comparative studies evaluating patients with various types of AF found no difference between treatment groups (0%–2% vs. 0%, respectively).<sup>78, 79</sup> One study reported that two (of 11) patients

with phrenic nerve palsy did not resolve until 7 and 15 months postprocedure,<sup>80</sup> another reported two (of two) cases of this complication did not recover until 3 and 14 months following ablation,<sup>78</sup> and one study did not report details regarding resolution of this event.<sup>81</sup>

Three comparative observational studies reported on atriovenous fistula occurrences resulting from ablation procedures. Across all three studies, there was only one case of this adverse event and it was in a RFA patient (N=4304) (Table 29).<sup>76, 80, 81</sup> The patient underwent a vascular intervention and required two additional days in the hospital.

One RCT reported one case of hemoptysis secondary to a hematoma surrounding the right inferior pulmonary vein in a cryoballoon ablation patient (Table 30).<sup>75</sup>

## **Drug Therapy-Related Adverse Events**

One poor-quality retrospective observational study of mixed AF patients (N=124) reported no difference between cryoballoon ablation and RFA groups in the percentage of patients who had renal infarction (1.6% vs. 0%) (Table 29).<sup>79</sup> No other drug-related adverse events were described.

## **Peripheral Vascular Complications**

Peripheral vascular complications were reported by a total of four studies. One RCT found no difference between cryoballoon ablation versus RFA groups in terms of a major groin hematoma (3% vs. 0%) (Table 30);<sup>74</sup> one nonrandomized comparative study reported slightly higher incidence of groin hematoma following cryoballoon ablation versus RFA (1.5% vs. 0%),<sup>80</sup> while another cohort study noted similar rates of hematoma at catheter insertion site or pseudoaneurysm was reported by one poor-quality retrospective cohort study (4.8% vs. 4.8%) (Table 29). Femoral pseudoaneurysm occurred in similar percentages of patients between groups as reported by one RCT<sup>74</sup> and one nonrandomized comparative study<sup>80</sup> (Tables 30 and 29, respectively). One RCT reported a case of femoral arteriovenous fistula requiring surgical repair in the RFA group and none in the cryoballoon ablation group.<sup>75</sup> Finally, one registry-based comparative study reported significantly fewer cases of minor bleedings (not requiring intervention) following cryoballoon ablation compared with RFA (2.3% vs. 3.8%, p=0.0336; N=3775) (Table 29).<sup>81</sup>

## **Other Adverse Events**

Neither RCT reported any other adverse events. Three nonrandomized comparative studies reported other adverse events, and there were no differences between treatment groups in the occurrences of any.<sup>79-81</sup> Additional events included pneumothorax, hemothorax, significant hypotension, transient ST elevation, and contrast reactions (Table 29).

Of note, the large comparative registry study of 3775 paroxysmal AF patients found that there was a significantly lower overall procedural complication risk (excluding phrenic nerve palsy) in patients treated with cryoballoon ablation than those who received RFA (2.7% [24/905] vs. 4.6% [132/2870], p=0.0103), but no difference between groups in the overall complication risk (4.6% [42/905] vs. 4.6% [132/2870]) (Table 29).<sup>81</sup>

**Table 29. Adverse events for comparative observational studies comparing cryoballoon ablation with RFA**

Adverse Event		AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	Cryoablation % (n/N)	RFA % (n/N)
<b>Major Events</b>	Mortality (cardiovascular) <30 days	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0% (0/905)	0% (0/2,870)
			Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0% (0/260)
	Mortality (all cause) <30 days	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0% (0/905)	0% (0/2,870)
			Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0% (0/260)
	Stroke (any type) <30 days	Paroxysmal (2 <sup>nd</sup> line)	Chierchia 2010 <sup>76</sup>	Periprocedural	0% (0/46)	0% (0/87)
	Stroke/TIA	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.3% (3/905)	0.3% (9/2,870)
			Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0% (0/260)
Myocardial infarction	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.1% (1/905)	0% (0/2,870)	
Major bleeding	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.6% (5/905)	1.1% (30/2,870)	
"Major adverse cardiac and cerebrovascular events"	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.4% (4/905)	0.2% (6/2,870)	
<b>Ablation-Related Events*</b>	Cardiac tamponade	Paroxysmal (2 <sup>nd</sup> line)	Chierchia 2010 <sup>76</sup>	Periprocedural	2.2% (1/46)	1.1% (1/87)
			Schmidt 2014 <sup>81</sup>	Periprocedural	0.8% (7/905)	1.4% (37/2,870)
			Mugnai 2014 <sup>80</sup>	Periprocedural	0.7% (1/136)	1.5% (4/260)
	Pericardial effusion	Paroxysmal (2 <sup>nd</sup> line)	Chierchia 2010 <sup>76</sup>	In-hospital	8.7% (4/46)	13.8% (12/87)
			Mugnai 2014 <sup>80</sup>	Periprocedural	7.3% (10/136)	10% (26/260)
			Mixed (1 <sup>st</sup> /2 <sup>nd</sup> line)	Mandell 2013 <sup>79</sup>	Periprocedural	0% (0/62)
	Pulmonary vein stenosis	Paroxysmal (2 <sup>nd</sup> line)	Kojodjojo 2010 <sup>78</sup>	Periprocedural	1.1% (1/90)	3.8% (2/53)
			Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0% (0/2,870)
			Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0% (0/260)
	Phrenic nerve palsy	Mixed (1 <sup>st</sup> /2 <sup>nd</sup> line)	Mandell 2013 <sup>79</sup>	Periprocedural	0% (0/62)	0% (0/62)
			Chierchia 2010 <sup>76</sup>	Periprocedural	6.5% (3/46)	0% (0/87)
			Schmidt 2014 <sup>81</sup>	Periprocedural	2.1% (18/905)	0% (0/2,870)
	Phrenic nerve palsy	Mixed (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Periprocedural	8.1% (11/136) <sup>§</sup>	0% (0/260) <sup>§</sup>
Kojodjojo 2010 <sup>78</sup>			Periprocedural	2.2% (2/90)	0% (0/53)	

Adverse Event		AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	Cryoablation % (n/N)	RFA % (n/N)
	Atriovenous fistula	Paroxysmal (2 <sup>nd</sup> line)	Chierchia 2010 <sup>76</sup>	Periprocedural	0% (0/46)	1.1% (1/87)
			Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0% (0/2,870)
			Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0% (0/260)
	Aneurysmal spurium/AV fistula	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.8% (7/905)	1.1% (33/2,870)
Arrhythmia (<3 Months) <sup>†</sup>	AF recurrence (<30 days)	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	In-hospital	5.9% (53/905)	5.6% (161/2,870)
	Recurrence of any arrhythmia	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	3 months	0.7% (1/136)	1.9% (5/260)
	Sinus arrest/third-degree atrioventricular block	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0.8% (2/260)
	AV block III	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.1% (1/905)	0.0% (0/2,870)
Drug Therapy-Related Adverse Events <sup>†</sup>	Renal infarction	Mixed (1 <sup>st</sup> /2 <sup>nd</sup> line)	Mandell 2013 <sup>79</sup>	Periprocedural	1.6% (1/62)	0% (0/62)
Peripheral Vascular Complications	Groin hematoma	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Periprocedural	1.5% (2/136)	0% (0/260)
	Hematoma at catheter site or Pseudoaneurysm	Mixed (1 <sup>st</sup> /2 <sup>nd</sup> line)	Mandell 2013 <sup>79</sup>	Periprocedural	4.8% (3/62)	4.8% (3/62)
	Femoral artery pseudoaneurysm	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0.8% (2/260)
	Minor bleedings not requiring interventions	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	2.3% (21/905)	3.8% (109/2,870)
Adverse Events (Not Ablation Dependent) <sup>‡</sup>	Pneumothorax	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0.3% (8/2,870)
	Hemothorax	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0.2% (6/2,870)
	Sepsis	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0.0% (1/2,870)
	Pulmonary embolism	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0.0% (1/2,870)
	Surgical accident	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.0% (0/905)	0.1% (3/2,870)
	Pacemaker implantation	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	0.2% (2/905)	0.2% (6/2,870)
	Significant hypotension	Mixed (1 <sup>st</sup> /2 <sup>nd</sup> line)	Mandell 2013 <sup>79</sup>	Periprocedural	3.2% (2/62)	0% (0/62)
	Transient ST elevation	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Periprocedural	1.5% (2/136)	0.8% (2/260)



Adverse Event		AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	Cryoablation % (n/N)	RFA % (n/N)
	Contrast reactions	Paroxysmal (2 <sup>nd</sup> line)	Mugnai 2014 <sup>80</sup>	Periprocedural	0% (0/136)	0.4% (1/260)
<b>Overall Adverse Events</b>	Overall complication risk	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	4.6% (42/905)	4.6% (132/2,870)
	Procedural complication risk <sup>††</sup>	Paroxysmal (2 <sup>nd</sup> line)	Schmidt 2014 <sup>81</sup>	Periprocedural	2.7% (24/905)	4.6% (132/2,870)

AF = atrial fibrillation; AV = atrioventricular; RFA = radiofrequency catheter ablation; TIA = transient ischemic attack.

\*Denominator is the number of patients who underwent the procedure.

†Analysis based on patients “as treated”.

\*Adverse events that could occur regardless of whether ablation was performed

§In 81.8% (9/11) phrenic nerve palsy was resolved before discharge while 18.2% (2/11) patients did not recover until 7 and 15 months.

\*\*Reported as persistent or transient phrenic nerve palsy, 1 patient in the cryoablation group had transient phrenic nerve palsy. The authors report the number of adverse events out of the total number of patients with cryoablation though 20 patients also had RFA.

††Excluding phrenic nerve palsy; otherwise includes all complications reported in the table for this study.

**Table 30. Adverse events for RCTs comparing cryoballoon ablation with RFA**

Adverse Event		AF Type (1 <sup>st</sup> /2 <sup>nd</sup> line therapy)	Study	Followup	Cryoablation % (n/N)	RFA % (n/N)
<b>Arrhythmia (&lt;3 Months)</b>	AV nodal reentrant tachycardia	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	2 months	3.3% (1/30)	0% (0/30)
<b>Ablation-Related Events *</b>	Pericardial pain (no pericardial effusion)	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	Periprocedural	3.3% (1/30)	0% (0/30)
	Phrenic nerve palsy (transient)	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	Periprocedural	6.7% (2/30)	0% (0/30)
	Diaphragmatic hypokinesia	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	Periprocedural	16.0% (4/25)	0% (0/25)
	Hemoptysis secondary to a hematoma surrounding the right inferior PV	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	Periprocedural	4.0% (1/25)	0% (0/25)
<b>Peripheral Vascular Complications</b>	Groin hematoma	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	Periprocedural	3.3% (1/30)	0% (0/30)
	Femoral pseudoaneurysm	Mixed (2 <sup>nd</sup> line)	Herrera Siklody 2012 <sup>74</sup>	Periprocedural	3.3% (1/30)	0% (0/30)
	Femoral arteriovenous fistula requiring surgical repair	Paroxysmal (2 <sup>nd</sup> line)	Perez Castellano 2014 <sup>75</sup>	Periprocedural	0% (0/25)	4.0% (1/25)

AF = atrial fibrillation; AV = atrioventricular; PV = pulmonary vein; RCTs = randomized controlled trials; RFA = radiofrequency catheter ablation.

\*Denominator is the number of patients who underwent the procedure.

**Key Question 3.** Are there modifications of efficacy, effectiveness, or harms of catheter ablation versus medical therapy or different energy sources by patient-level characteristics such as age, sex, type of AF, comorbidities, risk for stroke or bleeding events, condition (i.e., patients with significant left ventricular dysfunction/heart failure or patients with significant left atrial enlargement or left ventricular hypertrophy), provider/setting characteristics or technique/approach?

## **Key Points**

- Evidence was insufficient to draw conclusions on the potential impact of patient or provider characteristics on the efficacy, effectiveness, or harms of catheter ablation as compared with medical therapy or comparing ablation using different energy sources (insufficient strength of evidence).
- Studies conducted in specific subgroups of the population found the following:
  - Rates of 30-day cerebral thromboembolism and pericardial effusion were higher, but not significant, with RFA in patients 70 years or older; no differences were seen at 60 days in freedom from recurrence or adverse events.
  - In patients who were receiving RFA as either first- or second-line treatment for AF, both long- and short-term freedom from recurrence rates favored RFA over medical therapy.
  - In patients with heart failure, across three studies the MLHFQ showed improvement following RFA compared with medical treatment. RFA was associated with improved maintenance of sinus rhythm in two studies and greater freedom from arrhythmia recurrence in the third compared with medical therapy; however, reablation was common. In these studies the rate of major complications following RFA were 4 percent and 15 percent.
  - In patients with Type 2 diabetes, at 12 months quality of life was more improved and more patients were free of recurrence of AF with RFA treatment than with medical therapy.

## **Detailed Description**

All studies described in this Key Question were included in Key Question 1 and so detailed descriptions of their study designs, populations, and primary and intermediate outcomes are provided in that section. Here we focus on whether these studies provided evidence of modification of efficacy, effectiveness, or harms of catheter ablation by patient-level characteristics, provider/setting, or characteristics of technique/approach. Note that outcomes related to patients with different types of AF (permanent vs. paroxysmal) are contained in the main findings of Key Question 1.

### **Age**

None of the studies provided evidence as to how older age modified the effects of the interventions. While no RCTs focused on Medicare patients or included subgroup analyses focusing on patients aged 65 years and older, two comparative observational studies did provide limited data on elderly patients (and thus a Medicare-relevant population).<sup>48, 53</sup>

A fair-quality, prospective, observational study of 412 consecutively enrolled patients aged 70 years and older (mean age, 75 years) who underwent either ablation (n=153) or medical therapy (n=259).<sup>48</sup> Patients were followed for a mean of  $60 \pm 17$  months; the study's primary endpoints were freedom from AF recurrence and treatment-related adverse events. At 30 days, there were more cerebral thromboembolic events, six (4 strokes and 2 TIAs) versus two (1 stroke and 1 TIA), and cases of pericardial effusion (3 vs. 0) in the RFA group than in the medical therapy group, but neither reached statistical significance (p values 0.058 and 0.056, respectively). After the initial 30 days there were no significant differences between the groups in terms of death, thromboembolic events, MI, major bleeding, or CHF.

