Effective Health Care Program

Comparative Effectiveness Review
Number 119

Treatment of Atrial Fibrillation

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Comparative Effectiveness Review

Number 119

Treatment of Atrial Fibrillation

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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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 Informants' 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.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Treatment of Atrial Fibrillation

Structured Abstract

Objectives. There are two generally accepted strategies for managing atrial fibrillation (AF): rate control and rhythm control. However, within each strategic approach there are a large number of potential pharmacological and nonpharmacological therapies, and the comparative safety and effectiveness of these therapies—both within and between strategies—are uncertain.

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language comparative studies.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted data, rated quality and applicability, and graded evidence. When possible, random-effects models were used to compute summary estimates of effects.

Results. Our review included 182 articles (148 unique studies): 14 studies relevant to rate-control drugs, 3 relevant to strict versus lenient rate control, 6 relevant to rate-control procedures versus drugs in patients for whom initial pharmacotherapy was ineffective, 42 relevant to antiarrhythmic drugs and electrical cardioversion for conversion to sinus rhythm, 83 relevant to rhythm-control procedures and drugs for maintenance of sinus rhythm, and 14 focusing on the comparison of rate- and rhythm-control strategies. Our ability to draw conclusions for the Key Questions addressing rate-control strategies was limited by the small number of available studies that assessed comparable therapies and outcomes, although we found a high strength of evidence for consistent benefit of calcium channel blockers (verapamil or diltiazem) compared with digoxin for ventricular rate control. For comparisons of methods for electrical cardioversion for conversion to sinus rhythm, there was high strength of evidence that use of a single biphasic waveform was more effective than use of a single monophasic waveform (odds ratio [OR] 4.39; 95% confidence interval [CI], 2.84 to 6.78) and that a 200 Joules (J) biphasic shock was less effective than a 360 J monophasic shock (OR 0.16; 95% CI, 0.05 to 0.53). Drug enhancement of external electrical cardioversion demonstrated a benefit compared with no drug enhancement (moderate strength of evidence), but data evaluating whether any one antiarrhythmic agent was more effective than others at restoring sinus rhythm were inconclusive. Our review found high strength of evidence supporting pulmonary vein isolation (PVI) versus antiarrhythmic drugs for maintenance of sinus rhythm in a select subset of patients (those with paroxysmal AF who were younger and with no more than mild structural heart disease; OR 6.51; 95% CI, 3.22 to 13.16) and moderate strength of evidence for adding a surgical Maze procedure at the time of other cardiac surgery (specifically mitral valve surgery) as opposed to mitral valve surgery alone (OR 5.80; 95% CI, 1.79 to 18.81). Comparing rate- and rhythm-control strategies, there was moderate strength of evidence supporting comparable efficacy with regard to all-cause mortality (OR 1.34; 95% CI, 0.89 to 2.02); cardiovascular mortality (OR 0.96; 95% CI, 0.77 to 1.20); stroke (OR 0.99; 95% CI, 0.76 to 1.30); and bleeding events (OR 1.10; 95% CI, 0.87 to 1.38). Cardiovascular hospitalizations were lower with rate-control strategies than with rhythm-control strategies (OR 0.25; 95% CI, 0.14 to 0.43; high strength of evidence). We were unable to conclude whether treatment effects varied by patient characteristics due to the paucity of studies that focused on specific patient subgroups.

Conclusions. In assessing clinical outcomes associated with rate- versus rhythm-control strategies, our review of recent evidence agrees with prior reviews demonstrating little overall difference in outcomes between these two strategic approaches. Uncertainties still exist within specific subgroups of interest, among the wide variety of pharmacological and procedural therapies within each strategic approach, and in the impact of strategies on long-term clinical outcomes. Specifically, our review highlights the need for additional studies evaluating final outcomes such as mortality, stroke, and cardiovascular hospitalizations.

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Background

Definition and Impact of Atrial Fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia (any tachycardic rhythm originating above the ventricular tissue) and is characterized by uncoordinated atrial activation with consequent deterioration of mechanical function.[1] Different systems have been proposed to classify AF. Although the type of AF can change over time, it is often helpful to characterize it at a given moment, as this may guide treatment. Types of AF include first-detected, paroxysmal (arrhythmia terminates spontaneously within 7 days), persistent (arrhythmia is sustained beyond 7 days), longstanding persistent (usually lasting for more than 1 year), and permanent AF (in which cardioversion has failed or has not been attempted).[1]

It is estimated that more than 2.3 million Americans have AF.[2] The prevalence of AF increases with age and approaches 8 percent in patients older than 80 years of age.[3] AF is the most common sustained arrhythmia seen in clinical practice. It affects men and women equally; however, approximately 60 percent of patients older than 75 years of age are female.[1]

The impact of AF is compounded by its known association with significant mortality, morbidity, and health care costs. Not only is the risk of death in patients with AF twice that of patients without AF, but AF can result in myocardial ischemia or even infarction, heart failure exacerbation, and tachycardia-induced cardiomyopathy if the ventricular rate is not well controlled.[4-7] In some patients, AF can severely depreciate quality of life by causing shortness of breath, intractable fatigue, and near-syncope.[8-11] However, the most dreaded complication of AF is thromboembolism, especially stroke. The risk of stroke in patients with AF is up to 8 percent per year, depending on the presence of stroke risk factors.[12] Importantly, when ischemic stroke occurs in patients with AF, it is either fatal or of moderate to high severity in the majority of patients.[13] The management of AF and its complications is responsible for almost $16 billion in costs to the U.S. health care system each year.[14]

This substantial public health impact of AF in the United States led the Institute of Medicine (IOM) to designate AF as one of the top priority areas for comparative effectiveness research. Specifically, the IOM called on researchers to compare the effectiveness of treatment strategies for AF, including surgery, catheter ablation, and pharmacological treatment.[15]

Treatment Strategies

Management of AF involves three distinct areas: rate control (treatments to slow the heart rate to a normal range), rhythm control (treatments to revert the heart rhythm back to normal), and prevention of thromboembolic events. This Comparative Effectiveness Review (CER) covers the first two areas. A separate CER focusing on stroke prevention in patients with AF, also commissioned through the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ), is being conducted in parallel with this CER.

Rate Control

Whether or not a rhythm-control strategy is adopted, current treatment guidelines suggest that adequate rate control should be achieved in all patients with AF to prevent myocardial infarction (if significant coronary artery disease is present), exacerbation of heart failure, and

tachycardia-induced cardiomyopathy; to alleviate symptoms; and to improve exercise tolerance and quality of life. Thus, the 2006 Guidelines for the Management of Patients with Atrial Fibrillation—prepared jointly by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC)—highlight the need for adequate rate control in patients with AF and designate measurement of the heart rate at rest and control of the rate with pharmacological agents (either a beta blocker or a nonhydropyridine calcium channel blocker in most patients) as a Class I recommendation (evidence and/or general agreement that a given procedure or treatment is useful and effective).[14] However, since the development of the ACC/AHA/ESC Guidelines, many additional studies have been published on the comparative safety and effectiveness of the different available medications used for ventricular rate control in clinical practice.

If pharmacological therapy is insufficient for rate control and symptom management or is associated with side effects, the 2006 ACC/AHA/ESC Guidelines recommend ablation of the atrioventricular node (AVN) in conjunction with permanent pacemaker implantation to control heart rate.[14] As the latter involves implantation of an indwelling device that is not reversible, it is considered a treatment of last resort for patients for whom initial pharmacotherapy was ineffective. However, the most recent systematic review on this topic was published more than a decade ago. This review synthesizes the evidence that has been published since then to better define the role of AVN ablation plus pacemaker implantation in contemporary clinical practice and in specific subpopulations where it might be more or less effective and clinically needed.

Another clinical dilemma is whether patients with AF do better with strict or lenient rate control. In theory, strict control could reduce symptoms and prevent complications. However, stricter control requires more intensive use of medications, which carry their own side effects. The 2011 Focused Update on the Management of Patients With Atrial Fibrillation by the American College of Cardiology Foundation (ACCF), the AHA, and the Heart Rhythm Society (HRS) addressed the issue of strict versus lenient rate control in patients with AF.[16] Specifically, these guidelines emphasized the following Class III recommendation (evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful): "Treatment to achieve strict rate control of heart rate (<80 bpm at rest or <110 bpm during a 6-minute walk) is not beneficial compared with achieving a resting heart rate <110 bpm in patients with persistent AF who have stable ventricular function (left ventricular ejection fraction >0.40) and no or acceptable symptoms related to the arrhythmia."[16] This recommendation was based on the results of the Rate Control Efficacy in Permanent Atrial Fibrillation-II (RACE-II) trial,[17] which showed that lenient rate control, defined in RACE-II as resting heart rate <110 beats per minute (bpm), is as effective as strict rate control, defined as resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm, and is easier to achieve.[17] Because of some of the study's limitations (e.g., low prevalence of patients with concomitant heart failure, only 75% success rate at achieving targeted heart rate control in the strict control arm, relatively small sample size, enrollment of primarily low-risk patients, and lack of inclusion of more sedentary patients), the applicability of its findings to the broader AF population is uncertain; therefore, this review will examine all available evidence on strict versus lenient rate control.

Rhythm Control

If patients with AF continue to have significant symptoms despite adequate rate control through either pharmacological therapy or AVN ablation, then a rhythm-control strategy (either

pharmacological or electrical) is currently recommended. For pharmacological cardioversion of AF, the 2006 ACC/AHA/ESC Guidelines recommend flecainide, dofetilide, propafenone, and ibutilide as Class I recommendations, and amiodarone as a Class IIa recommendation (weight of evidence/opinion is in favor of usefulness/efficacy).[14] To enhance direct-current cardioversion, the 2006 ACC/AHA/ESC Guidelines recommend pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol. For maintenance of sinus rhythm after cardioversion, the 2006 ACC/AHA/ESC Guidelines list different antiarrhythmic medications for different clinical settings. The 2011 ACCF/AHA/HRS Focused Update builds on the recommendations in the 2006 ACC/AHA/ESC Guidelines using published data on new antiarrhythmic medications. However, which of these medications is best for which patients is uncertain. Therefore, this report reviews existing evidence and summarizes current evidence gaps on the comparative safety and effectiveness of available antiarrhythmic agents for conversion of AF to sinus rhythm, for facilitating successful electrical cardioversion, and for maintaining sinus rhythm after successful conversion of AF to sinus rhythm.

In addition to pharmacological and direct-current cardioversion, a number of surgical interventions are used for rhythm control. Catheter ablation for the treatment of AF, with pulmonary vein isolation (PVI) being the most commonly used ablation, has evolved rapidly from a highly experimental procedure to its current status as a commonly performed procedure that is widely regarded as a clinically useful treatment option for symptomatic patients with AF in whom medications are not effective or not tolerated.[14,16,18]

Many studies have provided information on the safety and efficacy of catheter ablation of AF. These studies vary from small and large single-center nonrandomized studies to multicenter prospective randomized controlled trials (RCTs). However, even the RCTs have several limitations. The relatively small number of patients included in each trial makes definitive conclusions about the safety and efficacy of PVI based on an individual study difficult and does not permit meaningful analyses of key subgroups of patients (e.g., older patients, patients with heart failure). None of the trials provides data on final outcomes such as mortality and stroke. Although the ongoing Catheter Ablation versus Antiarrhythmic Drug Therapy for AF (CABANA) study will provide important information on the effect of catheter ablation on final outcomes, this trial is not expected to end until several years from now.[19] The present review will increase the power of existing studies by synthesizing the evidence on this procedure by pooling data from existing studies and by exploring whether other types of studies or comparative effectiveness research would be helpful.

Several other procedures for the treatment of AF have been investigated. One such procedure is the surgical Maze procedure, which appears to confer some benefit to selected patients with AF.[20] Implantation of a cardiac resynchronization therapy (CRT) device is another procedure that may decrease the burden of AF in patients who are eligible for this device based on a left ventricular ejection fraction ≤35 percent, a wide QRS complex, and heart failure symptoms despite optimal medical therapy. Secondary analyses of major clinical trials have provided conflicting findings on the effect of CRT on AF burden.[21,22] This report reviews and synthesizes current published data on these novel procedures and helps to better define their risks and benefits in contemporary clinical practice.

Rate Control Versus Rhythm Control

Although several studies of rate- and rhythm-control strategies exist, to date no study has shown that maintaining patients with AF in sinus rhythm provides a long-term survival benefit.

We also do not know whether the risks and benefits of different therapies vary by AF type. Our review seeks to systematically review the comparative risks and benefits of specific outcomes to allow patients and providers to assess the patient-specific tradeoffs of the differing strategies.

Scope and Key Questions

This CER was funded by AHRQ and is designed to evaluate the comparative safety and effectiveness of a wide range of pharmacological and procedural rate- and rhythm-control strategies for the treatment of adult patients with paroxysmal, persistent, or permanent AF (including atrial flutter).

With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the populations, interventions, comparators, outcomes, timing, and settings of interest (PICOTS). See the section "Inclusion and Exclusion Criteria" in the Methods chapter of the full report for details.

The first three KQs considered in this CER focus on rate-control therapies. Specifically:

- **KQ 1:** What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 2:** What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 3:** What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients with atrial fibrillation for whom initial pharmacotherapy was ineffective? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

The next two KQs focus specifically on rhythm-control therapies:

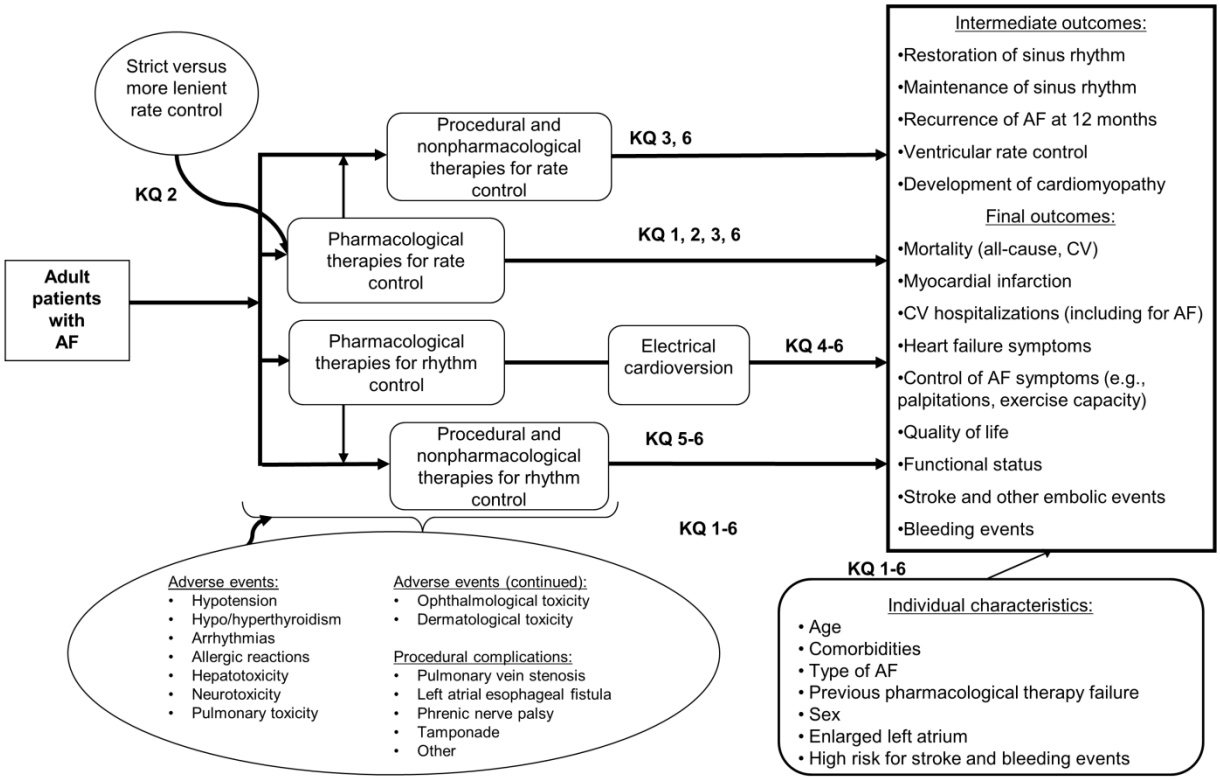
- **KQ 4:** What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 5:** What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents (either separately or in combination with each other) for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

The final KQ seeks to evaluate the comparison of the available rate- and rhythm-control therapies:

- **KQ 6:** What are the comparative safety and effectiveness of rate-control therapies versus rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Figure A depicts the KQs within the context of the PICOTS.