A poor-quality, case-control study included 351 matched patients who had undergone catheter ablation (n=146, mean age 67.2 years) or drug treatment (n=205, mean age 66.7 years).<sup>53</sup> Patients were followed for a mean  $69 \pm 27$  months. As measured to a mean followup of  $69 \pm 27$  months, there was a statistically lower risk of mortality following RFA compared with medical therapy (3/146 vs. 34/205); authors report an adjusted HR of 4.88 (95% CI 1.44 to 16.53; p=0.001) for medical therapy versus PVAI as the referent, adjusting for AF type and comorbidities.

## Patients with Heart Failure

While no studies evaluate whether the presence of heart failure modified treatment effect, three small fair-quality RCTs (total N=143) evaluated the comparative efficacy and safety of RFA versus medical therapy in patients with heart failure and persistent AF.<sup>37,39,40</sup> All three studies enrolled heart failure patients with New York Heart Association (NYHA) class II-IV symptoms and ejection fractions less than 35 percent despite receiving optimal heart failure therapy, with two studies following patients for 6 months and the other for 12 months.

All studies reported on health related quality of life, but found different results. Using the MLHFQ, improvements were seen following RFA in all three studies. Two studies reported statistically significant differences favoring RFA at 6 months; means were different in one study (23.7 versus 47.0, p=0.001)<sup>37</sup> and the other provided no data, (p=0.02).<sup>39</sup> No statistical difference between groups (6-month change from baseline  $-5.7 \pm 19.7$  for RFA vs.  $-2.8 \pm 17.9$ ) were seen in the third trial but tended to favor RFA.<sup>40</sup> One trial reporting a difference favoring RFA at 6 months reported that the improvement persisted to 12 months.<sup>39</sup> One study reported no difference between groups using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months, and no difference in functional outcomes using the SF-36.<sup>40</sup> A second study found a significant difference (p=0.02, no data provided) that was maintained at 12 months (mean  $21 \pm 19$  for RFA vs.  $41 \pm 21$ , p=0.02).<sup>39</sup> The final recent study also demonstrated a statistically significant difference favoring RFA at 6 months (23.7 versus 47.0, p=0.001).<sup>37</sup> The lack of consistency in these findings could be due to inadequate sample sizes.

Two trials reported improved maintenance of sinus rhythm following RFA (50.0%–88.0%) compared with medical therapy (0%–7.7%) at 6 to 12 months<sup>39,40</sup> and the third trial reported similar results concerning freedom from arrhythmia recurrence<sup>37</sup> at 6 months (RFA 80.8% vs. medical therapy 0%). Across the three studies, repeat ablation was common and occurred in 34 percent (95% CI 19.3 to 52.6) of patients. Two studies reported peak oxygen consumption, which was significantly better at 12 months following RFA versus medical treatment (p=0.02) in one trial<sup>39</sup> and at 6 months (p=0.01) in the other.<sup>37</sup>

Over 6 months, one study reported that 15 percent of RFA patients (4/27 procedures) experienced a study-defined major procedure-related complications within one week, including

cerebrovascular accident, cardiac tamponade, and hospital readmission.<sup>40</sup> The second 6-month study, found 4.2 percent of patients in the medical therapy arm suffering intracranial hemorrhage as compared to no patients in the RFA arm.<sup>37</sup> In the 12-month study, 4 percent (1/25 procedures) of RFA patients experienced a major complication (cardiac tamponade).<sup>39</sup> The single death reported in all studies was deemed unrelated to the procedure.

Because of the inconsistency of these RCTs, and the lack of evidence comparing patients with heart failure as compared to those without we were unable to evaluate the impact of heart failure on the effectiveness of the interventions.

## Diabetic Patients

One good-quality RCT reported on the effectiveness of RFA in 70 diabetes mellitus type 2 patients. Patients had either paroxysmal or persistent AF, and were followed for 12 months.<sup>36</sup> The trial demonstrated a significant improvement in HRQOL in terms of many of the SF-36 subscales in RFA versus medically treated patients. Further, RFA patients also favored RFA in terms of freedom from recurrence of AF (RR 1.87, 95% CI 1.23 to 2.83).

While this RCT suggests a benefit of ablation over medical therapy in patients with diabetes, no studies were identified which evaluated the comparative benefit of the interventions in patients with versus without diabetes which precluded analysis of modification of effect based on this comorbidity.

## First- Versus Second-Line Treatment

Patients underwent treatment as a first-line therapy in three RCTs<sup>35, 42, 46</sup> and as a second-line therapy (i.e., had failed previous medical therapy) in eight RCTs.<sup>36, 38, 40, 41, 43-45, 47, 83</sup> The outcomes of these studies were used to explore the impact of patients being treated with ablation as first- versus second-line treatment. Overall, although data were insufficient to test for an interaction, results suggest that RFA was favored in terms of short-term freedom from recurrence regardless of whether patients were treated with first- versus second-line therapy. The figures referenced below are included in the intermediate outcomes section of Key Question 1a and include footnotes indicating which studies are in population undergoing first- and second-line treatment.

Short-term ( $\leq 12$  months) freedom from recurrence from any arrhythmia in paroxysmal AF patients was reported by four fair-quality RCTs (Figure 4), one of which was a study of first-line therapy and three of which were studies of second-line therapy. The study of first-line therapy favored RFA (RR 3.54, 95% CI 2.48 to 5.06),<sup>46</sup> as did the pooled estimate from second-line therapy studies (RR 3.31, 95% CI 2.48 to 4.34).<sup>38, 44, 47</sup> All studies that included persistent<sup>39, 41, 43</sup> or a mix of paroxysmal and persistent AF<sup>36, 45</sup> patients that reported short-term freedom from recurrence similarly reported that this outcome was favored in the RFA group.

Long-term ( $>12$  months) freedom from recurrence of any arrhythmia in was reported by three fair-quality RCTs, all of which included paroxysmal AF patients (Figure 5). Of the two RCTs that included only first-line patients, the pooled estimate favored RFA at 24 months (RR 1.22, 95% CI 1.04 to 1.69).<sup>35, 42</sup> Similarly, the single RCT which included only second-line patients found similar results at 48 months (RR 1.29, 95% CI 1.04 to 1.59).<sup>83</sup>

## Other Factors

The included studies did not provide data to explore any other additional patient or provider subgroups.

# Discussion

## Key Findings and Strength of Evidence

The key findings of this review for the outcomes identified as being most clinically important are summarized in the evidence summary tables (Tables 31–38) and factors used to determine the overall strength of evidence are summarized in Appendix G.

Due to methodological limitations, only one randomized controlled trial (RCT) was considered to be high quality.<sup>45</sup>

For the comparison of radiofrequency ablation (RFA) with medical therapy, for the primary clinical outcomes (mortality, stroke, myocardial infarction (MI), chronic heart failure (CHF) and health related quality of life (HRQOL), all ratings were low or insufficient. Strength of evidence was low or insufficient for most intermediate outcomes as well. Exceptions were freedom from recurrence of any atrial arrhythmia in patients with paroxysmal atrial fibrillation (AF) in both the short term ( $\leq 12$  months) and longer term ( $> 12$  months) and for the pooled estimate across all studies regardless of AF type for which the strength of evidence was rated as moderate for the comparison of radiofrequency ablation with medical therapy. For many outcomes for a specific AF type, only single studies were available and conclusions were not possible secondary to study limitations (i.e. methodology), small sample sizes resulting in imprecise estimates and/or limited data from these single studies leading to a strength of evidence of insufficient. Overall, findings from observational studies did not alter conclusions or impact the strength of evidence for any of the specified outcomes.

Evidence was most robust for the comparison of RFA with medical therapy. Overall, data were sparse for primary clinical outcomes such as mortality and stroke for both the short term and long term. The differences in results for long versus short term, particularly with respect to freedom from recurrence and reablation, may be due to a variety of factors including fewer studies reporting longer-term outcome and the short-term followup being too short to capture later relapses, thus longer-term benefit appears lower. There were insufficient data to evaluate the extent to which differences in technique or population characteristics may have impacted outcomes.

Given that long-term outcomes ( $\geq 12$  months) and findings from studies in the Medicare population are of primary importance to Centers for Medicare and Medicaid Services (CMS), these are highlighted. The only information available on populations 65 years of age and older was from two observational studies comparing RFA with medical therapy.<sup>48, 53</sup>

## Longer-Term Efficacy and Effectiveness

Long-term outcomes were only available for the comparison of RFA with medical therapy. Outcomes for which there were longer-term data are summarized in Table 31.

## Medicare-Relevant Population

In the Medicare-relevant population, there were no RCTs to provide evidence for efficacy and included studies did not provide analyses of this subpopulation. Definitive conclusions cannot be drawn from the two comparative observational studies identified that reported on patients aged 65 years and older. One fair-quality study with mean of 60 months followup<sup>48</sup> was in patients with persistent AF and the other was a poor-quality case-control study with a mean of 69 months followup in patients with various AF types,<sup>53</sup> although approximately 70 percent were classified by the authors as having “nonparoxysmal” AF. This latter study was in a slightly

younger population mean age 67.2 years) compared with the study in those with persistent AF (mean age, 75 years). Across these studies, results were conflicting with regard to the impact of RFA on all-cause mortality, with one in patients with persistent AF reporting comparable mortality between treatment groups (RFA: 1.3%; medical therapy: 1.9%); and the other in the mixed population reporting more than a fourfold greater risk of mortality in the medical treatment group (RFA: 2.1%; medical therapy: 16.5%) that was statistically significant. Similarly, in the study of those with persistent AF, the development of CHF was comparable between groups (RFA: 0%; medical therapy: 1.2%) in contrast to the significantly higher frequency in medical treatment group in the study of the mixed population (RFA: 0.7%; medical therapy: 9.8%). The case-control study did not provide information on the timing of outcomes such as mortality and stroke during the followup period. Neither study reported on HRQOL. It is not clear to what extent population differences, control for confounding, study design and/or technical differences across these studies might have influenced the results. In patients with persistent AF sinus rhythm was maintained in 58 percent of the RFA group versus 43 percent and 18.3 percent of patients required reablation.<sup>48</sup> Evidence was insufficient for all outcomes due to methodological concerns, imprecision, particularly for rare outcomes and unknown consistency from single studies. The inconsistency of the findings from the two studies and insufficient strength of evidence may make it challenging to weigh overall benefits and risks of RFA compared with medical therapy in this population from an evidence-based perspective.

## General Population

In the general population, firm conclusions regarding the effect of RFA on the primary long-term clinical outcomes (e.g., mortality) were limited given the paucity of data available. Three trials of RFA versus medical therapy in patients with paroxysmal AF reported on outcomes >12 months<sup>35, 46, 83</sup> with longest followup of 48 months in one study. No randomized controlled trials reporting on longer-term outcomes in patients with persistent AF were identified. One comparative observational study which contained those with either paroxysmal or persistent AF reported followup means of 16 months.<sup>51</sup>

In patients with paroxysmal AF, the strength of evidence was low that RFA did not appear to affect long-term all-cause mortality in those with paroxysmal AF across two trials and no statistical difference between treatments was reported.<sup>35, 42</sup> Death was most commonly due to fatal MI. No differences between groups were seen for the outcomes of stroke or MI, but these were rare outcomes across studies which may have been insufficiently powered. Across AF types, observational studies with >12 months followup may suggest lower risk of stroke and CHF for RFA versus medical therapy, however, the limitations of these studies weaken confidence in these findings and more robust evidence is needed. SF-36 MCS and PCS were similar for treatment groups at 24 months<sup>35</sup> and 48 months<sup>83</sup> in patients with paroxysmal AF in two separate studies; however, firm conclusions regarding the impact of RFA on HRQOL in the long term are not possible; only two small studies measuring SF-36 at different times provided data. Up to 48 months, RFA remained superior to medical therapy at improving freedom from recurrence of any atrial arrhythmia in patients with paroxysmal AF (pooled RR 1.24, 95% CI 1.11 to 1.47), however, reablation was common (pooled estimate 24%, 95% CI 12.6 to 41.5). Rehospitalization for cardiac causes was more common in the medical treatment group in one trial of patients with paroxysmal AF followed to 48 months which included repeat procedures and crossover to ablation.<sup>83</sup> Another trial only reported hospitalization for heart failure in two patients in the medical therapy group by 24 months and none in the ablation arm.<sup>35</sup>

In the one comparative observational study of mixed AF types,<sup>51</sup> mortality was comparable between treatments at 16 months in one observational study, stroke was more common in the medical treatment group and a higher proportion of RFA patients maintained sinus rhythm compared with medical therapy. Conclusions regarding RFA superiority in this population are not possible due to study limitations and imprecision and the strength of evidence was insufficient for all outcomes.

### **Short-Term ( $\leq 12$ Months) Efficacy and Effectiveness**

Data were sparse for the primary short-term efficacy outcomes comparing catheter ablation (RFA or cryoballoon ablation) with medical therapy which limits the conclusions that can be drawn (Tables 32 and 33). None of the observational studies contributed data on outcomes  $\leq 12$  months.

### **Medicare-Relevant Population**

None of the included RCTs were in a Medicare-eligible population and no subanalyses by age were provided. Neither of the observational studies in people  $\geq 65$  years provided data on short-term effectiveness.

### **General Population**

For the comparison of RFA with medical therapy, the incidence of all-cause mortality  $>30$  days, stroke  $>30$  days and MI  $>30$  days was low for both treatment groups regardless of AF type and no distinct risk patterns based on treatment were seen. While there were seven small RCTs which reported on all-cause mortality  $>30$  days,<sup>38, 39, 41, 43, 45-47</sup> there was a paucity of trials reporting on stroke or MI  $>30$  days regardless of AF type.

In patients with paroxysmal AF, evidence was low across three trials that there were no statistical differences between RFA and medical therapy for all-cause mortality past 30 days and across two trials for MI  $>30$  days.<sup>38, 46, 47</sup> There is insufficient evidence regarding stroke from one trial, which reported none for RFA or medical therapy and no conclusions are possible.

Conclusions regarding the impact of RFA on HRQOL in both the short- or long-term were not possible. In general, for most HRQOL measures, findings were similar between treatment groups at six to 12 months followup with the few exceptions noted in the summary tables below.