Figure A. Analytic framework



Note: AF = atrial fibrillation; CV = cardiovascular; KQ = Key Question.

Methods

The methods for this CER follow those suggested in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[23]

Input From Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of general internal medicine, geriatrics, cardiology, electrophysiology, and primary care; patients; scientific experts; Federal agencies; and payers to help define the KQs. The KQs were then posted for public comment for 4 weeks from September 27 to October 25, 2011, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input to the draft protocol in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search.[24] Before involvement in the CER process, the Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report.

Literature Search Strategy

To identify relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies published from January 1, 2000, to August 1, 2012. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new-onset AF summarized the evidence prior to 2000.[25-27] Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian guided all searches. We supplemented the electronic searches with a manual search of citations from a set of key primary and systematic review articles, and also considered studies suggested by peer and public reviewers of the draft report. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We used several approaches to identify relevant gray literature, including requests to drug and device manufacturers for scientific information packets and searches of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases searched included ClinicalTrials.gov (final search date, August 17, 2012); the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (final search date, August 17, 2012); and ProQuest COS Conference Papers Index (final search date, August 1, 2012).

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 1 of the full report. Across all KQs, we focused on English-language studies published since January 1, 2000, that represented comparative assessments of pharmacological and nonpharmacological rate- or rhythm-control therapies aimed at treating adult patients with AF. We excluded patients whose AF was postoperative or had a known reversible cause. Study design criteria were KQ specific. For all KQs, RCTs were acceptable if they met a minimum sample size of 20 or more patients. Observational studies with a minimum sample size of 100 or more patients were also considered for KQ 2 and for studies providing data for CRT relevant to KQ 5. The following outcomes were considered: restoration of sinus rhythm (conversion); maintenance of sinus rhythm; recurrence of AF at 12 months; development of cardiomyopathy; mortality (all-cause and cardiovascular); myocardial infarction; cardiovascular hospitalizations; heart failure symptoms; control of AF symptoms (e.g., palpitations, exercise capacity); quality of life; functional status; stroke and other embolic events; bleeding events; and adverse effects of therapy.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were reviewed independently by two investigators for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to include or exclude the article for data abstraction. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. Relevant review articles, meta-analyses, and methods articles were flagged for

manual searching of references and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners Inc., Manotick, Ontario, Canada).

Data Extraction

The research team created data abstraction forms and evidence table templates for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer's opinion if consensus could not be reached.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[23] To assess quality, we used the following strategy: (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, and differential loss to followup between the compared groups or overall high loss to followup. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling for confounding were considered. We summarized our assessments by assigning overall ratings of good, fair, or poor to each study.

Data Synthesis

We began our data synthesis by summarizing key features of the included studies for each KQ: patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes.

We grouped interventions by drug class; in this context, we considered all non-dihydropyridine calcium channel blocker drugs to be similar enough to be grouped together and all beta blocker drugs to be similar enough to be grouped together. Similarly, we categorized procedures into electrical cardioversion, AVN ablation, AF ablation by PVI (either open surgical, minimally invasive, or transcatheter procedures), and surgical Maze procedures, and explored comparisons among these categories. For the KQs focusing on pharmacological agents versus procedures (KQ 3 and KQ 5), we also explored grouping all pharmacological agents together and comparing them with all procedures. Finally for our evaluation of rate- versus rhythm-control strategies (KQ 6), we grouped all rate-control strategies together and all rhythm-control strategies together regardless of the specific agent or procedure.

We determined the appropriateness of a quantitative synthesis (i.e., meta-analysis) based on the volume of relevant literature, conceptual homogeneity of the studies in terms of study population and outcomes, and completeness of the reporting of results. Where at least three comparable studies reported the same outcome, we used random-effects models to synthesize the available evidence quantitatively using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics

(Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we also performed fixed-effect meta-analyses. We present summary estimates, standard errors, and confidence intervals in our data synthesis. Unless noted otherwise, when we were able to calculate odds ratios (ORs), we assumed that an OR between 0.9 and 1.1, with a confidence interval that also crossed 1.0, suggested that there was no clinically significant difference between treatment strategies; in such cases, we describe the treatment strategies being compared as having "comparable efficacy." For some outcomes, study quality or other factors affected comparability; these exceptions are explained on a case-by-case basis.

Strength of the Body of Evidence

We rated the strength of evidence for each KQ and outcome using the approach described in the Methods Guide.[23,28] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate: strength of association (magnitude of effect) and publication bias (as assessed through a search of ClinicalTrials.gov). These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make—for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned.

Applicability

We assessed applicability across the KQs using the method described in the Methods Guide.[23,29] In brief, we used the PICOTS format to organize information relevant to applicability. The most important applicability issue is whether the outcomes observed in any individual study, with its specific patient population and method of implementing treatments, can confidently be extrapolated to a broader context. Differences in study population characteristics (e.g., age, comorbidities) or methods of implementing interventions can affect the rates of events observed in both control and intervention groups, and may limit the generalizability of the findings. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population compared with the target population, characteristics of the intervention used compared with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

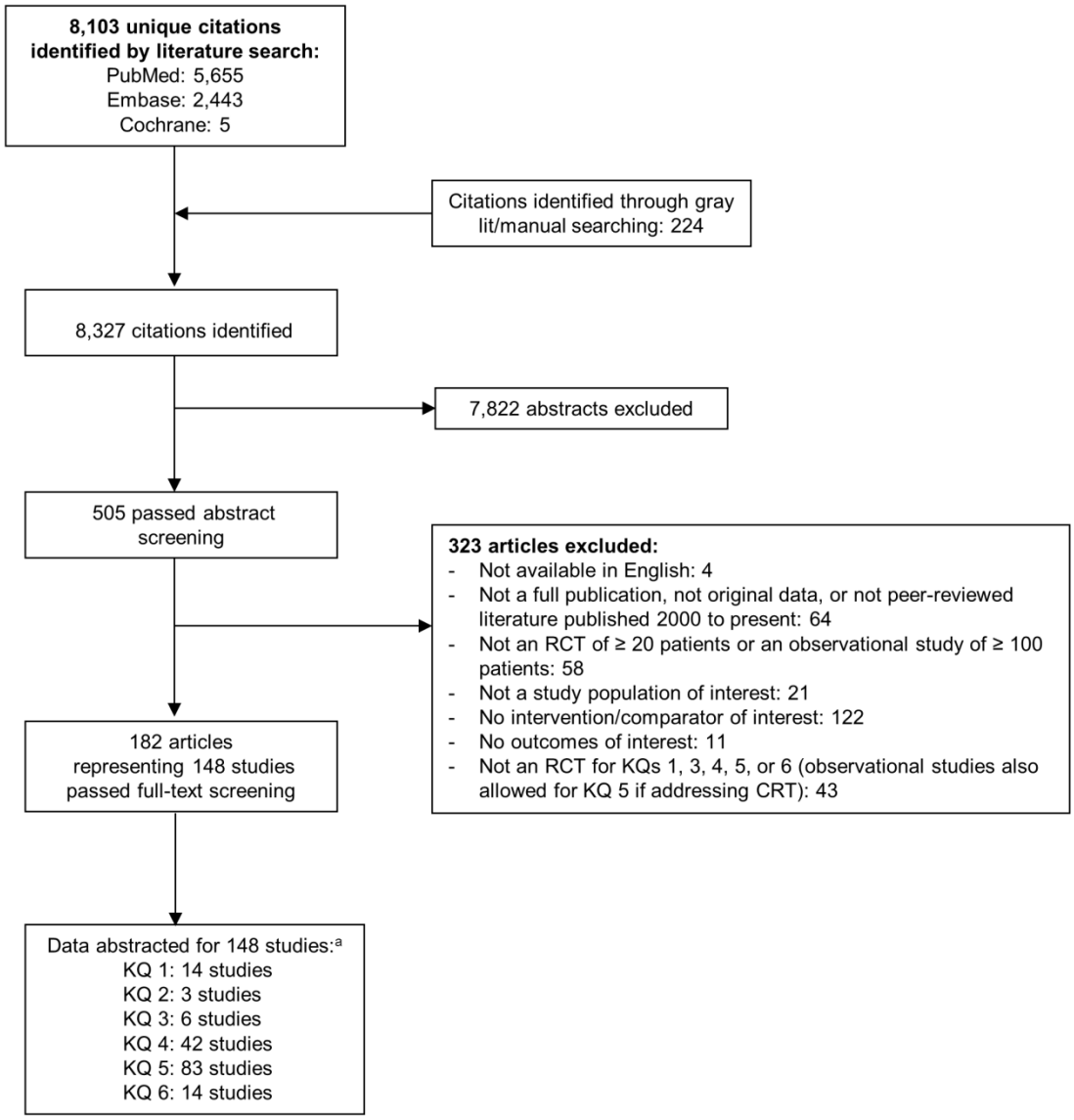
Results

Figure B depicts the flow of articles through the literature search and screening process. Searches of PubMed, Embase, and CDSR yielded 8,103 unique citations. Manual searching of gray literature databases, bibliographies of key articles, and information received through requests for scientific information packets identified 224 additional citations, for a total of 8,327 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 505 full-text articles were retrieved and screened. Of these, 323 were excluded at the full-text screening stage, leaving 182 articles for data abstraction. These 182 articles described 148 unique studies. The relationship of studies to the review questions is as follows: 14 studies relevant to KQ 1, 3

studies relevant to KQ 2, 6 studies relevant to KQ 3, 42 studies relevant to KQ 4, 83 studies relevant to KQ 5, and 14 studies relevant to KQ 6. (Some studies were relevant to more than one KQ.) Studies were conducted wholly or partly in continental Europe (57%), the United States or Canada (22%), the United Kingdom (10%), Asia (9%), South America (5%), Australia or New Zealand (3%), and other locations (7%). The full report provides a detailed list of included articles, along with a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

As described in the Methods chapter of the full report, we searched ClinicalTrials.gov as a mechanism to ascertain publication bias by identifying studies that have been completed but are as yet unpublished. We acknowledge that this is not an exhaustive strategy, as several other registries also exist with differing geographical focus and varying degrees of overlap in their trial listings; however, in the opinion of the investigators, the large, widely used, U.S.-based ClinicalTrials.gov registry provided the information most relevant to the populations and interventions of interest in this review. The sample sizes of the potentially relevant unpublished studies we identified corresponded to 8 percent of the included population for published studies relevant to KQ 1 and 12 percent for KQ 5. Because of the relatively low proportion of unpublished studies identified through our ClinicalTrials.gov registry analysis, we do not believe these findings indicate a significant publication bias in the evidence base that would impact our overall conclusions.

Figure B. Literature flow diagram



[a]Some studies were relevant to more than one KQ.
Note: CRT = cardiac resynchronization therapy; KQ = Key Question; RCT = randomized controlled trial.

Key Question 1. Rate-Control DrugsKey points from the Results chapter of the full report are as follows:

- Based on three studies (two good, one fair quality) involving 271 patients, evidence suggests that amiodarone is comparable to the calcium channel blocker diltiazem for rate control (low strength of evidence).
- Based on three studies (two good, one fair quality) involving 390 patients, evidence suggests that amiodarone provides better rate control than digoxin (low strength of evidence).
- Based on four studies (one good, three fair quality) involving 422 patients, evidence suggests that the calcium channel blockers verapamil and diltiazem provide better rate control than digoxin (high strength of evidence).

- Many outcomes/comparisons were rated to have insufficient strength of evidence. These include improvement of AF symptoms in patients receiving combined treatment with carvedilol plus digoxin compared with digoxin alone, rate control in patients using metoprolol versus diltiazem or sotalol, and the safety of any one pharmacological agent used for ventricular rate control in patients with AF.
- Data are also insufficient as to whether the safety and effectiveness of these therapies differ among specific patient subgroups of interest.
- Included studies focused on the control of ventricular rate as the outcome of interest; there was no evidence as to the safety and effectiveness of therapies on final outcomes.

A total of 14 RCTs involving 1,017 patients were identified that assessed the use of pharmacological agents for ventricular rate control in patients with AF. Six studies were considered to be of good quality, eight of fair quality, and none of poor quality. Only one study included a site in the United States; eight included sites in continental Europe; two included sites in Asia; and one each included sites in Canada, the United Kingdom, and Australia/New Zealand. The study population consisted entirely of patients with persistent AF in four studies, and entirely of patients with paroxysmal AF in one study. Mean age varied from 63 to 71.5 years. Most of the studies included patients with no history of heart failure, and the mean ejection fraction varied from 23.7 to 66 percent. Only a few studies included patients with coronary artery disease.

Two studies compared beta blockers with digoxin, one compared beta blockers with calcium channel blockers, and one compared beta blockers with calcium channel blockers in patients using digoxin. One study compared two beta blockers (sotalol and metoprolol) in patients receiving digoxin. Amiodarone was compared with calcium channel blockers in three studies, and with digoxin in three. One study evaluated the benefits of adding calcium channel blockers to digoxin compared with digoxin alone, and four studies compared calcium channel blockers with digoxin. Note that although amiodarone and sotalol are evaluated under this KQ for their rate-controlling potential, these agents are also potent membrane-active, type III antiarrhythmics, thereby having potential rhythm-control benefits (and risks).

The primary outcome reported for this KQ, assessed in all but one study, was control of ventricular rate.

Table A summarizes the strength of evidence for the most commonly used classes of therapies and evaluated outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report. For ventricular rate control, most comparisons were evaluated in one small study, resulting in insufficient evidence to support conclusions about comparative effectiveness. Exceptions were as follows. There was low strength of evidence that amiodarone was comparable to the calcium channel blocker diltiazem and that amiodarone controlled ventricular rate better than digoxin, and there was high strength of evidence for a consistent benefit of verapamil or diltiazem compared with digoxin for rate control. There was insufficient evidence regarding the effect of rate-control therapies on quality of life.

Table A. Summary of strength of evidence and effect estimate for KQ 1

Treatment Comparison	Ventricular Rate Control	Quality of Life
Beta blockers vs. digoxin	SOE = Insufficient (1 study, 47 patients)	SOE =Insufficient (no studies)
Beta blockers vs. calcium channel blockers	SOE = Insufficient (1 study, 40 patients)	SOE = Insufficient (no studies)
Beta blockers vs. calcium channel blockers in patients taking digoxin	SOE = Insufficient (1 study, 29 patients)	SOE = Insufficient (1 study, 29 patients)
Sotalol vs. metoprolol in patients taking digoxin	SO = Insufficient (1 study, 23 patients)	SOE = Insufficient (no studies)
Amiodarone vs. calcium channel blockers	SOE = Low (3 studies, 271 patients) Amiodarone is comparable to the calcium channel blocker diltiazem for rate control.	SOE = Insufficient (no studies)
Amiodarone vs. digoxin	SOE = Low (3 studies, 390 patients) Amiodarone controlled ventricular rate better than digoxin across 2 studies (both p = 0.02) but did not demonstrate a difference in a third study.	SOE = Insufficient (no studies)
Calcium channel blockers plus digoxin vs. digoxin alone	SOE = Insufficient (1 study, 52 patients)	SOE = Insufficient (no studies)
Calcium channel blockers vs. digoxin	SOE = High (4 studies, 422 patients) There was consistent benefit of verapamil or diltiazem compared with digoxin (p <0.05 across studies).	SOE = Insufficient (no studies)

Note: KQ = Key Question; SOE = strength of evidence.

Key Question 2. Strict Versus Lenient Rate-Control Strategies

Key points from the Results chapter in the full report are as follows.

- Based on one RCT and one observational study (both good quality) involving 828 patients, there was low strength of evidence to support a decrease in strokes for patients on lenient rate control. This decrease was statistically significant in the RCT but not in the observational study.
- There was insufficient strength of evidence to support comparisons between strict and lenient rate control for other outcomes, specifically for all-cause and cardiovascular mortality, cardiovascular hospitalizations, heart failure symptoms, control of AF symptoms, quality of life, and composite measures.

Three studies—one RCT and two observational studies representing secondary analyses of RCTs—were included in our analyses. We also included data from a separately published subgroup analysis of the one RCT directly included in our analysis. All studies were performed in continental Europe. Of the included studies, two were of good quality and one was of fair quality. The number of patients included in studies ranged from 214 to 1,091, with some overlap in patient populations across studies. A total of approximately 1,705 unique patients were included. Rate control was deemed "strict" for 1,177 and deemed "lenient" for 528. Included studies used varying definitions of "strict" and "lenient" rate control. The single included RCT used a resting heart rate <80 bpm as the definition of strict rate control and a resting heart rate <110 bpm as the definition of lenient rate control. One observational study compared patients

from the rate-control arms of two prior RCTs; the RCT that used a resting rate-control goal of <80 bpm was deemed "strict," and the RCT that used a resting rate-control goal of <100 bpm was deemed "lenient." A second observational study examined data from the rate-control arm of a prior RCT and established post hoc definitions of strict (<80 bpm) and lenient (>80 bpm) rate control.

Table B summarizes the strength of evidence for strict versus lenient rate control and the outcomes of interest. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report. Across outcomes, data were limited by the number of studies and the imprecision of their findings. We based our findings on the evidence from the one RCT and then evaluated whether the observational studies were consistent with these findings or not. In general, the included studies were consistent in showing no significant difference between strict and lenient rate control with respect to mortality, cardiovascular hospitalizations, heart failure symptoms, quality of life, thromboembolic events, bleeding events, and composite outcomes. However, the RCT differed from the observational studies in showing a statistically significantly lower stroke rate with lenient rate control.

Table B. Summary of strength of evidence and effect estimate for KQ 2

Outcome	Strength of Evidence and Effect Estimate
All-cause mortality	SOE = Insufficient (1 study, 614 patients)
CV mortality	SOE = Insufficient (2 studies, 828 patients)
CV hospitalizations	SOE = Insufficient (2 studies, 1,705 patients)
Heart failure symptoms	SOE = Insufficient (2 studies, 828 patients)
Quality of life	SOE = Insufficient (2 studies, 828 patients)
Thromboembolic events	SOE = Low (2 studies, 828 patients) The HR was 0.35 (90% CI, 0.13 to 0.92) in the RCT favoring lenient control; while also favoring lenient control, the observational study did not demonstrate a statistically significant difference (absolute difference of 1.6; 95% CI, -5.3 to 8.6).
Bleeding events	SOE = Insufficient (2 studies, 828 patients)

Note: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KQ = Key Question; RCT = randomized controlled trial; SOE = strength of evidence.

Key Question 3. Rate-Control Procedures Versus Drugs or Versus Other Procedures in Patients for Whom Initial Pharmacotherapy Was Ineffective

Key points from the Results chapter of the full report are as follows.

Procedures versus drugs:

- Based on three studies (one good, two poor quality) involving 175 patients, patients undergoing a procedural intervention had a significantly lower heart rate at 12 months than those receiving a primarily pharmacological intervention (moderate strength of evidence).
- There was no difference by treatment arm in all-cause mortality (two studies [one good, one fair quality], 201 patients); cardiovascular mortality (one study [good quality], 102 patients); or exercise capacity (two studies [one good, one fair quality], 135 patients) (all low strength of evidence).

- There was insufficient strength of evidence to support findings for other outcomes, including quality of life.

One procedure versus another:

- Based on one study (fair quality) involving 40 patients, there was no difference in ventricular rate control between those assigned to an anterior versus posterior ablation approach (low strength of evidence).
- Based on one study (fair quality) involving 184 patients, there was no significant difference in all-cause mortality between those receiving biventricular pacing versus those receiving right ventricular (RV) pacing (low strength of evidence).
- Based on one study (fair quality) involving 184 patients, there were significant improvements in exercise capacity for those in the biventricular pacing group compared with those receiving RV pacing (low strength of evidence).
- There was insufficient strength of evidence to support findings of other outcomes, including quality of life.

Six RCTs (two good, three fair, and one poor quality) involving a total of 537 patients met the inclusion criteria for KQ 3, evaluating the comparative effectiveness of a procedural intervention versus a primarily pharmacological intervention for rate control of AF or comparing two primarily procedural interventions. We also included data from a separately published subgroup analysis of one of the RCTs. One study each was based in the United Kingdom, continental Europe, and Asia; one was a multicenter trial based in Australia; one was a multicenter trial in the United States and Canada; and one did not specify the geographical location. All studies were unblinded due to the nature of the interventions. Four studies recruited patients with only one specific type of AF, either permanent (three studies) or persistent (one study); one study recruited patients with "resistant chronic" AF; and one study recruited patients with permanent or paroxysmal AF. These studies, however, evaluated and compared different types of treatments, preventing conclusions about whether effectiveness varied by type of AF. Treatment arms ranged in size from 18 to 103 patients.

The included studies varied in the types of procedures and pharmacological interventions tested. In line with our a priori definition of rate-control procedures, all studies included at least one treatment arm with radiofrequency ablation of either the AVN or His bundle, most often in conjunction with pacemaker placement. Based on the description of outcomes, we deduced that the comparison arms included a pharmacological intervention whose main purpose was to control ventricular heart rate rather than converting the underlying rhythm of AF; this was combined with a procedure in some studies.

Tables C and D summarize the strength of evidence for rate-control procedures versus drugs and for one rate-control procedure versus another, respectively. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report. Across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias and the outcomes were direct, the findings were often imprecise and based on only one or two studies.

Table C. Summary of strength of evidence and effect estimate for KQ 3—rate-control procedures versus drugs

Outcome	Strength of Evidence and Effect Estimate
Ventricular rate control	SOE = Moderate (3 studies, 175 patients) Using different metrics, all 3 studies found that patients in the procedure arm had a significantly lower heart rate at 12 months than those on drugs.
All-cause mortality	SOE = Low (2 studies, 201 patients) No significant difference was found.
CV mortality	SOE = Low (1 study, 102 patients) No significant difference was found.
Exercise capacity	SOE = Low (2 studies, 135 patients) Studies did not show significant differences between procedure and drug arms.
Quality of life	SOE = Insufficient (2 studies,135 patients)

Note: CV = cardiovascular; KQ = Key Question; SOE = strength of evidence.

Table D. Summary of strength of evidence and effect estimate for KQ 3—one rate-control procedure versus another

Outcome	Strength of Evidence and Effect Estimate
Ventricular rate control	SOE = Low (1 study, 40 patients) No difference was found between those assigned to anterior vs. posterior approach.
All-cause mortality	SOE = Low (1 study, 184 patients) No significant difference was found between those in the biventricular pacing group and those receiving RV pacing (p = 0.16).
Exercise capacity	SOE = Low (1 study, 184 participants) Improvement in walking distance was significantly greater among those in the biventricular pacing group than among those receiving RV pacing (p = 0.04).
Quality of life	SOE = Insufficient (1 study, 184 participants)

Note: KQ = Key Question; RV = right ventricular; SOE = strength of evidence.

Key Question 4. Antiarrhythmic Drugs and Electrical Cardioversion for Conversion to Sinus Rhythm

Key points from the Results chapter of the full report are as follows.

- Based on four RCTs (two good, two fair quality) involving 411 patients, use of a single biphasic waveform is more effective in restoring sinus rhythm than use of a single monophasic waveform in patients with persistent AF (high strength of evidence).
- Based on four RCTs (one good, three fair quality) involving 393 patients, there was no statistically significant difference in restoration of sinus rhythm with use of anterolateral versus anteroposterior positioning of cardioversion electrodes in patients with persistent AF (low strength of evidence).
- Based on three studies (one good, two fair quality) involving 432 patients, a 360 Joules (J) monophasic shock restores sinus rhythm more effectively than a 200 J monophasic shock (high strength of evidence).
- Although based on limited studies and use of different drugs for pretreatment, current evidence suggests that drug pretreatment does not enhance electrical cardioversion in terms of restoration of sinus rhythm (two studies [one good, one fair quality], 218 patients, moderate strength of evidence), but does increase maintenance of sinus rhythm (two studies [one good, one fair quality], 195 patients, moderate strength of evidence)

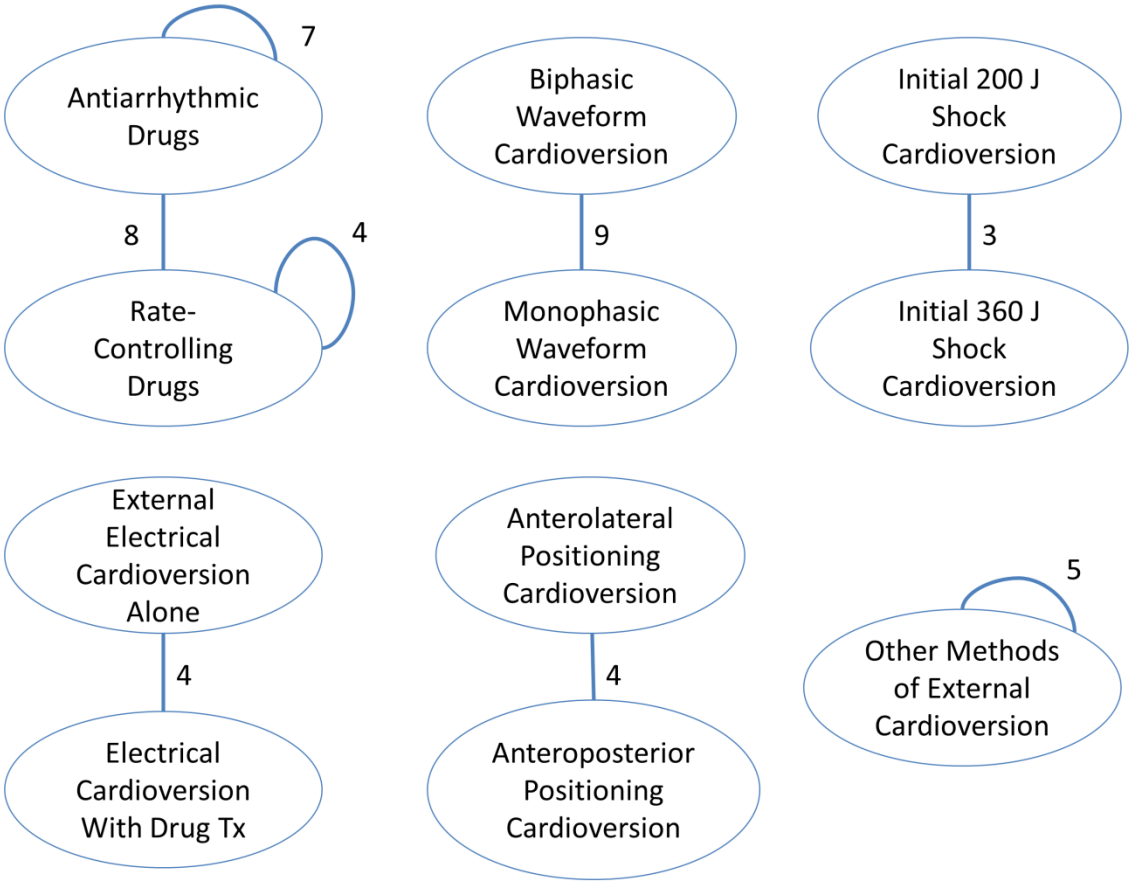
and decrease recurrence of AF (one poor-quality study, 88 patients, low strength of evidence).

- Based on four studies (two good, two fair quality) involving 736 patients, amiodarone demonstrates a potential benefit compared with sotalol for restoring sinus rhythm, although the difference did not reach statistical significance (low strength of evidence).

A total of 42 RCTs involving 5,780 patients were identified that assessed the use of antiarrhythmic drugs or electrical cardioversion for the conversion of AF to sinus rhythm. Thirteen studies were considered to be of good quality, 27 of fair quality, and 2 of poor quality. Only 7 studies included sites in the United States; 25 included sites in continental Europe. The study population consisted entirely of patients with persistent AF in 25 studies, entirely of patients with paroxysmal AF in 1 study, and entirely of patients for whom prior rate- or rhythm-control therapy had been ineffective in 2 studies.

Figure C represents the treatment comparisons evaluated for this KQ.

Figure C. Overview of treatment comparisons evaluated for KQ 4



Notes: Lines running from one oval back to the same oval (e.g., "Antiarrhythmic Drugs" oval) indicate intraclass comparisons (e.g., comparison of one antiarrhythmic drug with another). Numbers refer to numbers of comparisons.
KQ = Key Question; J = Joules; Tx = treatment.

Table E summarizes the strength of evidence for the available comparisons and evaluated outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report. Across outcomes and comparisons,

although the included evidence was from RCTs with an overall low risk of bias and the evidence was based on direct outcomes, some findings were limited in terms of precision and consistency, as well as by the available number of studies.

Table E. Summary of strength of evidence and effect estimate for KQ 4

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF
Various methods for external electrical cardioversion: biphasic vs. monophasic waveforms	SOE = High (4 studies, 411 patients) OR 4.39 (95% CI, 2.84 to 6.78) favoring biphasic waveform	SOE = Insufficient (1 study, 83 patients)	SOE = Low (1 study, 216 patients) No difference
Various methods for external electrical cardioversion: anterolateral vs. anteroposterior cardioversions	SOE = Low (4 studies, 393 patients) OR 0.87 (95% CI, 0.20 to 3.72), showing potential benefit of anterolateral electrode placement, which did not reach statistical significance	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Various methods for external electrical cardioversion: energy protocols	SOE = High (3 studies, 432 patients) OR 0.16 (95% CI, 0.05 to 0.53) favoring 360 J vs. 200 J monophasic shock	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Drug enhancement of external electrical cardioversion vs. no drug enhancement	SOE = Moderate (2 studies, 218 patients) No significant benefit for patients given ibutilide or metoprolol pretreatment (p values NR)	SOE = Moderate (2 studies, 195 patients) Significant benefit for patients given verapamil or metoprolol pretreatment (p values of 0.04 and 0.027 in the 2 studies)	SOE = Low (1 study, 88 patients) Significant benefit of verapamil pretreatment (p = 0.02)
Drugs for pharmacological cardioversion: amiodarone vs. sotalol	SOE = Low (4 studies, 736 patients) OR 1.12 (95% CI, 0.81 to 1.56), demonstrating a potential benefit of amiodarone, which did not reach statistical significance	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Drugs for pharmacological cardioversion: amiodarone vs. rate-control drugs	SOE = High (7 studies, 613 patients) OR 2.99 (95% CI, 1.64 to 5.44), demonstrating a significant benefit of amiodarone	SOE = Insufficient (no studies)	SOE = Low (1 study, 152 patients) No difference between amiodarone vs. ibutilide within 24 hours

Note: AF = atrial fibrillation; CI = confidence interval; J = Joules; KQ = Key Question; NR = not reported; OR = odds ratio; SOE = strength of evidence.