This is not to say that there is not improvement in HRQOL or symptoms following ablation, but there are challenges in confirming this with the currently available evidence from comparative studies that met the inclusion criteria. While individual studies reported statistically significant results favoring RFA over medical therapy for specific measures or isolated domains of measures, others did not. The variety of measures used, varied measurement timing and extensive cross-over make it difficult to draw firm conclusions regarding the impact of catheter ablation on HRQOL compared with use of antiarrhythmic drugs (AADs) as it is difficult to effectively evaluate consistency across measures and effect sizes. This was the basis for the rating of insufficient evidence. Although the Short Form-36 (SF-36) questionnaire was employed most frequently, measurements occurred at a variety of time points across studies and data were presented in different ways. These factors, combined with possible differences in patients receiving catheter ablation as a first line treatment versus a second line treatment precluded meaningful pooling of data. Where data were pooled, for the SF-36 Physical Component Score (PCS), different analysis methods yielded differing results, calling the stability of the estimate into question. Across four clinically heterogeneous trials with discrepant time frames (6-48 months), the SF-36 bodily pain domain was significantly improved in the RFA groups in three<sup>36</sup>.



<sup>37, 46, 83</sup> of the four trials that provided data, however, given the differences in clinical populations and time frames, definitive conclusions are not advisable. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was reported in three small trials in patients with persistent AF and concomitant heart failure. Two of three studies reported improvement favoring RFA at 6 months; the third didn't reach significance but tended to favor RFA (low strength of evidence). One of the trials reported that the difference was also evident at 12 months (insufficient strength of evidence). For all measures, there was likely insufficient sample size in many studies to detect differences between treatments. Clinically, a primary indication for performing RFA is to improve symptoms. While it may be that patients experience relief of symptoms following RFA, the majority of the HRQOL measures reported may not capture the type and range of symptoms experienced by those with AF or the potential impact of RFA on patient symptoms. There were inadequate data to evaluate the influence of use of RFA as a first versus second-line treatment on HRQOL.

There was moderate evidence that RFA was superior to medical therapy at improving freedom from recurrence (pooled RR 3.06, 95% CI 2.35 to 3.90 across 4 RCTs)<sup>38, 44, 46, 47</sup> of any atrial arrhythmia in patients in patients with paroxysmal AF and low strength of evidence that maintenance of sinus rhythm was significantly better following RFA compared with medical therapy in the short term, based in intention-to-treat analysis. In interpreting these findings, differences in definitions, methods of measurement and symptom status across studies need to be considered as does the substantial crossover which occurred in most studies. The need for reablation by 12 months varied widely across studies in patients with paroxysmal AF (0% to 43%). Overall, hospitalization was more frequent in patients who received medical therapy versus RFA. In those with paroxysmal AF, rehospitalization was more common in the medical treatment groups by 12 months across two studies<sup>44, 46</sup> and the trial population followed to 48 months previously described.<sup>83</sup> Studies did not provide detail regarding reasons for hospitalization and the extent to which hospitalization for reablation procedures or crossover from medical therapy to ablation were included. Variability in reporting across trials makes it difficult to synthesize information.

In patients with persistent AF, strength of evidence for all outcomes was low or insufficient. Similar to findings in those with paroxysmal AF, there was low evidence that there was no difference between treatments for all-cause mortality and insufficient information for no difference for stroke. There is insufficient evidence on the impact of RFA on HRQOL compared with medical therapy. RFA was again superior to medical therapy for keeping patient free from recurrent atrial arrhythmia with rates of 58 to 74 percent in the RFA group versus 4 to 58 percent in the medical therapy group across three trials<sup>35, 42, 83</sup> but strength of evidence was considered low as was the case for improved maintenance of sinus rhythm following RFA. The need for reablation by 12 months in those with persistent AF was variable (pooled estimate 20.1%, 95% CI 11 to 34).

Data for the comparison of cryoballoon ablation versus medical therapy was limited; only one moderate-sized RCT which combined patients with different AF types was identified and provided data on short-term outcomes only (Table 33).<sup>86</sup> Freedom from protocol-defined treatment failure, which was defined as absence of detectable AF after the blanking period, use of a nonstudy AAD, or any nonprotocol intervention (e.g., RFA), was significantly greater in the cryoballoon ablation group compared with the group treated medically (cryoballoon ablation: 69.9%; medical therapy: 7.3%). The strength of evidence for this outcome was low and strength

of evidence was insufficient for other outcomes. Again, there was substantial crossover from medical therapy to cryoballoon ablation.

Conclusions regarding the primary outcomes of interest for this report are not possible for the comparison of cryoballoon ablation with RFA (Tables 34 and 35). Neither of the identified trials, one in those with paroxysmal AF and one in a mixed population reported on these outcomes. Both trials suggest that freedom from recurrence is lower and need for reablation is higher following cryoablation compared with RFA, but small trial sizes may preclude demonstration of statistical significance and strength of evidence is insufficient. Observational studies reported no significant differences between treatments for these outcomes and didn't alter the strength of evidence.

## Harms

Primary clinically important outcomes related to harms were mortality <30 days, stroke <30 days, atrial fibrillation <3 months post-ablation, cardiac tamponade, pericardial effusion, pulmonary vein stenosis, and drug intolerance requiring discontinuation.

Harms were reported for RFA versus medical therapy by 13 RCTs<sup>35-47, 83</sup> and six comparative observational studies (Table 36).<sup>48-53</sup> In order to better assess the risk of rare adverse events, data from 16 case series of at least 1000 patients specifically designed to evaluate the incidence of adverse events following catheter ablation were also included.<sup>55-65, 67-71</sup> In addition, one meta-analysis of case series was also included.<sup>66</sup> While most case series used RFA, some used a mix of different energy sources.

## Medicare-Relevant Population

One observational study in patients with persistent AF reported on outcomes for 412 patients over the age of 70, thus pertinent to the Medicare population, however no differences were seen in harms rates from this study compared to those from other studies of the general population.<sup>48</sup> A significantly higher stroke risk following RFA (2.6%) versus medical therapy (0.4%) and significantly lower risk of antiarrhythmic drug intolerance requiring discontinuation following RFA (2.6%) versus medical therapy (12.7%) were reported. Due to study limitations and the fact that these data were from a single study, it is difficult to draw definitive conclusions.

## General Population

Overall in the general population, risk of any major adverse event within 30 days (all-cause mortality, stroke, myocardial infarction, major bleeding/hemorrhage, need for transfusion and heart failure) from RCTs ranged from 0 to 6.3 percent in those receiving RFA and from 0 to 5.7 percent for those receiving medical therapy. Cardiac tamponade risk ranged from 0 to 9.5 percent following RFA. In studies of patients with heart failure and AF risks were higher; overall risk of any major complication was 14.8 percent of all procedures in one RCT and risk of cardiac tamponade ranged from 3.8 to 9.5 percent across three RCTs. These overall ranges are from controlled studies conducted in tertiary referral centers with procedures performed by experienced personnel and may not reflect broader clinical practice outside of such centers.

With regard to individual harms, both all-cause mortality and stroke within 30 days of treatment were relatively rare events as reported in the comparative studies, and no patterns were detected according to type of AF. Overall 30-day mortality rates ranged from 0 to 0.7 percent in the RFA group and 0 to 4.2 percent in the medical therapy group as reported by five RCTs<sup>35, 37, 41, 42, 47</sup> and one cohort study.<sup>48</sup> Data from 11 case series supported the conclusion that 30-day mortality rates are low following ablation, with mortality reported in 0 to 0.8 percent of

procedures or patients.<sup>55-57, 59-62, 64, 65, 67, 70</sup> Stroke within 30 days of treatment was reported to occur in 0 to 4.8 percent of RFA patients (three strokes total) and 0 percent of medical therapy patients based on data from eight RCTs.<sup>35, 37, 40-42, 45, 46</sup> Data from eight case series and one meta-analysis of case series reported low 30-day stroke rates that ranged from 0.08 to 0.8 percent patients or procedures.<sup>55, 57, 59, 61, 64, 66-68, 70</sup>

There was no difference in the 3-month AF recurrence rate in two RCTs of paroxysmal AF patients.<sup>35, 46</sup> Two RCTs of persistent AF patients (with heart failure) suggested a lower 2- to 3-month risk of AF following RFA versus medical therapy.<sup>37, 43</sup>

The risk of cardiac tamponade following RFA was moderate in four RCTs of paroxysmal AF patients (pooled risk 1.7%, 95% CI 0.8 to 3.6).<sup>35, 38, 42, 47</sup> Although risk was higher in three very small RCTs (i.e., 73 patients total) of persistent AF patients (pooled risk 5.5%, 95% CI 2.1 to 13.7), small sample sizes may preclude accurate determination of risk.<sup>39, 40, 60</sup> No cases were reported in two comparative observational studies.<sup>48, 52</sup> Across eight case series plus one meta-analysis of case series, cardiac tamponade was reported in 0.6 to 6.7 percent of ablation patients or procedures.<sup>55-57, 59-61, 66, 69</sup> Comparative studies with greater sample size are needed to determine whether the risk of this complication is higher in persistent versus paroxysmal AF patients.

Pericardial effusion risk ranged from 0.5 to 4.5 percent as reported by six RCTs<sup>35, 41, 42, 45, 47, 83</sup> and were less than 2 percent in one cohort study<sup>48</sup> and four case series.<sup>55, 58, 64, 65</sup> Pulmonary vein stenosis developed in 0 to 3 percent of RFA patients as reported by seven RCTs; there was not a clear difference in this risk in RCTs of paroxysmal versus persistent AF patients or between those with 12 versus 24 months of followup. Pulmonary vein stenosis was reported in 0 to 7.1 percent (i.e., 6/85) of patients across three comparative observational studies, though definitive conclusions could not be made due to study limitations,<sup>48, 51, 52</sup> and in 0 to 1.5 percent of ablation patients or procedures across six case series.<sup>55, 57-60, 64</sup>

Drug intolerance requiring discontinuation was reported in three RCTs, in which 0 to 23 percent of medical therapy patients discontinued antiarrhythmic medication due to adverse events such as pro-arrhythmia, bradycardia, thyroid dysfunction, and sexual impairment.<sup>36, 44, 47</sup> However, due to limited duration and/or usage of medical therapy in the RFA group it is difficult to make comparative conclusions.

Data on harms for the comparison of cryoballoon ablation versus medical therapy were limited as a single study was available (Table 37).<sup>86</sup> There were no deaths in either group and one stroke in the cryoballoon ablation group within 30 days of treatment initiation. The incidence of cardiac tamponade following cryoballoon ablation was also low (0.9%).<sup>86</sup> Limited data on harms for the comparison of cryoballoon ablation with RFA were available; with two small RCTs<sup>88, 89</sup> and two comparative observational studies<sup>76, 79</sup> identified (Table 38), very few definitive conclusions can be made. Due to limited reporting on harms from the RCTs<sup>74, 75</sup> and general poor quality of the comparative observational studies<sup>78-81</sup> reporting major outcomes, no definitive conclusions can be made.

## Differential Efficacy and Harms

Conclusions regarding the extent to which catheter ablation may be more efficacious or harmful for specific population subgroups are not possible. None of the RCTs provided sufficient data to stratify by subgroups. Two studies in patients with concomitant heart failure and persistent AF reported that maintenance of sinus rhythm<sup>39, 40</sup> was improved within the ablation patients in the short term and a third trial reported similar results concerning freedom from

arrhythmia recurrence,<sup>37</sup> however, reablation was common. RFA was associated with improved HRQOL (i.e., MLHFQ) across all three studies<sup>37, 39, 40</sup> and with improved functional outcomes in two studies.<sup>37, 39</sup> However, given that these studies did not directly compare treatment effect in those who did not have heart failure, modification of treatment effect by presence of heart failure could not be confirmed. Similarly, one study in diabetic patients who had either paroxysmal or persistent AF reported a significant benefit in HRQOL and freedom from recurrent in ablation patients.<sup>36</sup> Again, modification of treatment effect by diabetes cannot be verified. With regard to use of catheter ablation as a first versus second-line treatment for any AF type, there were insufficient data to effectively stratify on this across studies. Based on information available, however, it appears that the relative risk point estimates for the one small study (N=65) where RFA was used as first-line treatment<sup>46</sup> and the seven studies where it was used following failure of AADs,<sup>36, 38, 41, 43-45</sup> are in the same direction (favoring RFA) for freedom from recurrence to 12 months and that there is substantial overlap in the confidence intervals. Similarly, followup >12 months, the point estimates for the two studies where RFA was used as the first-line treatment<sup>35, 42</sup> are similar to the one study where RFA was used as a second-line treatment and there is substantial overlap in the confidence intervals.<sup>83</sup> These findings suggest that freedom from recurrence is similar for RFA when used as a first- or second-line treatment; however, additional data and evaluation of the effect on other clinically important outcomes are needed before drawing firm conclusions.