Key Question 5. Rhythm-Control Procedures and Drugs for Maintenance of Sinus Rhythm

Key points from the Results chapter of the full report are as follows.

Procedural therapies:

- ***Transcatheter PVI versus antiarrhythmic drugs***
  - Based on eight RCTs (five good, three fair quality) involving 921 patients, transcatheter PVI is superior to antiarrhythmic drugs for maintenance of sinus rhythm over 12 months of followup in patients with paroxysmal AF (high strength of evidence). This evidence is strongest in younger patients with little to no structural heart disease and with mild or no enlargement of the left atrium.
  - Based on two RCTs (both good quality) involving 268 patients, transcatheter PVI is superior to antiarrhythmic medications in reducing cardiovascular hospitalizations (moderate strength of evidence).
- ***Transcatheter PVI with complex fractionated atrial electrogram (CFAE) ablation versus transcatheter PVI without CFAE ablation***
  - Based on nine RCTs (six good, three fair quality) involving 817 patients, CFAE ablation done in addition to transcatheter PVI showed a potential benefit in the maintenance of sinus rhythm at 12 months compared with PVI alone, which did not reach statistical significance (low strength of evidence).
- ***Surgical Maze versus standard of care (mitral valve surgery)***
  - Based on seven RCTs (one good, six fair quality) involving 361 patients, surgical Maze at the time of other cardiac surgery (specifically mitral valve surgery) is superior to mitral valve surgery alone for maintenance of sinus rhythm over at least 12 months of followup in patients with persistent AF (moderate strength of evidence).
- ***PVI done at the time of cardiac surgery versus cardiac surgery alone or cardiac surgery in combination with antiarrhythmic drugs (AADs) or catheter ablation***
  - Based on eight RCTs (five good, three fair quality) involving 532 patients, PVI done at the time of cardiac surgery is superior to cardiac surgery alone or cardiac surgery in combination with AADs or catheter ablation for maintenance of sinus rhythm over 12 months of followup in patients with persistent AF (high strength of evidence).
- ***All comparisons***
  - There are insufficient data on the effect of rhythm control with PVI or surgical Maze on final outcomes, such as all-cause mortality, stroke, heart failure, and left ventricular ejection fraction, and on the safety and durability of the effectiveness of these procedures beyond 12 months.

Pharmacological therapies:

- Based on nine studies (one good, eight fair quality) involving 2,095 patients, amiodarone appears to be better than sotalol but no different from propafenone in maintaining sinus rhythm (low strength of evidence).
- Based on 10 studies (4 good, 6 fair quality) involving 3,223 patients, amiodarone appears to be better than dronedarone or sotalol but no different from propafenone in reducing AF recurrence (low strength of evidence).

- Only one fair-quality study, a substudy of the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study involving 256 patients, systematically assessed differences in all-cause mortality between AADs; it found no statistically significant difference after a mean followup of 3.8 years between those receiving amiodarone versus sotalol (insufficient strength of evidence).
- Based on one good-quality study of 403 patients, amiodarone lowered AF hospitalizations compared with sotalol or propafenone (low strength of evidence) but did not demonstrate a benefit in control of AF symptoms (low strength of evidence).
- Based on two good-quality studies involving 1,068 patients, there was no difference among agents in impact on quality of life (low strength of evidence).

A total of 83 studies met our inclusion criteria and assessed the comparative safety and effectiveness of new procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents for the maintenance of sinus rhythm in patients with AF. These were broken down into those focusing on procedural therapies and those focusing on pharmacological therapies.

Procedural Therapies

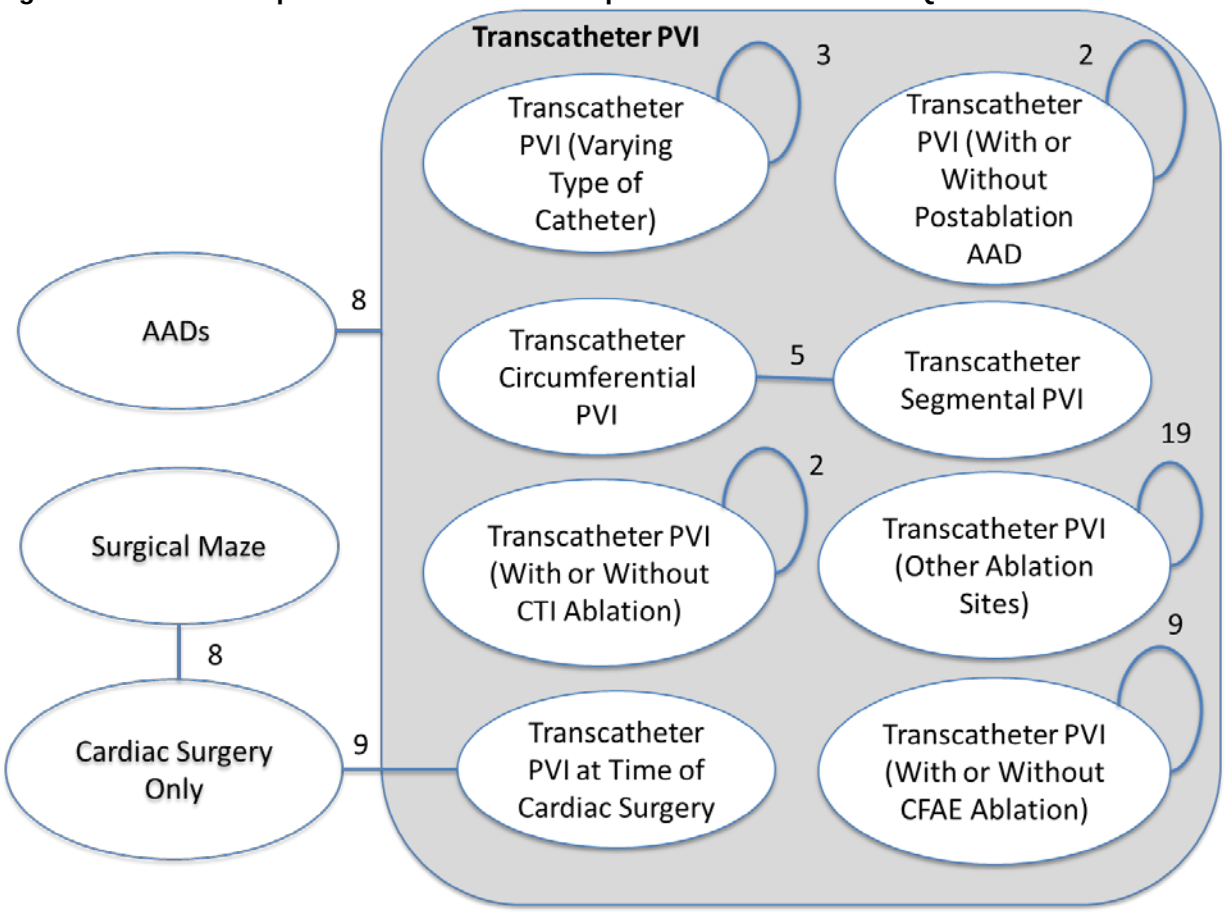
We identified 65 studies enrolling 6,739 patients that evaluated procedures for rhythm control that were relevant to this KQ. All of these studies were RCTs. Thirty-one studies were rated as good quality, 32 as fair quality, and 2 as poor quality.

Fourteen studies included patients from the United States, four included the United Kingdom, six included Canada, nine included Asia, four included South America, and one included Australia/New Zealand. Thirty-six studies included patients from continental Europe. Three studies did not report their locations.

Several studies focused on specific populations. Eleven included only patients with longstanding persistent AF, 17 studies included only patients with paroxysmal AF, and 4 studies included only patients with persistent AF. Finally, two studies enrolled only patients who had comorbid heart failure.

Figure D represents the procedural treatment comparisons evaluated for this KQ.

Figure D. Overview of procedural treatment comparisons evaluated for KQ 5



Notes: Lines running from one oval back to the same oval (e.g., "Transcatheter PVI (Varying Type of Catheter)" oval) indicate intraclass comparisons (e.g., comparison of one transcatheter PVI catheter with another). Numbers refer to numbers of comparisons.
AAD = antiarrhythmic drug; CFAE = complex fractionated atrial electrogram; CTI = cavotricuspid isthmus; KQ = Key Question; PVI = pulmonary vein isolation.

Pharmacological Therapies

A total of 18 studies involving 4,300 patients compared the safety or effectiveness of pharmacological agents with or without external electrical cardioversion for maintaining sinus rhythm in patients with AF. Six studies were of good quality, 10 were of fair quality, and 2 were of poor quality. One study was conducted entirely in the United States, 5 were conducted entirely in Greece, 10 were conducted entirely in other parts of continental Europe, 1 was conducted completely in Canada, and 1 was conducted on several continents. Four studies included patients with paroxysmal or persistent AF, and seven studies included patients with persistent AF.

Five studies evaluated the use of one or more pharmacological agents with external electrical cardioversion as a primary component of the tested intervention; 1 study compared an AAD drug with a rate-controlling drug (sotalol vs. bisoprolol); 1 study primarily evaluated the effect of the addition of verapamil to either amiodarone or flecainide; 1 study compared the effect of two beta blockers for maintenance of sinus rhythm after cardioversion; and 10 studies compared two or more AADs.

Tables F and G summarize the strength of evidence for the evaluated rhythm-control therapies and outcomes. Details about the specific components of these ratings (risk of bias,

consistency, directness, and precision) are available in the full report. Across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias and was direct, the findings were often inconsistent or imprecise, limiting our findings.

Table F. Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events, Including Stroke)	Bleeding Events
Transcatheter PVI vs. AADs	SOE = Insufficient (no studies)	SOE = High (8 studies, 921 patients) OR 6.51 (95% CI, 3.22 to 13.16) favoring transcatheter PVI	SOE = Insufficient (no studies)	All-cause: SOE = Insufficient (1 study, 69 patients) Cardiac: SOE = Insufficient (no studies)	CV: SOE = Moderate (2 studies, 268 patients) Significant increase in CV hospitaliza-tions in the AAD arm vs. PVI demonstrated in both studies AF: SOE = Insufficient (1 study, 67 patients)	SOE = Insufficient (no studies)	SOE = Insufficient (6 studies, 647 patients)	Stroke: SOE = Insufficient (no studies) Mixed: SOE = Low (2 studies, 140 patients) No embolic events in either the PVI or AAD arm	SOE = Insufficient (1 study, 67 patients)
Transcatheter PVI using different types of ablation catheters	SOE = Insufficient (no studies)	SOE = Low (3 studies, 264 patients) No difference between different types of ablation catheters	SOE = Low (1 study, 102 patients) No difference between a multipolar circular ablation catheter and a point-by-point PVI ablation catheter with an irrigated tip (p = 0.8)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	Stroke: SOE = Insufficient (1 study, 82 patients) Mixed: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)

Table F. Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies (continued)

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events, Including Stroke)	Bleeding Events
Transcatheter circumferential PVI vs. transcatheter segmental PVI	SOE = Insufficient (1 study, 80 patients)	SOE = Low (5 studies, 500 patients) OR 1.31 (95% CI, 0.59 to 2.93), demonstrating a potential benefit of circumferential PVI, which did not reach statistical significance	SOE = Insufficient (no studies)	All-cause: SOE = Low (1 study, 110 patients) No events in either arm after 48 months Cardiac: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Transcatheter PVI with CTI ablation vs. transcatheter PVI without CTI ablation	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (2 studies, 257 patients)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Transcatheter PVI with CFAE ablation vs. transcatheter PVI without CFAE ablation	SOE = Low (2 studies, 247 patients) 2 studies showing significant benefit of CFAE arm	SOE = Low (9 studies, 817 patients) OR 1.48 (95% CI, 0.74 to 2.98), showing a potential benefit of CFAE, which did not reach statistical significance	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (1 study, 60 patients)	Stroke: SOE = Low (1 study, 144 patients) No events in any arm after 16 months Mixed: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)

Table F. Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies (continued)

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events, Including Stroke)	Bleeding Events
Transcatheter PVI vs. transcatheter PVI with additional ablation sites other than CTI and CFAE and transcatheter PVI involving all 4 PVs vs. transcatheter PVI involving arrhythmogenic PVs only	SOE = Insufficient (2 studies, 384 patients)	SOE = Insufficient (15 studies, 1,926 patients)	SOE = Insufficient (6 studies, 572 patients)	All-cause: SOE = Insufficient (2 studies, 405 patients) Cardiac: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Low (2 studies, 152 patients) No significant difference between arms in 2 studies	Stroke: SOE = Insufficient (2 studies, 361 patients) Mixed: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Transcatheter PVI alone vs. transcatheter PVI plus postablation AADs	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (2 studies, 217 patients)	SOE = Insufficient (no studies)	CV: SOE = Insufficient (no studies) AF: SOE = Low (1 study, 110 patients) No difference between arms	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)

Table F. Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies (continued)

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events, Including Stroke)	Bleeding Events
Surgical Maze vs. standard of care (mitral valve surgery)	SOE = Insufficient (no studies)	SOE = Moderate (7 studies, 361 patients) OR 5.80 (95% CI, 1.79 to 18.81), demonstrating large and significant benefit of Maze	SOE = Insufficient (no studies)	All-cause: SOE = Low (6 studies, 384 patients) OR 1.97 (95% CI, 0.81 to 4.80), demonstrating potentially greater mortality with Maze, which did not reach statistical significance Cardiac: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (1 study, 30 patients)	SOE = Insufficient (no studies)	Stroke: SOE = Insufficient (1 study, 30 patients) Mixed: SOE = Insufficient (1 study, 67 patients)	SOE = Insufficient (1 study, 60 patients)
PVI at the time of cardiac surgery vs. cardiac surgery alone or in combination with AADs or catheter ablation	SOE = High (3 studies, 181 patients) OR 12.30 (95% CI, 1.31 to 115.29), demonstrating statistically significant benefit of PVI at time of cardiac surgery	SOE = High (8 studies, 532 patients) OR 3.91 (95% CI, 1.54 to 9.91), demonstrating statistically significant benefit of PVI at time of cardiac surgery	SOE = Insufficient (no studies)	All-cause: SOE = Low (2 studies, 88 patients) 2 studies showing no difference between groups Cardiac: SOE = Insufficient (1 study, 97 patients)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (2 studies, 229 patients)	Stroke: SOE = Low (2 studies, 140 patients) 2 studies showing no difference between groups Mixed: SOE = Insufficient (no studies)	SOE = Insufficient (1 study, 43 patients)

Note: AAD = antiarrhythmic drug; AF = atrial fibrillation; CFAE = complex fractionated atrial electrogram; CI = confidence interval; CTI = cavotricuspid isthmus; CV = cardiovascular; KQ = Key Question; OR = odds ratio; PV = pulmonary vein; PVI = pulmonary vein isolation; SOE=strength of evidence.