**Table 31. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) comparative efficacy and effectiveness of RFA versus medical therapy for AF**

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality (All Cause) &gt;30 Days</b>	Paroxysmal AF	2 RCTs (N=408)	Low	At 24 months, one RCT reported no deaths in either group; the other, two (1.4%) in RFA and four (2.8%) in the medical treatment group.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable mortality in both groups at 60 months: 1.3% RFA, 1.9% medical therapy. Definitive conclusions are not possible.*
	Mixed	1 comparative observational (N=170)	Insufficient*	Comparable mortality in both groups at 16 months: 0% RFA, 1.2% medical therapy. Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	Greater mortality in the medical therapy arm at 69 months (2.1% RFA, 16.5% medical therapy); Definitive conclusions are not possible.*
<b>Stroke &gt;30 Days</b>	Paroxysmal AF	1 RCT (N=127)	Insufficient*	No strokes reported at 24 months. Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable frequency in both groups for stroke or TIA at 60 months (1.3% RFA, 1.9% medical therapy). Definitive conclusions are not possible.*
	Mixed	2 comparative observational (N=1772 )	Insufficient*	Increased stroke risk in medical therapy group (0% RFA vs. 4.7% medical therapy at 16 months in one study; annualized rate 3.4% RFA vs. 5.5% medical therapy in an administrative database study with a mean followup of 27 months). Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	At 69 months, risk 0% RFA versus 1.5% medical therapy group. Definitive conclusions are not possible.*
<b>Myocardial Infarction &gt;30 Days</b>	Paroxysmal AF	1 RCT (N=294)	Insufficient*	One (0.7%) fatal MI in the medical treatment group by 24 months. Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable MI events in both groups at 60 months (0% RFA, 0.4 % medical). Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	Greater MI events in ablation group at 69 months (1.4% RFA, 0% medical therapy). Definitive conclusions are not possible.*
<b>Congestive Heart Failure</b>	Paroxysmal AF	1 RCT (N=294)	Insufficient*	By 24 months, no one in the RFA group and two people (1.4%) in medical therapy group developed CHF. Definitive conclusions are not possible.*

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Comparable CHF development in both groups at 60 months (0% RFA, 1.2% medical therapy). Definitive conclusions are not possible.*
	Mixed	1 comparative observational (N=1602)	Insufficient*	Comparable annualized rates of hospitalization for heart failure: 1.5% RFA, 2.2% medical therapy in one administrative data study with a mean followup of 27 months. Definitive conclusions are not possible.*
	Mixed: Medicare population	1 comparative observational (N=351)	Insufficient*	Greater CHF in medical therapy group at 69 months (0.7% RFA, 9.8% medical therapy). Definitive conclusions are not possible.*
<b>Health-Related Quality Of Life: SF-36</b>	Mental Component Score and Physical Component Score: Paroxysmal AF	1 RCT (N=294) at 24 months; 1 RCT (N=198) at 48 months	Insufficient*	Mean MCS was similar between groups at 24 months (RFA: 51.1 ± 9.2; Medical therapy: 50.9 ± 8.0) (1 RCT) and at 48 months (RFA: 52.9 ± 9; Medical therapy: 51.9 ± 9) (1 RCT); Mean PCS was similar between groups at 24 months (RFA: 50.0 ± 8.8; Medical therapy: 47.9 ± 8.9) (1 RCT) and at 48 months (RFA: 52.3 ± 9; Medical therapy: 52.6 ± 8) (1 RCT). Definitive conclusions are not possible.*
<b>Freedom From Recurrence (Any Arrhythmia)</b>	Paroxysmal AF	3 RCTs (N=619)	Moderate	At 24–48 months, RFA was associated with greater freedom from recurrence compared with medical therapy (pooled RR 1.24; 95% CI 1.11 to 1.47).
	Mixed	1 comparative observational (N=85 in RFA arm)	Insufficient*	Rate was 74% at 15 months for RFA group; not reported for medical therapy. Definitive conclusions are not possible.*
<b>Maintenance Of Sinus Rhythm</b>	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	At 60 months, rate was 58% in the RFA group versus 43% in the medical therapy group. Definitive conclusions are not possible.*
	Mixed	1 comparative observational (N=170)	Insufficient*	At 15 months, rate was 82% in the RFA group versus 40% in the medical therapy group. Definitive conclusions are not possible.*
<b>Reablation (Any Arrhythmia)</b>	Paroxysmal AF	4 RCTs (N=337)	Low	Over followup periods ranging from longer than 12 months to 48 months, frequency of reablation varied across trials (range, 12.5%–49.2%) with a pooled risk of 24.2% (95% CI 12.6 to 41.5).
	Persistent AF: Medicare population	1 comparative observational (N=153 ablation group only)	Insufficient*	Rate was 18.3% at 60 months for RFA group; not reported for medical therapy. Definitive conclusions are not possible.*

AF = atrial fibrillation; CHF = congestive heart failure; KQ = Key Question; MCS = Mental Component Score; MI = myocardial infarction; PCS = Physical Component Score; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations (i.e. methodology), small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table 32. Key findings and strength of evidence for Key Question 1: Short-term ( $\leq 12$  months) comparative efficacy and effectiveness of RFA versus medical therapy for AF**

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality (All Cause) &gt;30 Days</b>	All RCTs (regardless of AF type)	7 (N=814)	Low	Low frequency of mortality with risk similar between groups (0%–3.8% for RFA and 0%–2.9% for medical therapy).
	Paroxysmal AF	3 RCTs (N=333)	Low	One death was reported in the RFA group, two in the medical treatment group.
	Persistent AF	3 RCTs (N=344)	Low	Two deaths were reported in the RFA group with none reported for medical treatment.
	Mixed	1 RCT (N=137)	Low	One death was reported in the RFA group and two in the medical therapy group.
<b>Stroke &gt;30 Days</b>	Paroxysmal AF	1 RCT (N=67)	Insufficient*	No strokes were reported for either treatment. Definitive conclusions are not possible.*
	Persistent AF	1 RCT (N=146)	Insufficient*	No strokes were reported for either treatment. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=70) (Diabetic patients)	Insufficient*	No strokes were reported for either treatment. Definitive conclusions are not possible.*
<b>Myocardial Infarction &gt;30 Days</b>	Paroxysmal AF	2 RCTs (N=270)	Insufficient*	Two fatal MIs occurred, one in each treatment group. Definitive conclusions are not possible.*
<b>Congestive Heart Failure</b>	None for any AF type	None	Insufficient	No data available
<b>Health-Related Quality Of Life: SF- 36</b>	Mental Component Score: Paroxysmal AF	2 RCTs (N=406); 1 comparative observational (N=166)	Insufficient*	No statistical difference between treatment: pooled estimates for difference in change scores (1.88; 95% CI -0.47 to 4.50) and difference in mean scores (2.26; 95% CI -2.12 to 7.40) based on RCTs.
	Mental Component Score: Persistent AF (Patients with heart failure)	1 RCT (N=41) at 6 months	Insufficient*	No difference in mean change from baseline between groups (RFA: +0.4 $\pm$ 9.5; Medical Therapy: +5.9 $\pm$ 8.5). Definitive conclusions are not possible.*
	Physical Component Score: Paroxysmal AF	2 RCTs (N=406); 1 comparative observational (N=166)	Insufficient*	No statistical difference between treatments based on the pooled estimate from RCTs for difference in change scores (2.88; 95% CI -0.18 to 5.25); however, RFA was favored based on the pooled estimate using difference in mean scores (2.85; 95% CI 0.93 to 4.82). Definitive conclusions are not possible.*
	Physical Component Score: Persistent AF (Patients with heart failure)	1 RCT (N=41) at 6 months	Insufficient*	Greater change from baseline for RFA group reached statistical significance (+4.0 $\pm$ 9.5 vs. -1.0 $\pm$ 4.4 for medical therapy). Definitive conclusions are not possible.*

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Other Health-Related Quality Of Life Measures</b>	<i>Minnesota Living with Heart Failure Questionnaire</i> : Persistent AF in heart failure patients	3 RCTs (N=141) (heart failure)	Low (6 months) Insufficient* (12 months)	Two studies reported statistically significant differences favoring RFA at 6 months; means were different in one study (23.7 versus 47.0, p=0.001) and the other provided no data, (p=0.02). No statistical difference between groups (change from baseline -5.7 ± 19.7 for RFA vs. -2.8 ± 17.9) were seen in the third trial but tended to favor RFA. One trial reporting a difference favoring RFA at 6 months which persisted to 12 months. Definitive conclusions beyond 6 months are not possible.*
	<i>EuroQOL -5D and Symptom Check List</i> : Paroxysmal AF	1 RCT (N=127) EQ5D; 1 RCT (N=112) Symptom Check List	Insufficient*	Small, single RCTs each reported different measures. No differences between treatments for EQ5D (one trial). Another reported no differences in the Symptom Checklist Frequency Scale but a difference favoring RFA in the Severity Scale. Definitive conclusions are not possible.*
	<i>AFQOL, KCCQ, and NYHA score</i> : Persistent AF	1 RCT (N=146) AF-QOL; 1 RCT (N=127) KCCQ; 1 RCT (N=48) NYHA score	Insufficient*	No differences between treatments for AFQOL and KCCQ; RFA favored at 6 months based on NYHA score. Definitive conclusions are not possible.*
	<i>Zung Self-Rating Anxiety Scale and Depression Scale</i> : Paroxysmal AF	2 comparative observational (N=365)	Insufficient*	Mean SAS and SDS scores were significantly decreased compared with baseline scores in ablation group but not in the medical group. Magnitude not reported in one study. Definitive conclusions are not possible.*
<b>Freedom From Recurrence (Any Arrhythmia)</b>	All RCTs (regardless of AF type)	9 (N=1089)	Moderate	Freedom from recurrence of any arrhythmia was greater for RFA versus medical therapy (pooled RR 2.62; 95% CI 1.90 to 3.96).
	Paroxysmal AF	4 RCTs (N=538); 2 comparative observational (N=322)	Moderate	Freedom from recurrence of any arrhythmia was greater for RFA versus medical therapy (pooled RR 3.06; 95% CI 2.35 to 3.90).
	Persistent AF	3 RCTs (N=344)	Low	Rate is 58%–74% in the RFA group versus 4%–58% in the medical therapy group. Studies are too heterogeneous to combine. Findings are suggestive of benefit, but more data are needed.
	Mixed	2 RCTs (N=207)	Low	Rate is 56%–80% in the RFA group versus 9%–43% in the medical therapy group. Studies are too heterogeneous to combine. Findings are suggestive of benefit, but more data are needed.
<b>Maintenance Of Sinus Rhythm</b>	Paroxysmal AF	2 RCTs (N=310); 2 comparative observational (N=385)	Low	Rate is 88%–92.9% for RFA group versus 35.4%–87% for medical therapy arm across RCTs; Rate is 71.1%–72% in the RFA arm vs. 20.2%–47.1% in the medical therapy arm in comparative observational studies.



Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Persistent AF (patients with heart failure)	2 RCTs (N=93)	Low	Rate 50.0%–88.0% for RFA group versus. 0%–7.7% for medical therapy group.
<b>Reablation (Any Arrhythmia)</b>	All RCTs (regardless of AF type)	8 (N=430) (ablation group only)	Low	The frequency of reablation following RFA varied across eight RCTs (range, 0%–53.8%).
	Paroxysmal AF	3 RCTs (N=184); 1 comparative observational (N=82) (ablation groups only)	Low	Rates varied widely (0%–43.3%) and consequently were not pooled.
	Persistent AF	5 RCTs (N=246) (ablation group only)	Low	Rates ranged from 8.1%–53.8% with a pooled estimate of 25.5% (95% CI 13.6% to 42.6%).
	Persistent AF (patients with heart failure)	3 RCTs (N=71) (ablation group only)	Low	Pooled estimate: 34% (95% CI 19.3% to 52.6%).

AF = atrial fibrillation; AFQOL = Atrial Fibrillation Quality of Life Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; KQ = Key Question; MCS = Mental Component Score; MI = myocardial infarction; PCS = Physical Component Score; RCT = randomized controlled trial; RFA = radiofrequency ablation; SAS = Zung Self-Rating Anxiety Scale; SDS = Zung Self-Rating Depression Scale.

\*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table 33. Key findings and strength of evidence for Key Question 1: Short-term ( $\leq 12$  months) efficacy and effectiveness outcomes comparing cryoballoon ablation with medical therapy for AF**

<b>Outcomes*</b>	<b>Number of Studies (N)</b>	<b>Strength of Evidence Grade</b>	<b>Conclusions, Effect Size</b>
<b>Mortality (All Cause) &gt;30 Days</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	One unrelated fatal MI at 10 months reported in the cryoballoon ablation group. Definitive conclusions are not possible. <sup>†</sup>
<b>Stroke &gt;30 Days</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	Three strokes occurred >30 days from randomization (with one being 5 days after repeat RFA for atrial flutter). Definitive conclusions are not possible. <sup>†</sup>
<b>Myocardial Infarction &gt;30 Days</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	One unrelated fatal MI at 10 months reported in the cryoballoon ablation group. Definitive conclusions are not possible. <sup>†</sup>
<b>Congestive Heart Failure</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	One cryoballoon ablation patient was hospitalized with AF-related congestive heart failure. Definitive conclusions are not possible. <sup>†</sup>
<b>Health-Related Quality Of Life</b>	1 RCT (N=245)	Insufficient <sup>†</sup>	Reported that SF-36 symptoms improved in cryoballoon ablation population but did not publish data or include comparison with medically treated patients. Definitive conclusions are not possible. <sup>†</sup>
<b>Freedom From Protocol-Defined Treatment Failure</b>	1 RCT (N=245)	Low	Cryoballoon ablation was associated with greater freedom from protocol-defined treatment failure compared with medical therapy: 69.9% versus 7.3%.

AF = atrial fibrillation; KQ = Key Question; MI = myocardial infarction; RCT = randomized controlled trial; RFA = radiofrequency ablation; SF-36 = Short-Form 36 questionnaire.

\*All outcomes are for the same RCT in a mixed population (no other studies were identified for this comparison).