Table G. Summary of strength of evidence and effect estimate for KQ 5—pharmacological rhythm-control therapies

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	AF and CV Hospitalizations	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events, Including Stroke)	Bleeding Events
Pharmacological therapy in which electrical cardioversion is a key component of the treatment	SOE = Insufficient (no studies)	SOE = Insufficient (1 study, 168 patients)	SOE = Insufficient (4 studies, 414 patients)	All-cause: SOE = Insufficient (1 study, 168 patients) Cardiac: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE = Insufficient (no studies)	SOE= Insufficient (1 study, 144 patients)	Stroke: SOE = Insufficient (1 study, 168 patients) Mixed: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)
Comparison of pharmacological agents	SOE = Insufficient (no studies)	SOE = Low (9 studies, 2,095 patients) Amiodarone appears to be better than sotalol but no different from propafenone.	SOE = Low (10 studies, 3,223 patients) Amiodarone appears to be better than dronedarone or sotalol but no different from propafenone.	All-cause: SOE = Insufficient (5 studies, 2,076 patients) Cardiac: SOE = Low (4 studies, 1,664 patients) No difference was found between study arms in arrhythmic deaths.	CV: SOE = Insufficient (no studies) AF: SOE = Low (1 study, 403 patients) Rate and mean length of stay of AF hospitalization were lower with amiodarone than with sotalol or propafenone.	Heart failure: SOE = Insufficient (no studies) AF symptoms: SOE = Low (1 study, 403 patients) No difference was found between amiodarone vs. sotalol or propafenone.	SOE = Low (2 studies, 1,068 patients) No significant difference was found in either study.	Stroke: SOE = Insufficient (2 studies, 1,068 patients) Mixed: SOE = Insufficient (no studies)	SOE = Insufficient (no studies)

Note: AF = atrial fibrillation; CV = cardiovascular; KQ = Key Question; SOE = strength of evidence.

Key Question 6. Rate- Versus Rhythm-Control Therapies

Key points from the Results chapter of the full report are as follows.

- Based on evidence from three RCTs (two good, one fair quality) involving 439 patients, pharmacological rate-control strategies with antiarrhythmic medications are superior to rhythm-control strategies in reducing cardiovascular hospitalizations (high strength of evidence).
- Among patients with AF, there is evidence that pharmacological rate-control strategies are comparable in efficacy to rhythm-control strategies with antiarrhythmic medications with regard to their effect on the following outcomes:
  - Cardiovascular mortality: Based on data from five RCTs (all good quality) involving 2,405 patients (moderate strength of evidence)
  - Stroke: Based on data from eight RCTs (five good, two fair, one poor quality) involving 6,424 patients (moderate strength of evidence)
  - All-cause mortality: Based on data from eight RCTs (five good, two fair, one poor quality) involving 6,372 patients (moderate strength of evidence)
- With regard to heart failure symptoms, there is evidence showing a potential benefit of rhythm-control strategies with antiarrhythmic medications compared with pharmacological rate-control strategies, which did not reach statistical significance. This finding is based on evidence from four RCTs (two good, two fair quality) involving 1,700 patients (low strength of evidence).
- Not surprisingly, based on evidence from seven RCTs (four good, two fair, one poor quality) involving 1,473 patients, rhythm-control strategies with antiarrhythmic medications are significantly more efficacious at maintaining sinus rhythm than pharmacological rate-control strategies (high strength of evidence).
- There was insufficient strength of evidence about outcomes comparing a rhythm-control strategy that involved PVI with a rate-control strategy that involved AVN ablation and implantation of a pacemaker (one good-quality study) or rate-controlling medications (one poor-quality study).

A total of 14 RCTs were included in our analysis, 12 that explored a rhythm-control strategy using pharmacological therapy versus a rate-control strategy and 2 that compared a rhythm-control strategy with PVI versus a rate-control strategy that involved AVN ablation and implantation of a pacemaker in one case and rate-controlling medications in the other. Nine studies were of good quality, three were of fair quality, and two were of poor quality. Ten studies were conducted in continental Europe; 1 was conducted in the United States and Canada only; 1 was conducted in Asia only; 1 was conducted in the United States, Canada, South America, and Israel; and 1 study did not report the location. The number of patients included ranged from 41 to 4,060, for a total of 7,556 patients across the 14 studies. The mean age of study participants ranged from 39 years to 72 years.

Five studies included only patients with persistent AF, one study included only patients with paroxysmal AF, two studies included both patients with paroxysmal and those with persistent AF, and six studies did not explicitly report type of AF. Four studies included only patients with heart failure.

Table H summarizes the strength of evidence for the rate- and rhythm-control therapies and evaluated outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report.

Table H. Summary of strength of evidence and effect estimate for KQ 6—rate- versus rhythm-control strategies

Outcome	Strength of Evidence and Effect Estimate
Maintenance of sinus rhythm	Using AADs for rhythm control: SOE = High (7 studies, 1,473 patients) OR 0.18 (95% CI, 0.11 to 0.28) favoring rhythm-control strategies Using PVI for rhythm control: SOE = Low (2 studies, 122 patients) Significantly better in rhythm-control strategies (OR not reported)
Ventricular rate control	Using AADs for rhythm control: SOE = Low (2 studies, 727 patients) Significantly better in rhythm-control strategies
All-cause mortality	Using AADs for rhythm control: SOE = Moderate (8 studies, 6,372 patients) OR 1.34 (95% CI, 0.89 to 2.02), demonstrating a potential benefit of a rhythm-control strategy, which did not reach statistical significance. Since 6 of the 8 studies had ORs that crossed 1 (including 95% of the patients) and given significant heterogeneity, we assessed these studies as demonstrating no difference between rate- and rhythm-control strategies.
CV mortality	Using AADs for rhythm control: SOE = Moderate (5 studies, 2,405 patients) OR 0.96 (95% CI, 0.77 to 1.20), demonstrating no difference between rate- and rhythm-control strategies
Myocardial infarction	Using AADs for rhythm control: SOE = Low (2 studies, 246 patients) No significant difference between rate- and rhythm-control strategies shown in either study
CV hospitalizations	Using AADs for rhythm control: SOE = High (3 studies, 439 patients) OR 0.25 (95% CI, 0.14 to 0.43) favoring rate-control strategies
Heart failure symptoms	Using AADs for rhythm control: SOE = Low (4 studies, 1,700 patients) OR 0.78 (95% CI, 0.42 to 1.44), showing a potential benefit of rhythm control, which did not reach statistical significance
Quality of life	Using AADs for rhythm control: SOE = Insufficient (9 studies, 5,806 patients) Using PVI for rhythm control: SOE = Insufficient (2 studies, 122 patients)
Stroke	Using AADs for rhythm control: SOE = Moderate (8 studies, 6,424 patients) OR 0.99 (95% CI, 0.76 to 1.30), demonstrating no difference between rate- and rhythm-control strategies
Mixed embolic events, including stroke	Using AADs for rhythm control: SOE = Low (3 studies, 866 patients) OR 1.24 (95% CI, 0.37 to 4.09), demonstrating a potential benefit of rhythm-control strategies, which did not reach statistical significance
Bleeding events	Using AADs for rhythm control: SOE = Moderate (5 studies, 5,072 patients) OR 1.10 (95% CI, 0.87 to 1.38), demonstrating no difference between rate- and rhythm-control strategies

Note: AAD = antiarrhythmic drug; CI = confidence interval; CV = cardiovascular; KQ = Key Question; OR = odds ratio; PVI = pulmonary vein isolation; SOE = strength of evidence.

Discussion

Key Findings

In this Comparative Effectiveness Review, we reviewed 148 studies represented by 182 publications and involving 25,524 patients that directly compared rate- and rhythm-control strategies in patients with AF. Although the ultimate goal with any therapy for AF is to improve long-term survival and quality of life, most studies to date have assessed rate control, conversion of AF to sinus rhythm, or maintenance of sinus rhythm. Very few studies focused on final outcomes such as survival, or on the relationship between intermediate outcomes such as ventricular rate or duration of sinus rhythm and final outcomes.

For KQ 1, despite strongly held convictions among clinicians about the superiority of individual beta blockers and calcium channel blockers, we found insufficient data to support any of these claims. Based on a limited number of comparative studies, our analysis suggests that either a calcium channel blocker (verapamil or diltiazem) or amiodarone is beneficial compared with digoxin for rate control. Given the widespread use of beta blockers and calcium channel blockers and the population-level impact of even small differences in safety and effectiveness, research comparing individual drugs in different patient populations is needed.

For KQ 2, by emphasizing the limitations in the available data and the paucity of data on lenient versus strict rate control, our findings highlight the need for more research in this area.

For KQ 3, our findings underscore the need for additional studies to compare rate-control drugs with rate-control procedures in relation to exercise capacity, mortality, cardiovascular events, and quality of life.

For KQ 4, although health care providers often debate the superiority of one positioning of cardioversion electrodes over another, we found that both positions gave comparable results, albeit with low strength of evidence. While data suggest that drug pretreatment enhances electrical cardioversion in terms of restoration and maintenance of sinus rhythm, our review does not support the current assumption that one AAD is clearly superior to others in such pretreatment. This finding challenges the assumption that one antiarrhythmic medication is clearly superior to others and underscores the need for more studies comparing the effectiveness and safety of different AADs in enhancing restoration of sinus rhythm.

For KQ 5, our review is the largest to date to address the clinical question of whether CFAE ablation in addition to PVI is better than PVI alone at maintaining sinus rhythm. Unlike prior reviews, our review showed a potential benefit to adding CFAE, but this finding did not reach statistical significance, and we therefore concluded that CFAE ablation in addition to PVI did not increase maintenance of sinus rhythm compared with PVI alone. This finding could inform clinical decisionmaking regarding the extent of ablation during a PVI procedure, especially given the potential for reduced atrial mechanical function from more scarring with CFAE. The rating of low strength of evidence for this comparison and outcome underscores the importance of conducting well-powered and designed RCTs to address the issue definitively. We also explored the use of surgical Maze or PVI at the time of cardiac surgery. By confirming the findings of some of the prior studies on these two interventions, our findings support exploring these interventions further with regard to their effect on final outcomes and in different patient populations. In examining the comparative effectiveness of different antiarrhythmic medications for reducing mortality, we found only one study, a substudy of the AFFIRM study, that systematically assessed differences in mortality between AADs; it found no statistically significant difference between amiodarone and sotalol. We found no data on the comparative

effectiveness of different AADs in relation to other final outcomes. Most studies examined the effect of different AADs on the maintenance of sinus rhythm; amiodarone, sotalol, and propafenone were the AADs most frequently studied in RCTs. With regard to maintaining sinus rhythm or decreasing recurrences of AF, amiodarone did not appear to be different from propafenone in the two studies of fair quality that reported results on this comparison. Comparisons of other AADs were infrequent and often led to conflicting results. Indeed, the superiority of one AAD over another has been debated for years, and there has been a longstanding need to better understand the comparative effectiveness of different AADs at maintaining sinus rhythm. Our findings further highlight the importance of future research to compare different AADs.

For KQ 6, our analysis is the largest to date addressing the comparative effectiveness of rate- and rhythm-control strategies, and provides further confirmation that rate-control strategies and rhythm-control strategies have comparable effect on all-cause mortality, cardiovascular mortality, and stroke in patients similar to patients enrolled in the RCTs (i.e., older patients with mild symptoms from AF). Our analysis adds to the established literature by showing that rate-control strategies are superior to rhythm-control strategies in reducing cardiovascular hospitalizations and suggests a potential benefit of rhythm-control strategies on the reduction of heart failure symptoms, although this latter benefit did not reach statistical significance.

Applicability

The main issues related to applicability of the evidence base included concerns about short-term or surrogate outcomes (37% of studies), whether the intervention team or level of training represented in the study would be widely available (30% of studies), and large potential differences between the study population and community patients (15% of studies). Although the included studies were conducted in a broad range of geographic locations, the 2006 guidelines jointly issued by the ACC, AHA, and ESC have guided most management of AF for the last 6 years. Therefore, we believe that clinical practice across the geographic locations is more similar than different and not a major detriment to the evidence base applicability.

Research Gaps

In our analyses, we found research gaps related to patient-centered outcomes for both established and newer therapies. Results are as follows.

KQ1. Research Gaps: Rate-Control Drugs

No comparator studies included in the review evaluated the long-term outcomes of all-cause mortality, cardiovascular mortality, or other cardiovascular-related outcomes either in general patients with AF or in patients with AF and heart failure. We identified only one study comparing the effectiveness of different beta blockers. Given that beta blockers are some of the most commonly used drugs for rate control, additional comparative studies are needed. Of particular interest would likely be the comparison between the beta blockers metoprolol and carvedilol; both of them are commonly used, but the two drugs have different properties that could make one or the other more suitable for certain subgroups of patients (e.g., patients with heart failure). An additional area of future research would be the exploration of beta blockers and calcium channel blockers used together. Patients in these studies should be followed to determine long-term outcomes.

KQ 2. Research Gaps: Strict Versus Lenient Rate-Control Strategies

Unfortunately, only one RCT and two observational studies, all using different definitions, examined the comparative effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with AF. The RCT found no significant difference in outcomes among patients treated with strict versus lenient rate control except for stroke risk, which favored lenient rate control. However, further studies are needed that are adequately powered to evaluate clinically meaningful outcomes, including stroke risk, and these studies should be carried out not only among general patients with AF but also among subgroups of patients, such as those with heart failure. In order to better compare future studies, achieving consensus on standardized definitions of strict and lenient rate control is needed. There is also a need to define how best to assess the adequacy of rate control. Some investigators have relied on periodic Holter monitoring, but it remains unclear whether this is the best way to assess this important outcome.

KQ 3. Research Gaps: Rate-Control Procedures Versus Drugs in Patients for Whom Initial Pharmacotherapy Was Ineffective

Given the renewed interest in treatment of AF with rate-control therapies, it is somewhat surprising how few studies compared the effectiveness of different rate-control strategies. Further study is needed to evaluate AVN (or His bundle) ablation with pacemaker placement as well as specific rate-control agents for rate control and symptom management for patients who cannot tolerate pharmacological therapies. AVN ablation with pacemaker placement needs to be studied further regarding its effects on patients with different duration and type of AF or underlying conditions such as heart failure. Further study is also needed to compare additional pacing strategies and the use of concomitant biventricular pacing. The timing of AVN ablation and pacemaker implantation needs to be better defined, given that this procedure is one of last resort in patients with AF. All of the above treatment strategies should be evaluated in subgroups of interest such as sex, age, left ventricular function, and other comorbidities. In addition, further studies are needed to determine if treatment outcomes vary in patients with different types of AF.

KQ 4. Research Gaps: Antiarrhythmic Drugs and Electrical Cardioversion for Conversion to Sinus Rhythm

Although 42 studies evaluated different approaches to cardioversion, the treatment arms were highly divergent and outcomes of interest were not reported for specific subgroups. Therefore, future research in this area needs to focus on subgroups of interest—in particular, patients with underlying heart disease or heart failure. Differences in the comparative effectiveness of such treatments may also exist by sex, race, or age of patients. In addition, further research is needed to determine the most appropriate subsequent treatment step following a failed electrical cardioversion. A specific area for future research would be to explore the risk for proarrhythmias, especially in women (and particularly with certain medications such as dofetilide).

KQ 5. Research Gaps: Rhythm-Control Procedures and Drugs for Maintenance of Sinus Rhythm

Despite the large number of trials, there is a need for further study to determine the comparative effectiveness of these procedures on longer term outcomes, including mortality, the occurrence of stroke, heart failure, and quality of life. It is not clear if certain procedures achieve better outcomes in subgroups of patients, based either on underlying cardiac characteristics or

duration or type of AF. It is also not clear if anticoagulation can be stopped safely after rhythm control has been achieved or the best timing for stopping anticoagulation.

Although there are numerous drug therapies available for rhythm control of AF, the included RCTs all compared different combinations of drugs, limiting our ability to synthesize results. In addition, most studies of drug therapies reported only outcomes related to rhythm control; fewer reported long-term outcomes or complications related to therapy. Future studies are needed to compare the effectiveness of the most commonly used agents for rhythm control, and future studies are needed to evaluate longer term outcomes, including mortality, heart failure, and quality of life as well as adverse effects, particularly for agents such as amiodarone that are known to have the potential for significant adverse effects.