<sup>†</sup>Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table 34. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF**

<b>Outcomes, Population</b>	<b>Number of Studies (N)</b>	<b>Strength of Evidence Grade</b>	<b>Conclusions, Effect Size</b>
<b>Mortality (all cause) &gt;30 days</b> (Paroxysmal AF)	1 comparative observational (N=396)	Insufficient*	At 23 months, mortality occurred in 1.2% (3/260) in the RFA arm versus none (0/136) in the cryoballoon ablation arm. Definitive conclusions are not possible.*
<b>Freedom from recurrence (any arrhythmia)</b> (Paroxysmal AF)	2 comparative observational (N=498)	Insufficient*	No statistical differences at 23–28 months with 55%–63% experiencing freedom from recurrence following cryoballoon ablation versus 55%–57% following RFA. Definitive conclusions are not possible.*
<b>Reablation (AF only)</b> (Mixed)	1 comparative observational (N=177)	Insufficient*	By 14 months, reablation for AF was performed in 14% of cryoballoon recipients versus 23% of those receiving RFA. Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table 35. Key findings and strength of evidence for Key Question 1: Short-term ( $\leq 12$  months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF**

Outcomes	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Freedom From Recurrence (AF only)</b>	Paroxysmal AF	1 RCT (N=50); 1 comparative observational (N=143)	Insufficient*	Freedom from AF recurrence was less common in the cryoballoon ablation group (48%) versus RFA (68%) in one RCT, however results failed to reach statistical significance. Rates were 77% and 72%, respectively, in one comparative observational study. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=60)	Insufficient*	Freedom from AF recurrence was less common in the cryoballoon ablation group (66.7%) versus RFA (86.7%) however results failed to reach statistical significance. Definitive conclusions are not possible.*
<b>Reablation (AF only)</b>	Paroxysmal AF	1 RCT (N=50)	Insufficient*	Reablation for AF only was more common following cryoballoon ablation (24%) versus none for RFA (0%); RR 0.22 (95% CI 0.07 to 0.37), p=0.0122. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=60)	Insufficient*	Reablation for AF only was more common following cryoballoon ablation (30%) versus RFA (13.3%), but statistical significance was not reached. Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

**Table 36. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with RFA versus medical therapy for AF**

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality &lt;30 Days</b>	All RCTs (regardless of AF type)	5 RCTs (N=761)	Low	Low frequency of 30-day mortality with similar risk between groups: RFA 0%–0.7%; medical therapy 0%–4.2% (1/24).
	Paroxysmal AF	3 RCT (N=570)	Low	Low frequency of 30-day mortality with similar risk between groups: RFA 0%–0.7%; medical therapy 0%. One death occurred following a procedure-related cerebral stroke.
	Persistent AF	2 RCTs (N=191)	Low	Low frequency of 30-day mortality with similar risk between groups: RFA 0%; medical therapy 0%–4.2%. One sudden cardiac death occurred in a heart failure patient.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Low 30-day mortality risk in both groups: RFA 0%; Medical therapy 0.4%. Definitive conclusions are not possible.*
<b>Stroke &lt;30 Days</b>	All RCTs (regardless of AF type)	8 RCTs (N=919)	Low	30-day stroke risk following both treatments: RFA 0%–4.8%; medical therapy 0%.
	Paroxysmal AF	3 RCTs (N=481)	Low	Low frequency of 30-day stroke with similar risk between groups: RFA 0%–0.7%; medical therapy 0%. One procedure-related cerebral stroke occurred (and resulted in death).
	Persistent AF	3 RCTs (N=231)	Low	Low 30-day stroke risk following both treatments: RFA 0%–4.8%; medical therapy 0%. Both strokes occurred in patients with heart failure: one during the procedure and the other 6 days post-ablation.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Higher 30-day stroke risk following RFA (2.6%) versus medical therapy (0.4%) (p=0.046). Definitive conclusions are not possible.*
	Mixed	2 RCTs (N=207); 1 comparative observational (N=166)	Low	Low 30-day stroke risk following both treatments: RFA 0%–1.5%; medical therapy 0%. One procedural stroke occurred. In the comparative observational study, 30-day stroke risk between groups: RFA 1.2%; medical therapy 1.2%.
<b>AF &lt;3 Months</b>	Paroxysmal AF	2 RCTs (N=183)	Low	No difference in 3-month AF risk between groups (pooled RR 0.67 [95% CI 0.40 to 1.10]).
	Persistent AF	2 RCTs (N=196)	Low	2- to 3-month risk of AF lower following RFA versus medical therapy (pooled RR 0.18 [95% CI 0.11 to 0.30]).
<b>Cardiac Tamponade<sup>†</sup></b>	Paroxysmal AF	4 RCTs (N=512); 1 comparative observational (N=85)	Low	The pooled cardiac tamponade risk following RFA was 1.7% (95% CI 0.8 to 3.6) based on data from four RCTs. The comparative observational study reported no cases of cardiac tamponade.

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Persistent AF	3 RCTs (N=73)	Insufficient*	The pooled cardiac tamponade risk following RFA was 5.5% (95% CI 2.1 to 13.7). Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=158)	Insufficient*	Cardiac tamponade occurred in 0% of patients. Definitive conclusions are not possible.*
<b>Pericardial Effusion</b> <sup>†</sup>	All RCTs (regardless of AF type)	5 RCTs (N=772)	Low	Low pericardial effusion risk following RFA (range, 0.5%–0.9%).
	Paroxysmal AF	3 RCTs (N=519)	Low	Low pericardial effusion risk following RFA (pooled risk 0.6% (95% CI 0.2 to 1.8).
	Persistent AF	1 RCT (N=116)	Insufficient*	Low pericardial effusion risk following RFA (0.9%). Definitive conclusions are not possible.*
	Persistent AF: Medicare population	1 comparative observational (N=158)	Insufficient*	Pericardial effusion occurred in 1.9% of patients. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=137)	Low	Low pericardial effusion risk following RFA (0.7%).
<b>Pulmonary Vein Stenosis</b> <sup>†</sup>	Paroxysmal AF	5 RCTs (N=433) 1 comparative observational (N=85)	Low	Low pulmonary vein stenosis risk following RFA from five RCTs with followup ranging from 1–24 months (range, 0%–3.1%). Pooled risk based on two trials with 12-month followup: 1.6% (95% CI 0.4 to 6.3). Pooled risk based on two trials with 24-month followup: 0.7% (95% CI 0.2 to 2.8). No cases reported in the comparative observational study with 12 months followup.
	Persistent AF	2 RCTs (N=137)	Low	Low pulmonary vein stenosis risk following RFA (range, 0%–0.9%). Pooled risk: 0.7% (95% CI 0.1 to 5.0).
	Persistent AF: Medicare population	1 comparative observational (N=158)	Insufficient*	There were no cases of pulmonary vein stenosis. Definitive conclusions are not possible.*
	Mixed	1 RCT (N=137); 1 comparative observational (N=85)	Low	No cases of pulmonary vein stenosis following RFA based on the RCT. In the comparative observational study, stenosis occurred in 7.1% of patients. Definitive conclusions are not possible from this study.*
<b>Drug Intolerance Requiring Discontinuation</b>	Paroxysmal AF	2 RCTs (N=155 medical therapy patients)	Low	Overall, 5% to 23% of patients randomized to medical therapy discontinued anti-arrhythmic drugs due to adverse events or intolerance; by 1 month in one trial, timing not reported in the second trial Due to limited duration and/or usage of medical therapy in the RFA group it is difficult to make comparative conclusions.
	Persistent AF: Medicare population	1 comparative observational (N=412)	Insufficient*	Lower risk of antiarrhythmic drug intolerance requiring discontinuation following RFA (2.6%) versus medical therapy (12.7%) (p=0.0005). Definitive conclusions are not possible.*

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
	Mixed	1 RCT (N=70)	Insufficient*	Low risk of antiarrhythmic drug intolerance requiring discontinuation following RFA and medical therapy (2.9% vs. 0%); timing not reported Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

†Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

**Table 37. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus medical therapy for AF**

Harms/complications*	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality &lt;30 days</b>	1 RCT (N=245)	Insufficient†	The 30-day all-cause mortality risk was 0% in both treatment groups. Definitive conclusions are not possible.†
<b>Stroke &lt;30 days</b>	1 RCT (N=245)	Insufficient†	The 30-day stroke risk was low in both groups: cryoballoon ablation 0.6%; medical therapy 1.2%. Definitive conclusions are not possible.†
<b>AF &lt;3 months</b>	1 RCT (N=163)	Insufficient†	Over half of cryoablation patients experienced AF recurrence within 3 months of treatment (51.5%); data was not reported for the medical therapy group. Definitive conclusions are not possible.†
<b>Cardiac tamponade‡</b>	1 RCT (N=228)	Insufficient†	The incidence of cardiac tamponade following cryoballoon ablation was low (0.9%). Definitive conclusions are not possible.†
<b>Pericardial effusion‡</b>	Not reported	Insufficient	No data available
<b>Pulmonary vein stenosis‡</b>	1 RCT (N=228)	Insufficient†	The incidence of pulmonary vein stenosis following cryoballoon ablation was low (3.1%). Definitive conclusions are not possible.†
<b>Drug intolerance requiring discontinuation</b>	Not reported	Insufficient	No data available

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial.

\*All harms/complications are for the same RCT in a mixed population (no other studies were identified for this comparison).

†Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

‡Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

**Table 38. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus RFA for AF**

Harms/ complications	Population	Number of Studies (N)	Strength of Evidence Grade	Conclusions, Effect Size
<b>Mortality &lt;30 Days</b>	Paroxysmal AF	2 comparative observational (N=4171)	Insufficient*	There were no cases reported in either group during the periprocedural period in two nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>Stroke &lt;30 Days</b>	Paroxysmal AF	1 comparative observational (N=133)	Insufficient*	There were no cases reported in either group in one nonrandomized comparative study. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>AF &lt;3 Months</b>	Paroxysmal AF	1 comparative observational (N=3775)	Insufficient*	One nonrandomized comparative study reported similar AF recurrence rates in both groups during the hospitalization period. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>Cardiac Tamponade<sup>†</sup></b>	Paroxysmal AF	3 comparative observational (N=4304)	Insufficient*	Periprocedural cardiac tamponade rates ranged from 0.7%–2.2% during cryoablation and from 1.1%–1.5% during RFA based on data from three nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF, Mixed	Not reported	Insufficient	No data available
<b>Pericardial Effusion<sup>†</sup></b>	Paroxysmal AF	2 comparative observational (N=529)	Insufficient*	Pericardial effusion occurred in 7.3%–8.7% of cryoablation patients and in 10.0%–13.8% of RFA patients based on data from two nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF	Not reported	Insufficient	No data available
	Mixed	2 comparative observational (N=267)	Insufficient*	Pericardial effusion occurred in 0%–1.1% of cryoablation patients and in 1.6%–3.8% of RFA patients based on data from two nonrandomized comparative studies. Definitive conclusions are not possible.*
<b>Pulmonary Vein Stenosis<sup>†</sup></b>	Paroxysmal AF	2 comparative observational (N=4171)	Insufficient*	There were no cases reported in either group during the periprocedural period in two nonrandomized comparative studies. Definitive conclusions are not possible.*
	Persistent AF	Not reported	Insufficient	No data available
	Mixed	1 comparative observational (N=124)	Insufficient*	There were no cases reported in either group during the periprocedural period in one nonrandomized comparative study. Definitive conclusions are not possible.*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

\*Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

†Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.



## Findings in Relationship to What is Already Known

Findings in this review are generally consistent with prior systematic reviews which included evaluation of catheter ablation versus medical therapy.<sup>22, 24</sup>

This review expands information available from previous reviews in a number of ways. First, more recent publications comparing RFA with medical therapy with information on longer-term outcomes (>12 months) were included as were studies comparing different energy sources. An attempt to specifically identify and summarize studies focused on the Medicare population was made. Based on input from Key Informants during Topic Refinement, analyses were stratified based on AF type (paroxysmal and persistent) when possible, as these are clinically different populations. Analyses to evaluate differential efficacy and harms for use of catheter ablation as a first-line treatment versus a second-line treatment, age, patient characteristics and comorbidities, provider characteristics and other factors were considered; however, data were too sparse to draw conclusions. This report also expands analyses of ablation-specific adverse events and includes a broader spectrum of outcomes such as reablation, echocardiographic parameters and biomarkers.

The two previous reviews yielded similar findings to the current review with respect to the benefit of RFA over medical therapy in improving freedom from recurrence of AF and/or maintenance of sinus rhythm.<sup>22, 24</sup> The current review, however, extends the findings of both reviews report to include longer-term outcome data and a broader spectrum of endpoints, stratifying them by AF type. Similar to this current report, the Washington State Health Technology Assessment (2013)<sup>24</sup> found low frequency of mortality or stroke not attributed to the procedure, with no differences between the ablation and medical therapy groups and there was low quality of evidence that there was no difference between RFA (or cryoablation) and medical therapy for the primary harms of interest. Both previous reports focused on the general population and reported a paucity of data in Medicare populations and for important clinical endpoints such as all-cause mortality, stroke, and heart failure, particularly in the long term.

Comparison of catheter ablation approaches/techniques to each other is an important question of interest to CMS but was beyond the scope of this review. There was substantial heterogeneity across included studies with respect to ablation techniques and sites which precluded their assessment in this review. Previous reviews provide some insight into this question. In the 2013 AHRQ review, information on the following aspects of the procedure was captured: type of ablation catheter used, whether cavo-tricuspid isthmus (CTI) ablation was performed in conjunction with the PVI, whether ablation of complex fractionated atrial electrograms (CFAEs) was done, and whether sites other than CTI and CFAEs were ablated. However, the data could not be pooled due to the insurmountable heterogeneity observed in different aspects of the procedure. RCTs that compared different approaches (i.e., PVI, wide area circumferential ablation [WACA], addition of right or left lines, CFAE) were included in the Washington State HTA.<sup>24</sup> In terms of freedom from recurrence, there was low quality evidence that WACA was favored over PVI, moderate-quality evidence that PVI plus CFE favored PVI alone, and moderate-quality evidence that there was no difference in recurrence following PVI versus PVI plus left lines or plus right lines. The HTA did not compare different ablation techniques.

## Applicability

The applicability of the findings from this review is described below.

## Patients

The bulk of the available trial data are in populations that were predominantly male (59% to 88%) with mean ages ranging from 51 to 64 years and two observational studies provided only limited information in people  $\geq 65$  years of age. Based on information from Key Informants during the topic refinement process, primary clinical decisionmaking regarding use of ablation and ablation approach is based on type and characteristics of AF, presence and type of other cardiac disease, and patient presentation, rather than on any specific age consideration or characteristics specific to the Medicare population. Patients with AF may have had a number of comorbid conditions and other underlying cardiovascular problems. Three RCTs investigated outcomes in populations with comorbidities often seen in conjunction with AF: two were conducted specifically in patients with heart failure (all with persistent AF)<sup>39, 40</sup> and one in patients with type 2 diabetes mellitus.<sup>36</sup> Mean left ventricular ejection fractions across studies that did not focus on heart failure were greater than 50 percent. Comorbidities were variably reported across the other RCTs. Hypertension was the most commonly reported comorbidity, with proportions ranging from 11 to 56 percent across studies. A number of subgroups of potential interest were identified by the Key Informants. However, there were insufficient data from included studies to evaluate the benefits and harms of catheter ablation in any subgroup. The evidence presented in this review may not apply to older people or to those with a greater number of comorbidities or more severe comorbidities (e.g., heart failure).

## Interventions

A wide variety of ablation strategies were used across studies. Based on input from Key Informants there is substantial variability in techniques and approaches used in clinical practice as well. There was noted variability among mapping systems reported within included studies (Appendix, Table H6); as such, analysis was not stratified by mapping technique. Sixteen studies utilized CARTO (Biosense Webster, Diamond Bar, CA, USA, or Tirat-Hacarmel, Israel) either alone or in conjunction with another mapping system. Ensite NAVX (Endocardial Solutions, St. Jude Medical, St. Paul, MN, USA) was the next most popular mapping system, used in eight studies either alone or in conjunction with another mapping system. Technologies also used for mapping in the included literature include Lasso Catheter (Biosense Webster, Inc, Diamond Bar, CA), used in seven studies; Inquiry Optima (St Jude Medical), used in two studies; Supertorque Plus (Cordis Corp, Miami, FL), used in one study; and AcuNav (Siemens Medical Solution, Malvern, PA, USA), used in one study. Heterogeneity across studies with respect to techniques used precluded evaluation or comparison of specific techniques (and such evaluation was beyond the scope of this report).

Findings from one small study comparing cryoballoon ablation to medical therapy may not be applicable to the broader population of AF patients eligible for catheter ablation. This is also true for the studies comparing energy sources.

## Comparators

The primary antiarrhythmic medications used in studies included amiodarone, sotalol, flecainide and propafenone. Amiodarone is the most commonly used antiarrhythmic in clinical practice, but the others are also used. Antiarrhythmic agents used in the included studies were considered to be reflective of clinical practice and applicable to broad clinical populations with AF.

## Outcomes

Findings related to rare outcomes may not be fully applicable to broader clinical populations in part due to small study sizes and inability to fully characterize such outcomes. The nature of the comorbidities and study settings of the study populations may have also influenced findings and may differ from broader clinical populations. “Freedom from recurrence” is a complex concept and there is no clear consensus in the medical community on how best to measure it and no standard of care for monitoring it. Definitions varied across trials with some counting any atrial arrhythmia, whether symptomatic or asymptomatic, as recurrence, while others specified symptomology, duration, and characteristics (Appendix, Table H7). There was noted variability of techniques used for monitoring recurrence within included studies (Appendix, Table H7); as such, analysis was not stratified by recurrence monitoring method. Twenty-eight studies utilized Holter monitoring, with the device being worn anywhere from 24 hours to 7 days in included studies. Sixteen studies utilized conventional ECG, seven studies used transtelephonic monitoring, four studies utilized self-assessment techniques requiring patients to self-report symptoms to the study site, three studies required office visits, two studies utilized event records, and one study used physical exams to monitor AF recurrence. Very rarely were any of these techniques utilized alone; only transtelephonic monitoring and ambulatory holter were used as solo techniques for tracking AF recurrence. The heterogeneity in definition and measurement of recurrence makes it challenging to fully evaluate freedom from recurrence as a benefit of catheter ablation.

## Settings

RCTs were primarily conducted in academically-oriented centers. Input from Key Informants suggested that there is great variability in practice in the clinical community. Findings from studies based in high volume centers with highly experienced providers may not be applicable to smaller centers and/or less experienced providers. Observational studies may be more reflective of the range of experience across settings. Both effectiveness and adverse events may differ by setting; however, there were insufficient data to evaluate this.

## Implications for Clinical and Policy Decisionmaking

RFA is increasingly being used to treat AF. The bulk of the available evidence compares RFA with medical therapy and in patients with paroxysmal AF. Evidence in this report provides insights that may be useful for clinical and policy decisionmaking on use of RFA compared with medical therapy to treat patients with paroxysmal AF and persistent AF as distinct clinical populations and on use of RFA as a first or second-line treatment. Evidence for shorter-term and longer-term efficacy, effectiveness, and safety is also valuable to decisionmaking. For clinical outcomes, there is insufficient evidence for the use of cryoballoon ablation compared with either medical therapy or RFA to support evidence-based decisionmaking in the general population and no evidence for these comparisons in the Medicare population.

## Medicare Population

Neither of the included comparative observational studies provided data for patients with paroxysmal AF for either short- or long-term effectiveness precluding evidence-based conclusions for this AF type in the Medicare population. One study was in patients with persistent AF<sup>48</sup> and the other in patients with various AF types,<sup>53</sup> although approximately 70

percent were classified by the authors as having “nonparoxysmal” without further description. No data on short-term outcomes were available and for all long-term outcomes, evidence was considered insufficient. RFA was used as second-line treatment in both studies, thus no evidence on the benefits or harms of RFA as a first-line therapy in the Medicare population is available to support evidence-based decision making. Conflicting findings across the two studies with regard to long-term mortality and development of CHF may be attributable to difference in comorbidities, study execution, and confounding control. Only the study in those with persistent AF provided data that long-term maintenance of sinus rhythm occurred more frequently following RFA (58%) compared with those remaining on medical therapy (43%).<sup>48</sup> Definitive conclusions regarding effectiveness are not possible based on the evidence available. Similarly, insufficient evidence on harms of RFA compared with medical therapy precludes drawing evidence-based conclusions in the Medicare population.

## General Population

In the general population, evidence on the long-term efficacy of RFA compared with medical therapy for reducing mortality was low for paroxysmal AF. Data on the other primary outcomes of stroke, MI and heart failure are sparse for patients with paroxysmal AF, and no long-term RCT data for any of these outcomes were found for those with persistent AF. Data on quality of life were not conclusive as results could not be pooled from studies due to substantial heterogeneity. In patients with persistent AF and concomitant heart failure, three small studies suggested better HRQOL following RFA compared with medical therapy at 6 months. For intermediate outcomes, moderate strength evidence indicates that for patients with either paroxysmal AF or persistent AF, radiofrequency ablation is effective in the short term ( $\leq 12$  months) for preventing recurrence of atrial arrhythmias compared with medical therapy. While this appears to be sustained over a longer term in patients with paroxysmal AF, there was insufficient evidence for this in patients with persistent AF. Thus, evidence-based decisionmaking regarding the long-term efficacy for those with persistent AF was limited.

Overall, hospitalization was more frequent in patients who received medical therapy versus RFA; however, studies did not provide detail regarding reasons for hospitalization and the extent to which hospitalization for reablation procedures or crossover from medical therapy to ablation were included.

This review found very limited evidence from one study that compared cryoballoon ablation with medical therapy and included patients with different AF types. Two small RCTs comparing cryoballoon ablation with RFA provided no data on primary outcomes of interest and neither reported on adverse events. Freedom from recurrence was less common following cryoballoon ablation and reablation was more common, but sample sizes may have precluded observation of statistical differences between treatments. There is limited evidence comparing cryoballoon ablation with other treatment options (including RFA) to inform policy or decisionmaking regarding the balance of benefits and risks based on current evidence.

In general, guidelines and consensus statements from professional societies such as the American College of Cardiology, American Heart Association, and Heart Rhythm Society recommend catheter ablation for symptomatic AF that is refractory or intolerant to antiarrhythmic medication(s); however, the specifics and strength of the recommendations vary by guideline.<sup>17, 18, 90, 91 92</sup> Current ACC/AHA/HRS guidelines recommend that AF catheter ablation: is useful for symptomatic paroxysmal AF refractory or intolerant to at least one antiarrhythmic medication (Class I); is reasonable for some patients with symptomatic persistent

AF refractory or intolerant to at least one antiarrhythmic medication (Class IIa); is reasonable as an initial rhythm-control strategy before drug therapy in patients with recurrent symptomatic paroxysmal AF (Class IIa); may be considered for symptomatic long-standing persistent AF refractory or intolerant to at least one antiarrhythmic medication (Class IIb); and may be considered in patients with symptomatic persistent AF (Class IIb). They further recommend that AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy with the sole intent of obviating the need for anticoagulation (Class III).<sup>93</sup> Evidence in our report suggested that effect sizes for freedom from recurrence are not different when RFA is used as a first-line treatment or as a second-line treatment, however, there is insufficient evidence to draw conclusions regarding how RFA as a first-line treatment versus a second-line treatment may influence a broader range of outcomes or for the long term, and no evidence on this in the Medicare population.

## **Limitations of the Review Process**

The findings presented have limitations related to the approach and scope of this review. First, comparative evaluation of ablation techniques and approaches was beyond the scope of this review. There was substantial heterogeneity across included studies with regard to techniques and approaches that precluded comparative evaluation of studies. Though evaluation of mapping modalities and strategies was also beyond the scope of this review, we found insufficient information from included studies to assess mapping.

Stratification by AF type was felt to be clinically important and stratification to assess data at followup at >12 months was important to answering Key Questions. This resulted in fewer studies available for pooling within followup strata. Profile likelihood methods were used to provide more conservative estimates and confidence intervals given the small number of studies. This, combined with sparse data for many outcomes, may have limited the ability to explore statistical heterogeneity and precluded ability for further subgroup analyses.

Non-English studies were excluded and searches for studies published only as abstracts were not conducted. Formal assessment of publication bias was not conducted as there were fewer than 10 studies available for outcomes based on AF type, and research indicates that such methods can be misleading with smaller numbers of studies.<sup>94</sup>

Every attempt was made to assure that variables and outcomes were assessed and abstracted accurately; however, wide variability across studies (in the quality of reporting of study methods, in how outcomes were defined, and in which patients were included) has the potential for introducing inaccuracies.

## **Limitations of the Evidence Base**

Important limitations of the evidence base include the sample size of the available trials, limited data available on primary clinical outcomes particularly at followup times >12 months, and the substantial crossover from medical therapy to catheter ablation in most trials. These factors make it difficult to draw strong conclusions regarding the effects and benefits of catheter ablation. Only one RCT comparing cryoballoon ablation with medical therapy was identified and two small trials comparing cryoballoon ablation with RFA were identified but didn't provide data on primary outcomes of interest. This precludes drawing conclusions regarding the comparative effectiveness of various energy sources.

The evidence base was constrained by the methodological limitations of the included studies. Common methodological shortcomings included unclear allocation concealment (only one trial

documented concealed allocation) and lack of assessor blinding for primary outcomes. Four studies did not report information on random sequence generation.<sup>38, 41, 44, 83</sup>

Although not a factor for determination of individual study quality or overall strength of evidence, the high frequency of crossover from medical therapy to ablation in most included studies may hinder drawing definitive conclusions regarding the full benefits and harms of catheter ablation compared with medical therapy.

Study sizes were likely insufficient to effectively determine risk of the primary clinical outcomes (e.g., mortality,) for either group or to detect statistical differences between treatment groups. Two recent large observational studies that reported on the primary outcomes of interest in this report were identified but were excluded as there was insufficient information on use of AADs (the focus of this review) versus rate control medications or no treatment in the control groups.<sup>95, 96</sup> Both studies suggest that risk of stroke was significantly lower in patients receiving catheter ablation for AF compared with those who did not receive ablation in followup to 3.5 years. One study, based on administrative data from a large regional registry stratified stroke risk by CHADS2 score and age reported that reduced stroke risk was present in all age groups and across all CHADS2 risk profiles.<sup>95</sup> The other study based on Taiwan's National Health Insurance claims database, reported that there was no association between RFA and lower mortality or hospitalization for heart failure.<sup>96</sup> Although both studies attempted to control for confounding, the possibility of residual confounding from unmeasured factors should be considered as should the limitations of administrative data (such as misclassification) when interpreting these findings.<sup>97</sup> Findings should be confirmed in additional high-quality studies that provide specifics regarding treatments received.

A variety of HRQOL measures were used at varied time frames across trials; this, along with small sample sizes, limited the ability to pool data or draw firm conclusions regarding the impact of catheter ablation on HRQOL, as discussed previously.

For the freedom from recurrence outcome, the definitions used by each study were accepted. This outcome was variably defined across studies, with variations in the type of arrhythmia (i.e., AF, AF or atrial flutter, or any atrial arrhythmia) and whether study reports were limited to symptomatic or asymptomatic AF or not. Maintenance of sinus rhythm appeared to be used interchangeably with freedom from recurrence in many studies, although these two outcomes are not the same.

Most studies focused on the intermediate outcome related to freedom from recurrence. This was variably defined and adjudicated across studies; there was heterogeneity across studies regarding whether recurrence included any atrial arrhythmia or AF only, whether symptomatic and asymptomatic recurrences were included, and whether characteristics related to duration were considered. In addition, blanking periods ranged from 1 to 3 months across 11 RCTs. This variability in study protocols likely introduces variation in the cross-study calculations of the proportion of those free from AF after the blanking period.

There is less evidence on the effectiveness of catheter ablation in patients with persistent AF and limited evidence on use of catheter ablation as a first-line treatment, limiting the conclusions that can be drawn in these instances. No data were available to assess the differential efficacy and harms of catheter ablation by patient or provider characteristics.

## Research Gaps

Gaps in evidence were identified for each Key Question.

### Key Question 1: RFA or cryoablation versus medical therapy and comparison of cryoablation versus RFA

- There were limited data on the impact of RFA compared with medical therapy on final clinical outcomes such as mortality, particularly in the long term. Long-term data are particularly sparse those with persistent AF.
- Data were sparse for the comparison of cryoballoon ablation versus medical therapy and for the comparison of cryoballoon ablation with RFA for all clinically-relevant outcomes.
- No data from high-quality comparative studies on Medicare-relevant populations were identified.
- Across studies, there was lack of a standardized, consistent method of measuring, monitoring and reporting “freedom from recurrence” or maintenance is sinus rhythm.
- Conclusions related to HRQOL and symptom relief were not possible from the included studies due the variety of HRQOL measures reported across different time frames and inconsistency in statistical significance.
- Ideally future studies would conceptualize strategies for treatment of AF, such as catheter ablation and medical therapy, and evaluate the impact of such strategies on hard clinical outcome such as death and stroke.

### Key Question 2: Harms

- Comparative data on rare harms were limited by study sample sizes and/or study quality particularly in those with persistent AF. This was true for the comparisons of RFA versus medical therapy as well as for the comparisons of cryoballoon ablation with medical therapy or RFA.