KQ 6. Research Gaps: Rate- Versus Rhythm-Control Therapies

While studies have shown that a rate-control strategy is at least as good as a rhythm-control strategy, this may be true only in patients similar to the patients enrolled in the clinical trials—i.e., older patients with no debilitating symptoms due to AF. Studies that focus on younger patients or patients with more symptomatic AF would be of interest. Also, trials evaluating longer term outcomes tended to include pharmacological agents, particularly for rhythm control. Few studies compared rate-control therapies with procedural-based rhythm-control therapies. These newer procedural-based rhythm-control therapies should be compared with rate-control therapies for longer term outcomes, including mortality, cardiac events, and stroke, as well as for adverse effects.

Conclusions

In assessing clinical outcomes associated with rate- versus rhythm-control strategies, our review of recent evidence agrees with prior reviews demonstrating little overall difference in outcomes between these two strategic approaches. However, it is important to acknowledge that these studies have focused primarily on a subset of patients with AF (typically older patients with fewer symptoms), and differences between the strategic approaches in other patients are largely unknown. In addition, there is a wide range of options within each strategic approach. Very few studies evaluated the comparative safety and effectiveness of specific rate-control drugs or procedures, especially within specific subgroups of patients who are likely to be encountered in clinical practice (such as those with heart failure). In addition, very few studies were done to assess outcomes associated with strict versus more lenient rate-control targets. The wide variety of rhythm-control drugs and procedures also posed a challenge to quantitative assessments of the comparative safety and effectiveness of these different drugs and procedures. Importantly, the review highlights the need for more data on the effect of these procedures on final outcomes such as mortality, stroke, and cardiovascular hospitalizations.

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Introduction

Background

Definition and Impact of Atrial Fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia (any tachycardic rhythm originating above the ventricular tissue) and is characterized by uncoordinated atrial activation with consequent deterioration of mechanical function.[1] Although the type of AF can change over time, it is often helpful to characterize it at a given moment, as this may guide treatment. Types of AF include first-detected, paroxysmal (arrhythmia terminates spontaneously within 7 days), persistent (arrhythmia is sustained beyond 7 days), long-standing persistent (usually lasting for more than 1 year), and permanent AF (in which cardioversion has failed or has not been attempted).[1]

It is estimated that more than 2.3 million Americans have AF.[2] The prevalence of AF increases with age and approaches 8 percent in patients older than 80 years of age.[3] As such, AF is the most common sustained arrhythmia seen in clinical practice. AF affects men and women equally; however, approximately 60 percent of patients older than 75 years of age are female.[1]

The impact of AF is compounded by its known association with significant mortality, morbidity, and health care costs. Not only is the risk of death in patients with AF twice that of patients without AF, but AF can result in myocardial ischemia or even infarction, heart failure exacerbation, and tachycardia-induced cardiomyopathy if the ventricular rate is not well-controlled.[4-7] In some patients, AF can severely depreciate quality of life by causing shortness of breath, intractable fatigue, and near-syncope.[8-11] However, the most dreaded complication of AF is thromboembolism, especially stroke. The risk of stroke in patients with AF is up to 8 percent per year, depending on the presence of stroke risk factors.[12] Importantly, when ischemic stroke occurs in patients with AF, it is either fatal or of moderate to high severity in the majority of patients.[13] The management of AF and its complications is responsible for almost $16 billion in additional costs to the U.S. health care system each year.[14]

This substantial public health impact of AF in the United States led the Institute of Medicine (IOM) to designate AF as one of the top priority areas for comparative effectiveness research. Specifically, the IOM called upon researchers to compare the effectiveness of treatment strategies for AF, including surgery, catheter ablation, and pharmacological treatment.[15]

Treatment Strategies

Management of AF involves three distinct areas, namely, rate control (treatments to slow the heart rate to a normal range), rhythm control (treatments to revert the heart rhythm back to normal), and prevention of thromboembolic events. This comparative effectiveness review (CER) covers the first two areas. A separate CER focusing on the prevention of thromboembolic events is being conducted in parallel, also commissioned through the Agency for Healthcare Research and Quality's (AHRQ's) Evidence-based Practice Center (EPC) Program.

Rate Control

Whether or not a rhythm-control strategy is adopted, current treatment guidelines suggest that adequate rate control should be achieved in all patients with AF to prevent myocardial

infarction (if significant coronary artery disease is present), exacerbation of heart failure, and tachycardia-induced cardiomyopathy; to alleviate symptoms; and to improve exercise tolerance and quality of life. Thus, the 2006 Guidelines for the Management of Patients with Atrial Fibrillation—prepared jointly by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC)—highlight the need for adequate rate control in patients with AF and designate measurement of the heart rate at rest and control of the rate with pharmacological agents (either a beta blocker or a nonhydropyridine calcium channel blocker in most patients) as a Class I recommendation (condition for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective).[14] However, since the development of the ACC/AHA/ESC Guidelines, many additional studies have been published on the comparative safety and effectiveness of the different available medications used for ventricular rate control in clinical practice. Thus, an updated review of published studies is timely.

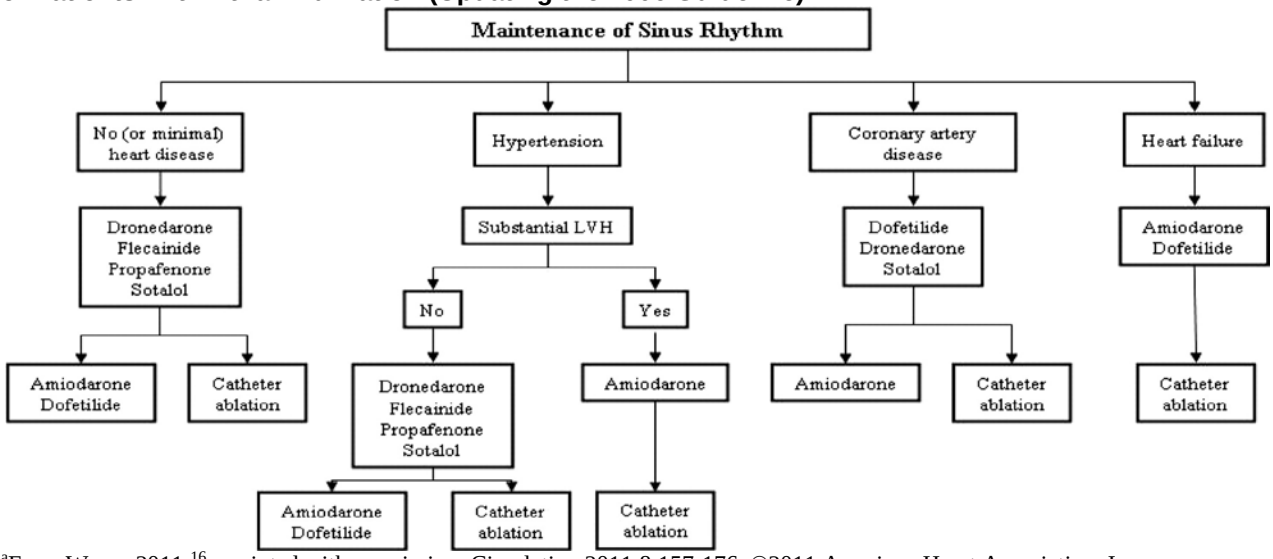
If pharmacological therapy is insufficient for rate control and symptom management, or is associated with side effects, the 2006 ACC/AHA/ESC Guidelines recommend ablation of the atrioventricular node (AVN) in conjunction with permanent pacemaker implantation to control heart rate.[14] As the latter involves implantation of an indwelling device that is not reversible, it is considered a treatment of last resort for patients for whom initial pharmacotherapy was ineffective. However, the most recent systematic review on this topic was published more than a decade ago. This review will synthesize the evidence that has been published since then to better define the role of this procedure in contemporary clinical practice and in specific subpopulations where it might be more or less effective.

Another clinical dilemma is whether patients with AF do better with strict or lenient rate control. In theory, strict control could reduce symptoms and prevent complications. However, stricter control requires more intensive use of medications which carry their own side effects. The 2011 Focused Update on the Management of Patients with Atrial Fibrillation by the American College of Cardiology Foundation (ACCF), the AHA, and the Heart Rhythm Society (HRS) addressed the issue of strict versus lenient rate control in patients with AF.[16] Specifically, these guidelines emphasized the following Class III recommendation (conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful): "Treatment to achieve strict rate control of heart rate (<80 bpm at rest or <110 bpm during a 6-minute walk) is not beneficial compared to achieving a resting heart rate <110 bpm in patients with persistent AF who have stable ventricular function (left ventricular ejection fraction >0.40) and no or acceptable symptoms related to the arrhythmia."[16] This recommendation was based on the results of the Rate Control Efficacy in Permanent Atrial Fibrillation-II (RACE-II) trial,[17] which showed that lenient rate control (defined in RACE-II as resting heart rate <110 beats per minute [bpm]) is as effective as strict rate control (defined as resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm) and is easier to achieve.[17] Because of some of the study's limitations (e.g., low prevalence of patients with concomitant heart failure, only 75% success rate at achieving targeted heart rate control in the strict control arm, relatively small sample size, enrollment of primarily low-risk patients, and lack of inclusion of more sedentary patients), the applicability of its findings to the broader AF population is uncertain; therefore, this review will examine all available evidence on strict versus lenient rate control.

Rhythm Control

If patients with AF continue to have significant symptoms despite adequate rate control through either pharmacological therapy or AVN ablation, then a rhythm-control strategy (either pharmacological or electrical) is currently recommended. For pharmacological cardioversion of AF, the 2006 ACC/AHA/ESC Guidelines recommend flecainide, dofetilide, propafenone, and ibutilide as Class I recommendations, and amiodarone as a Class IIa recommendation (weight of evidence/opinion is in favor of usefulness/efficacy).[14] To enhance direct-current cardioversion, the 2006 ACC/AHA/ESC Guidelines recommend pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol. For maintenance of sinus rhythm after cardioversion, the 2006 ACC/AHA/ESC Guidelines list different antiarrhythmic medications for different clinical settings. The 2011 ACCF/AHA/HRS Focused Update builds upon the recommendations in the 2006 ACC/AHA/ESC Guidelines using published data on new antiarrhythmic medications. Guideline recommendations from the 2011 Focused Update are depicted in Figure 1;[16] however, which of these medications is best for which patients is uncertain. Therefore, this report will review existing evidence and summarize current evidence gaps on the comparative safety and effectiveness of available antiarrhythmic agents for conversion of AF to sinus rhythm, for facilitating successful electrical cardioversion, and for maintaining sinus rhythm after successful conversion of AF to sinus rhythm.

Figure 1. Recommendations for maintenance of sinus rhythm in patients with recurrent paroxysmal or persistent AF from the 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline)[a]



[a]From Wann, 2011;[16] reprinted with permission, Circulation.2011;8:157-176, ©2011 American Heart Association, Inc.
Abbreviations: ACCF=American College of Cardiology Foundation; AHA=American Heart Association; HRS=Heart Rhythm Society; LVH=left ventricular hypertrophy

In addition to pharmacological and direct current cardioversion, a number of surgical interventions are used for rhythm control. Catheter ablation for the treatment of AF (with pulmonary vein isolation [PVI] being the most commonly used ablation) has evolved rapidly from an experimental procedure to a commonly performed procedure that is widely regarded as a useful treatment option for symptomatic patients with AF in whom medications are not effective or not tolerated.[14,16,18]

Many studies have provided information on the safety and efficacy of catheter ablation of AF. These studies vary from small and large single-center nonrandomized studies to multicenter prospective randomized controlled trials (RCTs). However, the relatively small number of patients included in each trial makes definitive conclusions about the safety and efficacy of pulmonary vein isolation based on an individual study difficult and does not permit meaningful analyses of key subgroups of patients (e.g., older patients, patients with heart failure). Although the ongoing Catheter Ablation vs. Antiarrhythmic Drug Therapy for AF (CABANA) study will provide important information on the effect of catheter ablation on final outcomes, this trial is not expected to end until several years from now.[18] The present review will increase the power of existing studies by synthesizing the evidence on this procedure by pooling data from existing studies and by exploring whether other types of studies or comparative effectiveness research would be helpful.

Several other procedures have been investigated in the treatment of AF. One such procedure is the surgical Maze procedure, which appears to confer some benefit to selected patients with AF.[19] Implantation of a cardiac resynchronization therapy (CRT) device is another procedure that may decrease the burden of AF in patients who are eligible for this device based on a left ventricular ejection fraction ≤35 percent, a wide QRS complex, and heart failure symptoms despite optimal medical therapy. Secondary analyses of major clinical trials have provided conflicting findings on the effect of CRT on AF burden.[20,21] This report will review and synthesize current published data on these novel procedures and will help to better define their risks and benefits in contemporary clinical practice.

Rate Control Versus Rhythm Control

Although several studies of rate- and rhythm-control strategy exist, to date no study has shown that maintaining patients with AF in sinus rhythm provides a long-term survival benefit. We also do not know whether the risks and benefits of different therapies vary by AF type. Our review seeks to systematically review the comparative risks and benefits of specific outcomes to allow patients and providers to assess the patient-specific tradeoffs of the differing strategies.

Scope and Key Questions

Scope of the Review

This CER was funded by AHRQ and is designed to evaluate the comparative safety and effectiveness of a wide range of pharmacological and procedural rate- and rhythm-control strategies for the treatment of adult patients with paroxysmal, persistent, or permanent AF (includes atrial flutter). To increase applicability to the U.S. setting, our review is restricted to interventions available in the United States.

Rate-control and rhythm-control strategies for patients with AF have been evaluated in numerous studies. Despite these studies, several uncertainties remain, and comparative safety and effectiveness analyses of the available management strategies for patients with AF are needed. Existing systematic reviews of the evidence either do not include the most recent clinical evidence or are inconclusive; moreover, for some important clinical and policy questions of interest, systematic reviews have not yet been performed. This new review of the available data not only addresses existing uncertainties, but also defines gaps in knowledge and identifies future research needs.

Key Questions

With input from our Key Informants, we constructed KQs using the general approach of specifying the Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods chapter for details).

The first three KQs considered in this CER focus on rate-control therapies. Specifically:

- **KQ 1:** What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 2:** What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 3:** What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients with atrial fibrillation for whom initial pharmacotherapy was ineffective? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

The next two KQs focus specifically on rhythm-control therapies:

- **KQ 4:** What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 5:** What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents (either separately or in combination with each other) for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

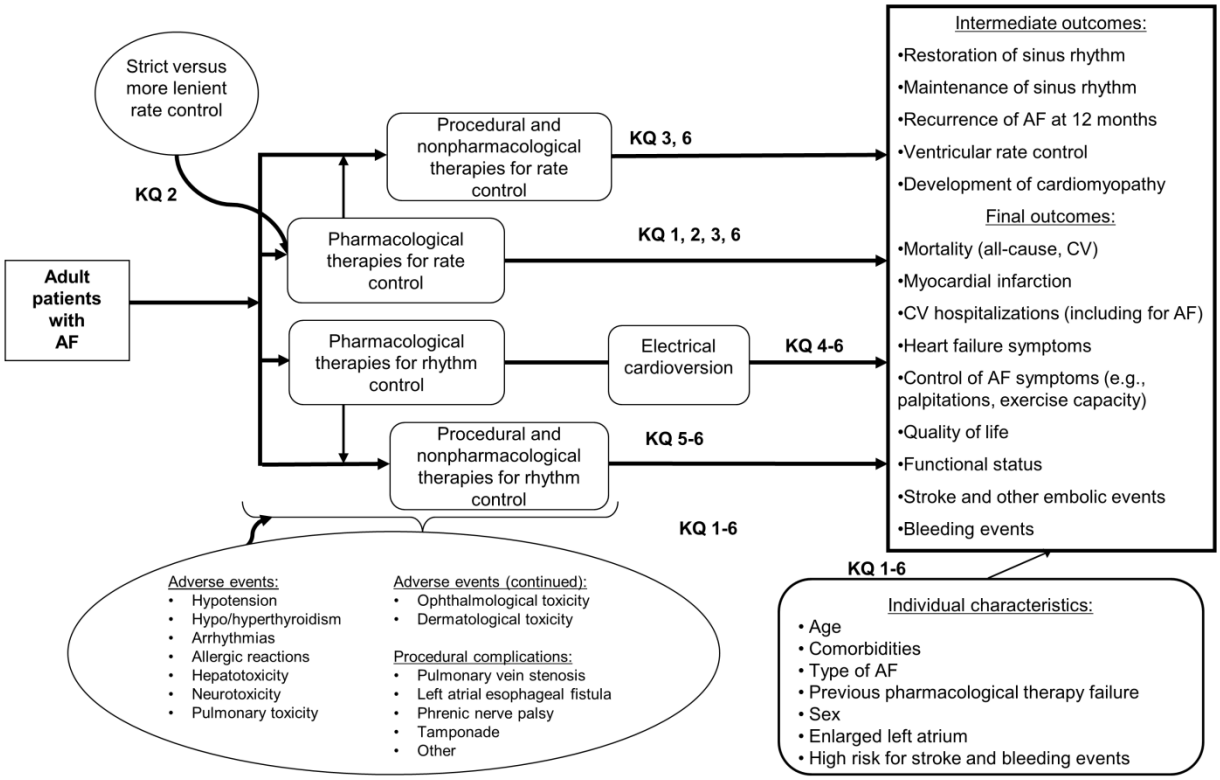
The final KQ seeks to evaluate the comparison of the available rate- and rhythm-control therapies.

- **KQ 6:** What are the comparative safety and effectiveness of rate-control therapies versus rhythm-control therapies in patients with atrial fibrillation? Does the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Analytic Framework

Figure 2 depicts the analytic framework for this project.

Figure 2. Analytic framework



Abbreviations: AF=atrial fibrillation; CV=cardiovascular; KQ=Key Question

This figure depicts the KQs within the context of the PICOTS described elsewhere in this document. The patient population of interest is adults with AF. Interventions of interest are procedural and nonpharmacological therapies for rate control (KQs 3 and 6), pharmacological therapies for rate control (KQs 1, 2, 3, and 6), pharmacological therapies for rhythm control (KQs 4, 5, and 6), electrical cardioversion (KQs 4, 5, and 6), and procedural and nonpharmacological therapies for rhythm control (KQs 5 and 6). Strict versus more lenient pharmacological therapies for rate control are considered in a separate question (KQ 2). Intermediate outcomes of interest are restoration of sinus rhythm, maintenance of sinus rhythm, recurrence of AF at 12 months, ventricular rate control, and development of cardiomyopathy. Final outcomes of interest are mortality (all-cause and cardiovascular), myocardial infarction, cardiovascular hospitalizations (including AF hospitalizations), heart failure symptoms, control of AF symptoms (e.g., palpitations, exercise capacity), quality of life, functional status, stroke and other embolic events, and bleeding events. Also of interest are the following adverse events associated with pharmacological treatment: hypotension, hypo/hyperthyroidism, arrhythmias, allergic reactions, hepatotoxicity, neurotoxicity, pulmonary toxicity, ophthalmological toxicity, and dermatological toxicity. Procedural complications of interest include pulmonary vein stenosis, left atrial esophageal fistula, phrenic nerve palsy, cardiac tamponade, and other complications (such as infection, bleeding, and thromboembolic events). For all six KQs, we will attempt to determine whether the comparative safety and effectiveness of the various therapies investigated differ among specific patient subgroups of interest. Patient characteristics to be assessed here include age, comorbidities, type of AF, previous pharmacological therapy failure, sex, enlarged left atrium, and high risk for stroke and bleeding events.

Methods

The methods for this comparative effectiveness review (CER) follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[22] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[23]

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of general internal medicine, geriatrics, cardiology, electrophysiology, and primary care; patients; scientific experts; Federal agencies; and payers to help define the Key Questions (KQs). The KQs were then posted for public comment for 4 weeks from September 27 to October 25, 2011, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input to the draft protocol in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search.[24] Before involvement in the CER process, the Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report.

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies published from January 1, 2000, to August 1, 2012. We believe that the evidence published from 2000 on represents the current standard of care for patients with atrial fibrillation (AF) and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000.[25-27] Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian guided all searches. Exact search strings are included in Appendix A. We supplemented the electronic searches with a manual search of citations from a set of key primary and systematic review articles.[16,19,25-135] We also considered studies identified through suggestions from external peer and public reviewers. Final updating of all database searches was performed during the review period. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We used several approaches to identify relevant grey literature including requests to drug and device manufacturers for scientific information packets and searches of study registries and conference abstracts for relevant articles from completed studies. Grey literature databases searched included ClinicalTrials.gov (final search date August 17, 2012); the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (final

search date August 17, 2012); and ProQuest COS Conference Papers Index (final search date August 1, 2012). Search terms used for all of the above sources are provided in Appendix A.

Inclusion and Exclusion Criteria

The PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 1.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria

Populations	• Humans
	• Adults (age ≥ 18 years of age)
	• Patients with AF (includes atrial flutter)
	  o Paroxysmal AF (recurrent episodes that self-terminate in less than 7 days)
	  o Persistent AF (recurrent episodes that last more than 7 days)
	  o Permanent AF (an ongoing, long-term episode)
	• Subgroups of potential interest include:
	  o Patients stratified by age (≤ 40, 41–64, 65–74, 75–84, 85+)
	  o Patients with different types of AF (paroxysmal, persistent, permanent)
	  o Patients with specific comorbidities (heart failure, coronary artery disease, kidney disease, hypertrophic cardiomyopathy, thyroid disease, pulmonary disease)
	  o Patients for whom a prior rate- (KQ 3) or rhythm-control (KQ 5) pharmacological strategy was ineffective
	  o Women
	  o Patients with an enlarged left atrium
	  o Patients at high risk for stroke and bleeding events (patients with diabetes, heart failure, and hypertension)
		• Patients who have known reversible causes of AF (including but not limited to postoperative, postmyocardial infarction, hyperthyroidism)
		• All subjects are <18 years of age, or some subjects are under <18 years of age but results are not broken down by age

Table 1. Inclusion and exclusion criteria (continued)

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Interventions	• Pharmacological agents for rate control (KQ 1, KQ 2, KQ 3, KQ 6): o Beta blockers (e.g., acebutolol, atenolol, bisoprolol, carvedilol, esmolol [acute rate lowering only], metoprolol, nadalol, nebivolol, timolol) o Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) o Other (digoxin, amiodarone, dronedarone) • Procedures for rate control (KQ 3, KQ 6) o AVN ablation and permanent pacemaker implantation • Pharmacological agents for rhythm control (KQ 4, KQ 5, KQ 6): o Amiodarone o Disopyramide o Dofetilide o Dronedarone o Flecainide o Ibutilide (acute conversion only) o Propafenone o Sotalol o Beta blockers (e.g., acebutolol, atenolol, bisoprolol, carvedilol, esmolol [acute rate lowering only], metoprolol, nadalol, nebivolol, timolol) o Calcium channel blockers (verapamil, diltiazem) • Procedures for rhythm control (KQ 5, KQ 6) o Electrical cardioversion o AF ablation by pulmonary vein isolation ▪ Open surgical procedures ▪ Minimally invasive procedures ▪ Transcatheter procedures o Surgical Maze procedure o Cardiac resynchronization therapy	• Studies comparing different imaging or mapping techniques (focus is on comparisons between treatment strategies) • Studies of intracardiac echocardiography, different ablation sources and energies, different techniques of septal puncture, and different diagnostic maneuvers during an ablation procedure • Studies of atrial flutter ablation, ablation for post-pulmonary vein isolation tachycardias including atrial flutter, and studies of internal cardioversion, transesophageal cardioversion and patient-enabled cardioversion using an ICD • Studies investigating use of antiarrhythmic drugs periablation or after failed pulmonary vein isolation • Studies of any intervention not available in the U.S., including intravenous formulations of medications that are available in the U.S. only in an oral form • Studies with a majority of patients taking an antiarrhythmic drug not specified as an intervention of interest, unless the study includes a comparison between a drug of interest and a control arm
Comparators	• KQ 1: Other rate-control pharmacological agents of interest • KQ 2: Other strict/lenient rate-control strategies of interest • KQ 3: Other procedural, nonpharmacological, and other specific pharmacological rate-control therapies of interest • KQ 4: Other antiarrhythmic agents of interest • KQ 5: Other procedural, nonpharmacological, and other specific pharmacological rhythm-control therapies of interest • KQ 6: Other rhythm-control or rate-control therapies of interest	None

Table 1. Inclusion and exclusion criteria (continued)

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Outcomes	Study assesses a patient-centered outcome of interest: • Intermediate outcomes: o Restoration of sinus rhythm (conversion) o Maintenance of sinus rhythm o Recurrence of AF at 12 months o Ventricular rate control o Development of cardiomyopathy • Final outcomes:[a] o Mortality (all-cause, cardiovascular) o Myocardial infarction o Cardiovascular hospitalizations (including AF hospitalizations) o Heart failure symptoms o Control of AF symptoms (e.g., palpitations, exercise capacity) o Quality of life o Functional status o Stroke and other embolic events o Bleeding events • Adverse events: o Adverse events from drug therapies (e.g., hypotension, hypothyroidism and hyperthyroidism, arrhythmias [bradyarrhythmias, tachyarrhythmias, or proarrhythmias], allergic reactions, hepatotoxicity, neurotoxicity, pulmonary toxicity, ophthalmological toxicity, dermatological toxicity) o Procedural complications (including pulmonary vein stenosis, left atrial esophageal fistula, and phrenic nerve palsy)	Study does not include any outcomes of interest
Timings	• Timing of followup not limited	None
Settings	• Inpatient and outpatient	None
Study designs	• Original data • KQ 1: RCTs (≥ 20 patients) • KQ 2: RCTs (≥ 20 patients) and prospective and retrospective observational studies or registries (≥ 100 patients) • KQ 3: RCTs (≥ 20 patients) • KQ 4: RCTs (≥ 20 patients) • KQ 5: RCTs (≥ 20 patients) and (for studies related to CRT) prospective and retrospective observational studies or registries (≥ 100 patients) • KQ 6: RCTs (≥ 20 patients)	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	• English-language publications only • Relevant systematic reviews, meta-analyses, or methods articles (used for background only)[b] • Published on or after January 1, 2000	• Non-English-language publications[c]

[a]Final outcomes are direct health outcomes that a patient experiences or feels.
[b]Systematic reviews and meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional citations to consider in the review. Articles providing methods information only (i.e., not reporting data) were not considered among the formal set of included articles, but were used to supplement the abstractions of the studies they referenced.
[c]Given the high volume of literature available in English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to settings in the United States, non-English articles were excluded.
Abbreviations: AF=atrial fibrillation; AVN=atrioventricular node; CRT=cardiac resynchronization therapy; KQ=Key Question; ICD=implantable cardioverter defibrillator; PICOTS=Populations, Interventions, Comparators, Outcomes, Timing, Settings; RCTs=randomized controlled trials

Study Selection

Using the prespecified inclusion and exclusion criteria described in Table 1, two investigators independently reviewed titles and abstracts for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to "include" or "exclude" the article for data abstraction. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching.

For citations retrieved by searching the grey literature, the above-described procedures were modified such that a single screener initially reviewed all search results; final eligibility of citations for data abstraction was determined by duplicate screening review. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, ON, Canada).

Data Extraction

The research team created data abstraction forms and evidence table templates for abstracting data for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer's opinion if consensus could not be reached. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR database.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We paid particular attention to describing the details of treatment (e.g., pharmacotherapy dosing, methods of procedural therapies), patient characteristics (e.g., etiology of AF), and study design (e.g., randomized controlled trial [RCT] versus observational) that may be related to outcomes. In addition, we described comparators carefully, as treatment standards may have changed during the period covered by this review. The safety outcomes were framed to help identify adverse events, including those from drug therapies (e.g., hypotension; hypothyroidism and hyperthyroidism; arrhythmias [bradyarrhythmias, tachyarrhythmias, or proarrhythmias]; allergic reactions; hepatotoxicity; neurotoxicity; pulmonary toxicity) and those resulting from procedural complications. Data necessary for assessing quality and applicability, as described in the Methods Guide,[22] were abstracted. Before the data abstraction form templates were used, they were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency/reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Some outcomes were reported only in figures. In these instances, we used the web-based software, EnGauge Digitizer (http://digitizer.sourceforge.net/) to convert graphical displays to numerical data. Appendix B provides a detailed listing of the elements included in the data abstraction forms.

Quality (Risk of Bias) Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[22] To assess quality, we used the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. We applied criteria for each study type derived from core elements described in the Methods Guide. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, and differential loss to followup between the compared groups or overall high loss to followup. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling for confounding were considered. To indicate the summary judgment of the quality of individual studies, we used the summary ratings of good, fair, or poor based on the classification scheme presented in Table 2.

Table 2. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Studies of different designs were graded within the context of their respective designs. Thus, RCTs were graded good, fair, or poor, and observational studies were separately graded good, fair, or poor.

Data Synthesis

We began our data synthesis by summarizing key features of the included studies for each KQ: patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes.

We grouped interventions by drug class; in this context, we considered all nondihydropyridine calcium channel blocker drugs to be similar enough to be grouped together and all beta blocker drugs to be similar enough to be grouped together. Similarly, we categorized procedures into electrical cardioversion, atrioventricular node (AVN) ablation, AF ablation by pulmonary vein isolation (either open surgical, minimally invasive, or transcatheter procedures), and surgical Maze procedures, and explored comparisons among these categories. For the KQs focusing on pharmacological agents versus procedures (KQ 3 and KQ 5), we also explored grouping all pharmacological agents together and comparing them to all procedures. Finally for

our evaluation of rate- versus rhythm-control strategies (KQ 6), we grouped all rate-control strategies together and all rhythm-control strategies together regardless of the specific agent or procedure.

We determined the appropriateness of a quantitative synthesis (i.e., meta-analysis) based on the volume of relevant literature, conceptual homogeneity of the studies in terms of study population and outcomes, and completeness of the reporting of results. Where at least three comparable studies reported the same outcome, we used random-effects models to synthesize the available evidence quantitatively using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we also performed fixed-effect meta-analyses. We present summary estimates, standard errors, and confidence intervals in our data synthesis. Unless noted otherwise, when we were able to calculate odds ratios (ORs), we assumed that an OR between 0.9 and 1.1, with a confidence interval that also crossed 1.0, suggested that there was no clinically significant difference between treatment strategies; in such cases, we describe the treatment strategies being compared as having "comparable efficacy." For some outcomes, study quality or other factors affected comparability; these exceptions are explained on a case-by-case basis.

We anticipated that intervention effects might be heterogeneous. We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation would be associated with the intervention effects. Where there were sufficient studies, we performed subgroup analyses and/or meta-regression analyses to examine these hypotheses.

Strength of the Body of Evidence

We rated the strength of evidence for each KQ and outcome using the approach described in the Methods Guide.[22,136] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision (Table 3).

Table 3. Strength of evidence—required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates

Abbreviation: RCT=randomized controlled trial

Additional domains were used when appropriate: strength of association (magnitude of effect) and publication bias (as assessed through a search of ClinicalTrials.gov). These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of

evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. This four-level rating scale consists of the following definitions:

- **High—**High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate—**Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low—**Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient—**Evidence either is unavailable or does not permit estimation of an effect.