### Key Question 3: Differential efficacy, effectiveness, harms

- Available RCTs did not have sufficient power to evaluate differential efficacy or harm of catheter ablation (RFA or cryoballoon ablation) versus medical therapy or for comparison of cryoballoon ablation with RFA for specific patient subgroups or provider settings. No conclusions regarding which patients may benefit most are possible or regarding which patients may not benefit from catheter ablation are possible with current evidence.
- Limited data on use of RFA as the first treatment of choice (first-line therapy) versus a second-line therapy following failure of antiarrhythmic medications were available. No data for cryoballoon ablation were available to evaluate its use as first versus second-line therapy.

Some of these gaps may be addressed via the CABANA Trial, (<https://www.cabanatrial.org/>), which is scheduled for completion in March 2018. This RCT conceptualizes ablation and medical therapy as strategies for treatment of AF and compares first-line ablation with pharmacologic therapy for reducing the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest in patients with atrial fibrillation. The target sample size is 2200 and current enrollment is about 1650 patients across 126 study sites in 10 countries. The trial will likely have good representation of Medicare patients, as to be eligible for the trial, patients must be either 65 years of age or older or have at least one risk factor for stroke. In addition, inclusion of patients with specific risk factors for stroke (e.g. hypertension, diabetes) may facilitate better understanding of the impact of catheter ablation in subpopulations with specific risk factors. One potential limitation of the trial include the use of a composite outcome,

which may preclude adequate characterization and representation of important individual outcomes. This may limit conclusions which can be drawn regarding the efficacy of catheter ablation versus medical therapy to affect clinical outcomes such as mortality, stroke, and development of CHF if there is insufficient power to evaluate these as separate outcomes although such outcomes are listed as s intermediate outcomes for this study. Another limitation is its span over a very long period of time (started in 2009) during which technology is evolving quickly. Thus, equipment and techniques that were used earlier in the trial may not be relevant to clinical practice when the trial ends. . It is not clear if there will be sufficient data to evaluate efficacy separately by AF type or to compare ablation techniques. The planned followup of approximately 5 years will provide additional evidence on the longer-term impact of catheter ablation on clinical outcomes. Results from CABANA will enhance the current evidence base and provide much needed information on efficacy and safety particularly in those >65 years of age. In addition to CABANA, several other trials are currently evaluating aspects of catheter ablation for the treatment of AF, including a total of 14 relevant ongoing clinical trials were identified using the United States National Institute of Health clinical registry ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) (Appendix, Table H8). There are three current ongoing trials comparing cryoablation to radiofrequency ablation which are estimated to be completed between June 2015 and January 2017. One study will examine the efficacies of two cryoablation procedures, standard and short, in comparison to radiofrequency ablation (NCT01913522). One study will utilize RFA in both treatment groups (NCT01521988). There are two current ongoing trials comparing cryoablation to medical therapy. Both trials are for first line treatments and are expected to be completed between January 2016 and June 2017. Patients in both trials have paroxysmal AF. Six trials comparing radiofrequency ablation to medical therapy are currently ongoing. The trials are expected to be completed between May 2015 and August 2019. All but one study includes a special patient population (NCT01341353). In one trial, the medical therapy group undergoes EEC in addition to antiarrhythmic drug treatment (NCT01850277). In this same study, the medical treatment group has the option to undergo ablation. Only one study is non-randomized (NCT01341353). Two studies appear to compare medical therapy to either cryoablation or radiofrequency ablation. The trials are expected to be completed between March and June of 2018. One study includes a special patient population that is over the age of 60 years old and has paroxysmal AF (NCT01570361). The second study includes a mixed AF patient population (NCT00911508). In addition to the evidence the CABANA trial and other currently open trials may yield, there is a need to evaluate effectiveness across clinical settings and provider skill levels outside of randomized trials. There are several key elements that might augment the productivity of future research. For example, high-quality clinical registries, designed *a priori* to address specific clinical questions, could provide an important source for addressing some research gaps. Such registries could be designed to extend the observations from randomized trials; this approach might differ from currently available study results by allowing for evaluation of the durability of the effects seen with longer followup, including a larger sample size to examine rare events, and including a broader range of patients to facilitate evaluation of how well patient groups are represented in clinical trials. Specific components that could be considered for capture include: more detailed information on patient and provider characteristics; AF details (duration, prior treatments, and episode severity); procedural details (e.g., mapping, catheter use, and technique/approach); management of patients before, during, and after procedure; and acute procedural outcomes as well as longer-term outcomes and complications. Such a registry could be used to address important issues such as how outcomes



in clinical practice compare with outcomes observed in clinical trials and how outcomes are associated with characteristics of patients and providers. Registries could help determine performance measures and assist with quality improvement, post-marketing safety public reporting as well. There are, however, a number of limitations and factors to consider for registries. One challenge of creating and maintaining a registry is that research questions may change after data collection begins which may shift the importance of some of the elements collected. Other challenges include potential difficulty in balancing the burden of high-quality data collection with acceptable registry size. Additionally, registries designed to test specific medical devices face practical problems including variability in insurance coverage for specific devices, influence of operator characteristics while using the same device, and difficulty in differentially identifying unique devices in use.<sup>98</sup>

Registry studies would not replace the need for high-quality comparative studies. Pragmatic trials and comparative observational studies that are designed to reduce bias may facilitate evaluation of effectiveness and safety in the “real world” and over the long term in particular. Such studies could provide a foundation for registry development. Methodologically rigorous prospective cohort studies comparing treatments based on standardized protocols can potentially provide high-quality data. Such studies might be complemented with data from registries.

There may be some value in performing meta-analysis on individual patient data from relevant clinical trials to more effectively stratify outcomes by patient characteristics, comorbidities, and factors such as use of catheter ablation as an initial first-line treatment versus a second-line treatment. The small sample sizes of individual trials may, however, limit such exploration.

In order to evaluate the extent to which there is differential efficacy or harm for specific subpopulations, clinical trials need to have sufficient statistical power to stratify by important groups and to test for statistical interaction. Future studies, regardless of design, would benefit from the use of standardized definitions and methods of measuring salient outcomes (e.g., freedom from recurrence) and detailed reporting of co-interventions that may influence outcomes (e.g., use of antiarrhythmic medications in ablation groups and use of anticoagulation).

The technology and strategies related to catheter ablation (and mapping) continues to evolve. Information on newer technologies including phased radiofrequency ablation (phased RFA), laser balloon ablation, contact force-guided radiofrequency (CF-guided RFA), and mesh ablation is emerging in the peer-reviewed literature. Present literature indicates they may be effective alternatives to currently available technologies; however additional evidence is needed to verify early findings.<sup>88, 89, 99-102</sup>

Future systematic reviews will need to include technologies as they are approved and become widely available as well as updated studies of newer technologies such as cryoballoon ablation that are already approved but have a limited evidence base. Given the rapid evolution of catheter ablation, it will be important to update reviews such as this in the near future.

## Conclusions

Evidence was insufficient to draw conclusions on the efficacy, effectiveness, and harms of catheter ablation for atrial fibrillation (AF) specific to the Medicare population. In the general population, conclusions regarding the long-term efficacy of catheter ablation to impact primary clinical outcomes are limited; in those with paroxysmal AF, strength of evidence was low that there is no difference between radiofrequency ablation (RFA) and medical therapy in all-cause-mortality. Low strength of evidence means that there is limited confidence that the effect estimate is close to the true effect. Evidence from RCTs was insufficient for no differences in stroke, myocardial infarction (MI) and chronic heart failure (CHF) after 12 months. Although observational studies may suggest lower stroke and heart failure risk following RFA versus medical therapy, the evidence was insufficient. In the short term, strength of evidence was low that there were no differences between treatments for all-cause mortality and MI and insufficient for stroke and CHF, regardless of AF type. No overall conclusions can be drawn regarding the impact of RFA on health-related quality of life across studies. In patients with heart failure and persistent AF, low strength of evidence suggests quality of life may be improved following RFA up to 6 months. No long-term randomized controlled trial (RCT) data in those with persistent AF for the primary outcomes of mortality, stroke, MI, or development of CHF were identified. For intermediate outcomes, moderate strength of evidence indicates that RFA is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in the short term in those with paroxysmal AF and appears to be sustained for the longer term. Strength of evidence was low for freedom from recurrence in those with persistent AF in the short term and insufficient in the longer term. Regarding harms, there was low strength of evidence for no difference between RFA and medical therapy in 30-day mortality or 30-day stroke. There was low strength of evidence that there was no difference between RFA and medical therapy in 3-month risk of AF in paroxysmal AF patients, but data from two trials of persistent AF patients suggested significantly lower risk of 2- to 3-month AF recurrence following RFA versus medical therapy (low strength of evidence). Risk estimates for cardiac tamponade following RFA were imprecise; the strength of evidence was low regardless of AF type. There is insufficient evidence comparing cryoballoon ablation with medical therapy for outcomes other than freedom from protocol defined treatment failure which favored cryoballoon ablation. There is insufficient evidence comparing cryoballoon ablation versus RFA to draw conclusions regarding efficacy or safety. In order to better understand the impact that catheter ablation has on key health outcomes such as stroke, mortality, quality of life, and symptom improvement in comparison to other AF treatment strategies, additional large methodologically sound studies are needed. Such studies are particularly needed on persistent AF patients, as well as on those in the Medicare population. Furthermore, studies with sufficient sample sizes are needed in order to effectively determine whether catheter ablation versus other treatment options will benefit certain patient subgroups more than others, including those for whom catheter ablation might best used as a first-line versus second-line treatment strategy.

In summary, there was insufficient evidence to draw conclusions regarding the efficacy, effectiveness and safety of catheter ablation in the Medicare population. In the general population, there is moderate evidence that RFA is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in both the short and long term regardless of AF type, but reablation is common. RFA does not appear to impact all-cause mortality in the short or long term in those with paroxysmal AF (low strength of evidence); however, there is insufficient evidence to draw conclusions regarding other primary clinical outcomes in the short

or long term. Firm conclusions regarding health-related quality of life are not possible given heterogeneity across studies for instruments employed, measurement timing and clinical characteristics. For harms, no differences between RFA and medical therapy in 30-day mortality, stroke, or three-month risk of AF were seen, with low strength of evidence. Evidence comparing cryoballoon ablation with medical therapy or with RFA was insufficient to draw conclusions regarding efficacy or safety, with the exception of low strength of evidence for greater freedom from protocol-defined failure following cryoballoon ablation versus medical therapy. To better understand the impact of catheter ablation on key outcomes (stroke, mortality, quality of life, and symptom improvement) compared to other treatment strategies, large methodologically sound studies are needed. Studies with sufficient sample sizes are needed to effectively determine whether catheter ablation versus other treatments will benefit certain patient subgroups more than others, and whether there are subgroups in which catheter ablation might best used as a first- versus second-line treatment.

## Abbreviations and Acronyms

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AF-QOL	Atrial Fibrillation Quality of Life Questionnaire
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
BNP	Brain natriuretic peptide
CER	Comparative effectiveness review
CFAE	Complex fractionated atrial electrogram
CHADS2	Cardiac failure, Hypertension, Age, Diabetes, Stroke system 2
CHF	Congestive heart failure
CI	Confidence interval
CMR	Cardiovascular magnetic resonance
CMS	Centers for Medicare and Medicaid
COI	Conflict of interest
COPD	Chronic obstructive pulmonary disease
EPC	Evidence-based Practice Center
EQ-5D	European Quality of Life Five Dimensions questionnaire
FDA	Food and Drug Administration
F/U	Followup
HR	Hazard ratio
HRQOL	Health-related Quality of Life
IQR	Interquartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
KQ	Key Question
LA	Left atrial
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCS	Mental Component Score of the SF-36
METS	Metabolic equivalents
MI	Myocardial infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NA	Not applicable
NR	Not reported
NS	Not statistically significant
PCS	Physical Component Score of the SF-36
PICOTS	Populations, interventions, comparators, outcomes, timing, settings
PVI	Pulmonary vein isolation
QOL	Quality of life
RCT	Randomized controlled trial
RF	Radiofrequency
RFA	Radiofrequency ablation
RNVG	Radionuclide ventriculography
RR	Relative risk

SAS	Zung Self-Rating Anxiety Scale
SD	Standard deviation
SDS	Zung Self-Rating Depression Scale
SF-36	Short Form 36 questionnaire
TEP	Technical Expert Panel
TIA	Transient ischemic attack
TR	Topic refinement
VO <sub>2</sub>	Volume of oxygen

## References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001 May 9;285(18):2370-5. PMID: 11343485.
2. Magnani JW, Rienstra M, Lin H, et al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. *Circulation*. 2011 Nov 1;124(18):1982-93. PMID: 22042927.
3. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *The Medical clinics of North America*. 2008 Jan;92(1):17-40, ix. PMID: 18060995.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014 Dec 2;64(21):2246-80. PMID: 24685668.
5. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *American Journal of Cardiology*. 1994 Aug 1;74(3):236-41. PMID: 8037127.
6. Schotten U, Verheule S, Kirchhof P, et al. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiological reviews*. 2011 Jan;91(1):265-325. PMID: 21248168.
7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991 Aug;22(8):983-8. PMID: 1866765.
8. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996 Oct;27(10):1760-4. PMID: 8841325.
9. Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *American Journal of Medicine*. 1995 May;98(5):476-84. PMID: 7733127.
10. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003 Jul 5;362(9377):7-13. PMID: 12853193.
11. Maggioni AP, Latini R, Carson PE, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). *American Heart Journal*. 2005 Mar;149(3):548-57. PMID: 15864246.
12. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003 Jun 17;107(23):2920-5. PMID: 12771006.
13. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *Journal of the American College of Cardiology*. 2006 Aug 15;48(4):721-30. PMID: 16904540.
14. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *Journal of the American College of Cardiology*. 2000 Oct;36(4):1303-9. PMID: 11028487.

15. Chung MK, Shemanski L, Sherman DG, et al. Functional status in rate- versus rhythm-control strategies for atrial fibrillation: results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Functional Status Substudy. *Journal of the American College of Cardiology*. 2005 Nov 15;46(10):1891-9. PMID: 16286177.
16. Hagens VE, Ranchor AV, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *Journal of the American College of Cardiology*. 2004 Jan 21;43(2):241-7. PMID: 14736444.
17. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011 Mar 15;123(10):e269-367. PMID: 21382897.
18. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS 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: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm*. 2012 Apr;9(4):632-96 e21. PMID: 22386883.
19. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace*. 2006 Sep;8(9):651-745. PMID: 16987906.
20. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011 Jan 4;123(1):104-23. PMID: 21173346.

21. Ip S, Terasawa T, Balk EM, et al. Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation. AHRQ Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009.
22. Al-Khatib SM, Allen Lapointe N, Chatterjee R, et al. Treatment of Atrial Fibrillation. AHRQ Comparative Effectiveness Reviews, No. 119. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
23. Chen HS, Wen JM, Wu SN, et al. Catheter ablation for paroxysmal and persistent atrial fibrillation. *Cochrane Database Syst Rev*. 2012;4:CD007101. PMID: 22513945.
24. Hashimoto RE, Raich AL, Junge M, et al. Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation. Olympia, WA: Washington State Health Care Authority, Health Technology Assessment Program. [www.hta.hca.wa.gov/svta.html](http://www.hta.hca.wa.gov/svta.html): 2103.
25. Ellis ER, Culler SD, Simon AW, et al. Trends in utilization and complications of catheter ablation for atrial fibrillation in Medicare beneficiaries. *Heart Rhythm*. 2009 Sep;6(9):1267-73. PMID: 19716081.
26. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010 Feb;3(1):32-8. PMID: 19995881.
27. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England)*. 2010;8(5):336-41. PMID: 20171303.
28. Agency for Healthcare Research and Quality. Methods guide for Effectiveness and Comparative Effectiveness Reviews. . AHRQ Publication No. 10(14)-EHC063-EF. Rockville MD: Agency for Healthcare Research and Quality; January 2014. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov). Accessed July 30, 2014.
29. Higgins JPT GS, ed *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. ed; 2011.
30. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. *J Clin Epidemiol*. 2010 May;63(5):513-23. PMID: 19595577.
31. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. *Statistics in medicine*. 1996 Mar 30;15(6):619-29. PMID: 8731004.
32. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed.)*. 2003 Sep 6;327(7414):557-60. PMID: 12958120.
33. Fu R, Vandermeer BW, Shamliyan TA, et al. AHRQ Methods for Effective Health Care Handling Continuous Outcomes in Quantitative Synthesis. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
34. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. PMID: 21463926.
35. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012 Oct 25;367(17):1587-95. PMID: 23094720.



36. Forleo GB, Mantica M, De Luca L, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *Journal of Cardiovascular Electrophysiology*. 2009 Jan;20(1):22-8. PMID: 18775050.
37. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol*. 2014 Feb;7(1):31-8. PMID: 24382410.
38. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study.[Erratum appears in *Circulation*. 2009 Sep 8;120(10):e83]. *Circulation*. 2008 Dec 9;118(24):2498-505. PMID: 19029470.
39. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *Journal of the American College of Cardiology*. 2013;61(18):1894-903. PMID: CN-00907192 NEW.
40. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart*. 2011 May;97(9):740-7. PMID: 21051458.
41. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *European heart journal*. 2013 Oct 17; PMID: 24135832.
42. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA*. 2014 Feb 19;311(7):692-700. PMID: 24549549.
43. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006 Mar 2;354(9):934-41. PMID: 16510747.
44. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *Journal of the American College of Cardiology*. 2006 Dec 5;48(11):2340-7. PMID: 17161267.
45. Stabile G, Bertaglia E, Senatore G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *European heart journal*. 2006 Jan;27(2):216-21. PMID: 16214831.
46. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA*. 2005 Jun 1;293(21):2634-40. PMID: 15928285.
47. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010 Jan 27;303(4):333-40. PMID: 20103757.
48. Blandino A, Toso E, Scaglione M, et al. Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation. *Journal of Cardiovascular Electrophysiology*. 2013 Jul;24(7):731-8. PMID: 23551460.
49. Lan X, Su L, Ling Z, et al. Catheter ablation vs. amiodarone plus losartan for prevention of atrial fibrillation recurrence in patients with paroxysmal atrial fibrillation. *Eur J Clin Invest*. 2009 Aug;39(8):657-63. PMID: 19490069.

50. Reynolds MR, Gunnarsson CL, Hunter TD, et al. Health outcomes with catheter ablation or antiarrhythmic drug therapy in atrial fibrillation: results of a propensity-matched analysis. *Circ Cardiovasc Qual Outcomes*. 2012 Mar 1;5(2):171-81. PMID: 22373904.
51. Rossillo A, Bonso A, Themistoclakis S, et al. Role of anticoagulation therapy after pulmonary vein antrum isolation for atrial fibrillation treatment. *J Cardiovasc Med (Hagerstown)*. 2008 Jan;9(1):51-5. PMID: 18268419.
52. Sang C-H, Chen K, Pang X-F, et al. Depression, anxiety, and quality of life after catheter ablation in patients with paroxysmal atrial fibrillation. *Clin Cardiol*. 2013 Jan;36(1):40-5. PMID: 22777577.
53. Sonne K, Patel D, Mohanty P, et al. Pulmonary vein antrum isolation, atrioventricular junction ablation, and antiarrhythmic drugs combined with direct current cardioversion: survival rates at 7 years follow-up. *J Interv Card Electrophysiol*. 2009 Nov;26(2):121-6. PMID: 19789970.
54. Yu S, Zhao Q, Wu P, et al. Effect of anxiety and depression on the recurrence of paroxysmal atrial fibrillation after circumferential pulmonary vein ablation. *Journal of Cardiovascular Electrophysiology*. 2012 Nov;23 Suppl 1:S17-23. PMID: 22998234.
55. Bertaglia E, Zoppo F, Tondo C, et al. Early complications of pulmonary vein catheter ablation for atrial fibrillation: a multicenter prospective registry on procedural safety. *Heart Rhythm*. 2007 Oct;4(10):1265-71. PMID: 17905330.
56. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *Journal of Cardiovascular Electrophysiology*. 2011 Aug;22(8):839-45. PMID: 21410581.
57. Dages N, Hindricks G, Kottkamp H, et al. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: still cause for concern? *Journal of Cardiovascular Electrophysiology*. 2009 Sep;20(9):1014-9. PMID: 19490383.
58. Gibson DN, Di Biase L, Mohanty P, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors.[Erratum appears in *Heart Rhythm*. 2011 Nov;8(11):1828]. *Heart Rhythm*. 2011 Sep;8(9):1364-71. PMID: 21354332.
59. Hoyt H, Bhonsale A, Chilukuri K, et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. *Heart Rhythm*. 2011 Dec;8(12):1869-74. PMID: 21798230.
60. Hunter RJ, McCready J, Diab I, et al. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. *Heart*. 2012 Jan;98(1):48-53. PMID: 21930724.
61. Shah RU, Freeman JV, Shilane D, et al. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol*. 2012 Jan 10;59(2):143-9. PMID: 22222078.
62. Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation*. 2013;128(19):2104-12.
63. Sacher F, Monahan KH, Thomas SP, et al. Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. *J Am Coll Cardiol*. 2006 Jun 20;47(12):2498-503. PMID: 16781380.
64. Baman TS, Jongnarangsin K, Chugh A, et al. Prevalence and predictors of complications of radiofrequency catheter ablation for atrial fibrillation. *Journal of Cardiovascular Electrophysiology*. 2011;22(6):626-31.

65. Piccini JP, Sinner MF, Greiner MA, et al. Outcomes of Medicare beneficiaries undergoing catheter ablation for atrial fibrillation. *Circulation*. 2012 Oct 30;126(18):2200-7. PMID: 23019293.
66. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *International Journal of Cardiology*. 2013 Sep 1;167(5):1984-9.
67. Hao SC, Hunter TD, Gunnarsson C, et al. Acute safety outcomes in younger and older patients with atrial fibrillation treated with catheter ablation. *J Interv Card Electrophysiol*. 2012 Nov;35(2):173-82. PMID: 22714547.
68. Kosiuk J, Kornej J, Bollmann A, et al. Early cerebral thromboembolic complications after radiofrequency catheter ablation of atrial fibrillation: Incidence, characteristics, and risk factors. *Heart Rhythm*. 2014 Nov;11(11):1934-40. PMID: 25086257.
69. Michowitz Y, Rahkovich M, Oral H, et al. Effects of sex on the incidence of cardiac tamponade after catheter ablation of atrial fibrillation: results from a worldwide survey in 34 943 atrial fibrillation ablation procedures. *Circ Arrhythm Electrophysiol*. 2014 Apr;7(2):274-80. PMID: 24519888.
70. Srivatsa UN, Danielsen B, Anderson I, et al. Risk predictors of stroke and mortality after ablation for atrial fibrillation: The California experience 2005-2009. *Heart Rhythm*. 2014 Nov;11(11):1898-903. PMID: 25048442.
71. Zado E, Callans DJ, Riley M, et al. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. *J Cardiovasc Electrophysiol*. 2008 Jun;19(6):621-6. PMID: 18462325.
72. Packer DL, Irwin JM, Champagne J. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front STOP-AF pivotal trial. *J Am Coll Cardiol*. 2010;55:E3015-6.
73. Andrade JG, Khairy P, Macle L, et al. Incidence and significance of early recurrences of atrial fibrillation after cryoballoon ablation: insights from the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) Trial. *Circ Arrhythm Electrophysiol*. 2014 Feb;7(1):69-75. PMID: 24446022.
74. Herrera Siklody C, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. *Journal of the American College of Cardiology*. 2011 Aug 9;58(7):681-8. PMID: 21664090.
75. Perez-Castellano N, Fernandez-Cavazos R, Moreno J, et al. The COR trial: a randomized study with continuous rhythm monitoring to compare the efficacy of cryoenergy and radiofrequency for pulmonary vein isolation. *Heart Rhythm*. 2014 Jan;11(1):8-14. PMID: 24103221.
76. Chierchia GB, Capulzini L, Droogmans S, et al. Pericardial effusion in atrial fibrillation ablation: a comparison between cryoballoon and radiofrequency pulmonary vein isolation. *Europace*. 2010 Mar;12(3):337-41. PMID: 20056597.
77. Knecht S, Sticherling C, von Felten S, et al. Long-term comparison of cryoballoon and radiofrequency ablation of paroxysmal atrial fibrillation: a propensity score matched analysis. *Int J Cardiol*. 2014 Oct 20;176(3):645-50. PMID: 25149399.
78. Kojodjojo P, O'Neill MD, Lim PB, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. *Heart*. 2010 Sep;96(17):1379-84. PMID: 20801856.
79. Mandell J, Amico F, Parekh S, et al. Early experience with the cryoablation balloon procedure for the treatment of atrial fibrillation by an experienced radiofrequency catheter ablation center. *J Invasive Cardiol*. 2013 Jun;25(6):288-92. PMID: 23735354.

80. Mugnai G, Chierchia GB, de Asmundis C, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *The American journal of cardiology*. 2014 May 1;113(9):1509-13. PMID: 24630388.
81. Schmidt M, Dorwarth U, Andresen D, et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol*. 2014 Jan;25(1):1-7. PMID: 24134539.
82. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009 Oct;62(10):e1-34. PMID: 19631507.
83. Pappone C, Vicedomini G, Augello G, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. *Circ*. 2011 Dec;4(6):808-14. PMID: 21946315.
84. Reynolds MR, Walczak J, White SA, et al. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes*. 2010 Nov;3(6):615-23. PMID: 20940250.
85. Wynn GJ, Das M, Bonnett LJ, et al. Quality-of-life benefits of catheter ablation of persistent atrial fibrillation: a reanalysis of data from the SARA study. *Europace*. 2014 Jul 15; PMID: 25028177.
86. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *Journal of the American College of Cardiology*. 2013 Apr 23;61(16):1713-23. PMID: 23500312.
87. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *The New England journal of medicine*. 2005 Oct 6;353(14):1471-80. PMID: 16207849.
88. Koch L, Haeusler KG, Herm J, et al. Mesh ablator vs. cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation: results of the MACPAF study. *Europace*. 2012 Oct;14(10):1441-9. PMID: 22523379.
89. Malmborg H, Christersson C, Lonnerholm S, et al. Comparison of effects on coagulation and inflammatory markers using a duty-cycled bipolar and unipolar radiofrequency pulmonary vein ablation catheter vs. a cryoballoon catheter for pulmonary vein isolation. *Europace*. 2013 Jun;15(6):798-804. PMID: 23362019.
90. Bertaglia E, Fassini G, Anselmino M, et al. Comparison of ThermoCool Surround Flow catheter versus ThermoCool catheter in achieving persistent electrical isolation of pulmonary veins: a pilot study. *Journal of Cardiovascular Electrophysiology*. 2013 Mar;24(3):269-73. PMID: 23210452.
91. Verma A, Macle L, Cox J, et al. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: catheter ablation for atrial fibrillation/atrial flutter. *Can J Cardiol*. 2011 Jan-Feb;27(1):60-6. PMID: 21329863.
92. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. *European heart journal*. 2010;31.
93. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014 Mar 28; PMID: 24685669.
94. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical research ed.)*. 2011;343:d4002. PMID: 21784880.
95. Bunch TJ, May HT, Bair TL, et al. Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. *Heart Rhythm*. 2013 Sep;10(9):1272-7. PMID: 23835257.

96. Chang CH, Lin JW, Chiu FC, et al. Effect of radiofrequency catheter ablation for atrial fibrillation on morbidity and mortality: a nationwide cohort study and propensity score analysis. *Circ*. 2014 Feb;7(1):76-82.
97. Hashimoto RE, Brodt ED, Skelly AC, et al. Administrative database studies: goldmine or goose chase? *Evidence-based spine-care journal*. 2014 Oct;5(2):74-6. PMID: 25278880.
98. AHRQ Methods for Effective Health Care. In: Gliklich RE, Dreyer NA, Leavy MB, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
99. Malmborg H, Lonnerholm S, Blomstrom P, et al. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. *Europace*. 2013 Nov;15(11):1567-73. PMID: 23703361.
100. Hummel J, Michaud G, Hoyt R, et al. Phased RF ablation in persistent atrial fibrillation. *Heart Rhythm*. 2014 Feb;11(2):202-9. PMID: 24239841.
101. Bordignon S, Chun KR, Gunawardene M, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. *Journal of Cardiovascular Electrophysiology*. 2013 Sep;24(9):987-94.
102. Jourda F, Providencia R, Marijon E, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. *Europace*. 2014 Sep 3. PMID: 25186456.