Applicability

We assessed applicability across the KQs using the method described in the Methods Guide.[22,137] In brief, we used the PICOTS format to organize information relevant to applicability. The most important applicability issue is whether the outcomes observed in any individual study, with its specific patient population and method of implementing treatments, can confidently be extrapolated to a broader context. Differences in study population characteristics (e.g., age, comorbidities) or methods of implementing interventions can affect the rates of events observed in both control and intervention groups and may limit the generalizability of the findings. Specific criteria considered in applicability assessments are listed in Appendix B. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, the possibility of surgical learning curves, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Peer Review and Public Commentary

Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in general cardiology, heart failure, electrophysiology, ablation, cardioversion, cardiac resynchronization therapy (CRT), cardiothoracic surgery, pharmacological treatments for AF, geriatrics, health services research, and primary care, along with individuals representing stakeholder and user communities, were invited to provide external peer review of the draft report. AHRQ, an associate editor, and members of the TEP also provided comments. In addition, the draft report was posted on AHRQ's Web site for public comment for 4 weeks, from July 27, 2012, to August 24, 2012. We have addressed all reviewer comments, revising the text as appropriate, and have documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final report on AHRQ's Web site. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.

Results

Introduction

In what follows, we begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each of the six KQs, we begin by listing the key points of the findings, followed by a brief description of included studies and a detailed synthesis of the evidence. The detailed syntheses are organized first by treatment comparison and then by outcome. We conducted quantitative syntheses where possible, as described in the Methods chapter.

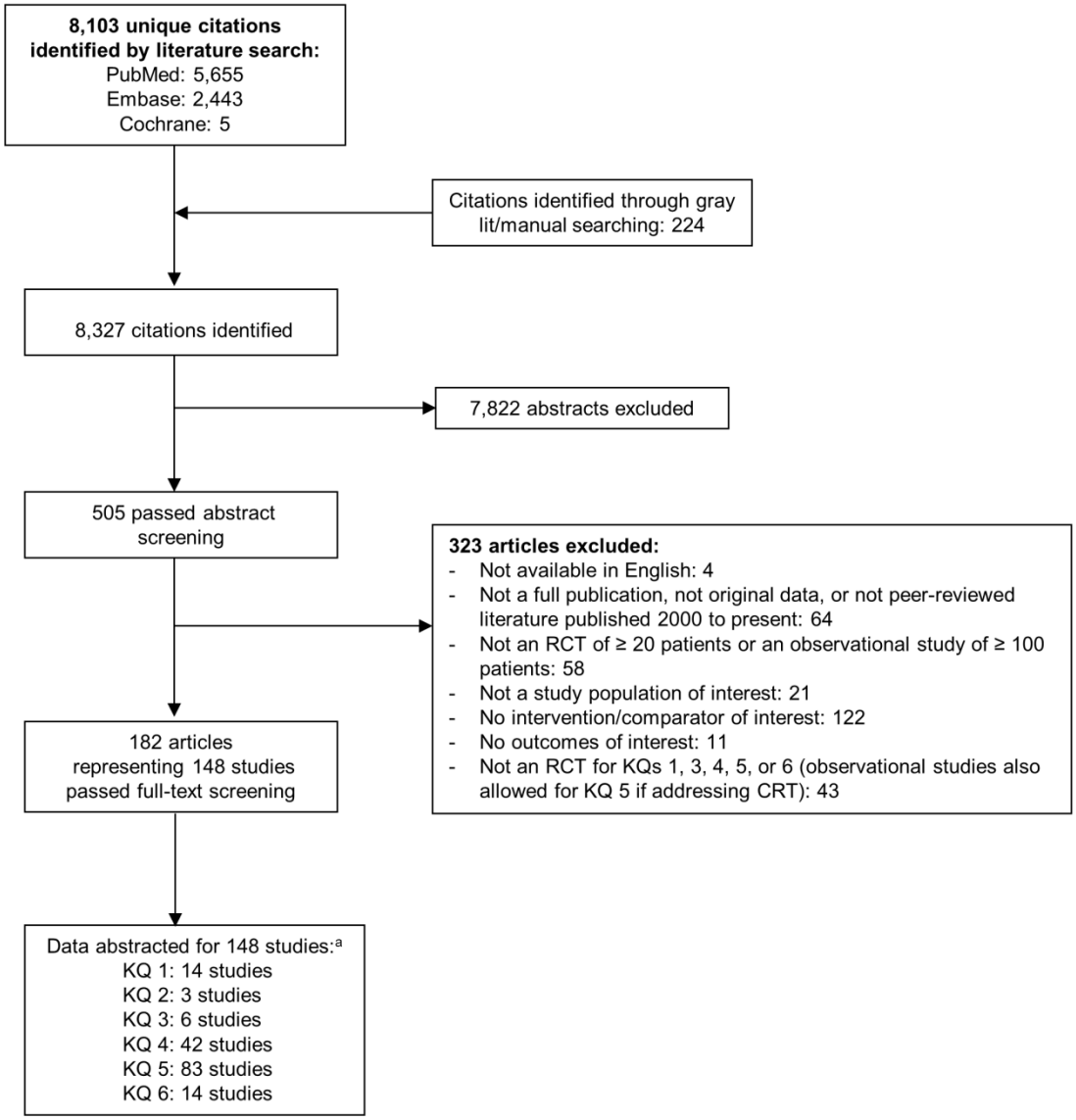
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 3 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and CDSR yielded 8,103 unique citations. Manual searching of grey literature databases, bibliographies of key articles, and information received through requests for scientific information packets identified 224 additional citations, for a total of 8,327 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 505 full-text articles were retrieved and screened. Of these, 323 were excluded at the full-text screening stage, leaving 182 articles for data abstraction. These 182 articles described 148 unique studies. The relationship of studies to the review questions is as follows: 14 studies relevant to KQ 1, 3 studies relevant to KQ 2, 6 studies relevant to KQ 3, 42 studies relevant to KQ 4, 83 studies relevant to KQ 5, and 14 studies relevant to KQ 6 (some studies were relevant to more than one KQ).

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix E provides a "study key" table listing the primary and companion publications for the 148 included studies.

Figure 3. Literature flow diagram



[a]Some studies were relevant to more than one KQ.
Abbreviations: CRT=cardiac resynchronization therapy; KQ=Key Question; RCT=randomized controlled trial

Description of Included Studies

Overall, we included 148 studies represented by 182 publications: 14 studies were relevant to KQ 1, 3 studies to KQ 2, 6 studies to KQ 3, 42 studies to KQ 4, 83 studies to KQ 5, and 14 studies to KQ 6. Studies were conducted wholly or partly in continental Europe (57%), the United States or Canada (22%), the UK (10%), Asia (9%), South America (5%), Australia or New Zealand (3%), and other locations (7%). Further details on the studies included for each KQ are provided in the relevant results sections, below, and in Appendix F.

We searched the ClinicalTrials.gov registry of clinical studies as a mechanism for ascertaining publication bias by identifying studies that have been completed but are as yet unpublished. We acknowledge that this is not an exhaustive strategy, as several other registries

also exist with differing geographical focus and varying degrees of overlap in their trial listings; however, in the opinion of the investigators, the widely used, U.S.-based ClinicalTrials.gov registry provided the most relevant information to the populations and interventions of interest in this review. Our search yielded 610 trial records; a single reviewer identified 77 of these records as potentially relevant to the review. Of these 77 records, 34 had expected completion dates 1 year or more prior to our search. From that group of 34 trials, we identified publications for 23. Of the remaining 11 trials for which we did not identify publications, 1 was considered potentially relevant to KQ 1, and 10 were potentially relevant to KQ 5.

The one unpublished study potentially relevant to KQ 1 was designed to compare the effects of metoprolol, verapamil, diltiazem, and carvedilol on ventricular rate, working capacity, and quality of life in 80 patients. In comparison, the 14 studies relevant to KQ 1 included in this review provide data for 1,017 patients.

Of the 10 unpublished studies potentially relevant to KQ 5, 8 addressed procedural interventions and 2 compared procedural interventions with medical management. One of the completed studies represents the pilot portion of the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, which has now moved forward to begin the full-scale trial phase of 3,000 patients comparing ablation to pharmacological therapies for rate and/or rhythm control. In total, data from these 10 unpublished trials could potentially provide additional evidence on the comparative safety and effectiveness of rhythm-control procedures for up to 1,374 patients. By contrast, 83 studies included for KQ 5 involved 11,014 patients.

In summary, because of the relatively low proportion of unpublished studies identified through our ClinicalTrials.gov registry analysis, we do not believe these findings indicate significant publication bias in the evidence base that would impact our overall conclusions.

Key Question 1. Rate-Control Drugs

KQ 1. What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Key Points

- Based on 3 studies (2 good, 1 fair quality) involving 271 patients, evidence suggests that amiodarone is comparable to the calcium channel blocker diltiazem for rate control (low strength of evidence).
- Based on 3 studies (2 good, 1 fair quality) involving 390 patients, evidence suggests that amiodarone provides better rate control than digoxin (low strength of evidence).
- Based on 4 studies (1 good, 3 fair quality) involving 422 patients, evidence suggests that the calcium channel blockers verapamil and diltiazem provide better rate control than digoxin (high strength of evidence).
- Many outcomes/comparisons were rated to have insufficient strength of evidence. These include improvement of AF symptoms in patients receiving combined treatment with carvedilol plus digoxin compared with digoxin alone, rate control in patients using

metoprolol versus diltiazem or sotalol, and the safety of any one pharmacological agent used for ventricular rate control in patients with AF.

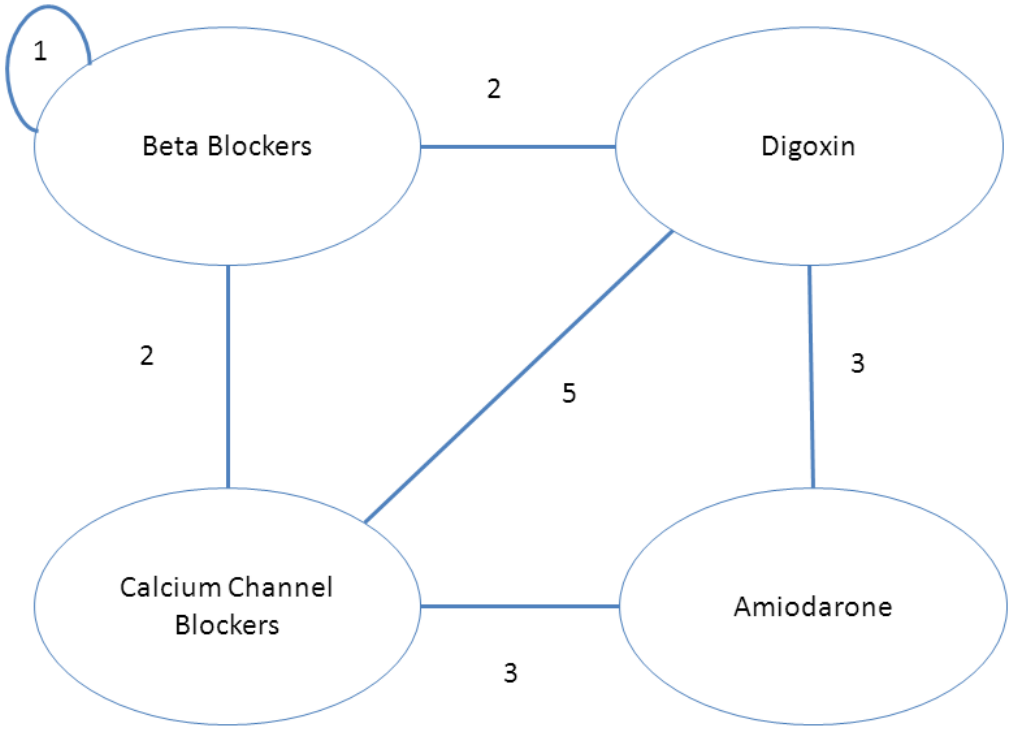
- Data are also insufficient as to whether the safety and effectiveness of these therapies differ among specific patient subgroups of interest.
- Included studies focused on the control of ventricular rate as the outcome of interest; there was no evidence as to the safety and effectiveness of therapies on final outcomes.

Description of Included Studies

A total of 14 RCTs involving 1,017 patients were identified that assessed the use of pharmacological agents for ventricular rate control in patients with AF (Appendix Table F-1). Six studies were considered to be of good quality,[138-143] eight of fair quality,[144-151] and none of poor quality. Thirteen studies were published between 2000 and 2006, and one[143] was published in 2009. Four studies were multicenter[145,147,148,150] and 10 were single-center.[138-144,146,149,151] Only one study included a site in the United States;[151] eight included sites in Europe,[138-140,142,144-147] two included sites in Asia,[143,150] and one each included sites in Canada,[148] the UK,[141] and Australia/New Zealand.[149] The study population consisted entirely of patients with persistent AF in four studies,[141,144,145,147] and entirely of patients with paroxysmal AF in one study.[143] Funding was unclear or not reported in 10 studies.[138-140,142-144,146-148,151] A total of three studies included funding from industry,[141,145,150] two received funding from nongovernment/nonindustry sources,[145,149] and no studies were government-only funded. In eight studies the setting was inpatient: five of these were in emergency rooms,[139,143,148,149,151] and the other three did not include emergency room patients.[138,140,144] In the remaining studies, five were classified as outpatient,[141,142,146,147,150] and in one the setting was unclear.[145] Mean age varied from 63–71.5 years. Most of the studies included patients with no history of heart failure, and the mean ejection fraction varied from 23.7–66 percent. Only a few studies included patients with coronary artery disease.

Figure 4 represents the treatment comparisons evaluated for this KQ.

Figure 4. Overview of treatment comparisons evaluated for KQ 1[a]



[a]Lines running from one oval back to the same oval (e.g., "Beta Blockers" oval) indicate intraclass comparisons (e.g., comparison of one beta blocker drug with another). Numbers refer to numbers of comparisons.
Abbreviation: KQ=Key Question

Two studies compared beta blockers with digoxin,[141,146] one compared beta blockers with calcium channel blockers,[139] and one compared beta blockers with calcium channel blockers in patients using digoxin.[150] One study compared two beta blockers (sotalol and metoprolol) in patients receiving digoxin.[142] Amiodarone was compared with calcium channel blockers in three studies,[138,143,144] and with digoxin in three.[140,143,149] One study evaluated the benefits of adding calcium channel blockers to digoxin compared with digoxin alone,[151] and four studies compared calcium channel blockers with digoxin.[143,145,147,148] Note that although amiodarone and sotalol are evaluated under this KQ for their rate-controlling potential, these agents are also potent membrane-active, type III antiarrhythmics, thereby having potential rhythm-control benefits (and risks).

The primary outcome reported for this KQ, assessed in all but one study,[150] was control of ventricular rate.

Detailed Synthesis

Beta Blockers Versus Digoxin

One study compared the beta blocker carvedilol with digoxin in patients with AF and heart failure.[141] The mean ejection fraction was 24 percent, and the study duration was 6 months. The combination of digoxin plus carvedilol was superior to digoxin alone for rate control at 4 months (65.2 bpm vs. 74.9 bpm; $p<0.0001$). After 4 months, digoxin was stopped in the combined arm and carvedilol alone was compared with digoxin alone. At 6 months, there was no difference in rate control between digoxin alone and carvedilol alone (75.7 bpm vs. 88.8 bpm; $p=0.13$). The

combination of carvedilol plus digoxin reduced the heart rate through steady-state exercise when compared with digoxin alone (106 bpm vs. 123 bpm; $p<0.05$). Carvedilol alone and digoxin alone were equally effective in controlling heart rate during exercise. Digoxin was more effective than carvedilol in reducing nocturnal heart rate. The improvement of AF symptoms was greater in patients receiving combined treatment with carvedilol plus digoxin than in patients receiving digoxin alone. Three patients receiving carvedilol withdrew from the study due to gastrointestinal disturbance, tiredness, and bronchospasm.

Another study compared the beta blocker sotalol with digoxin in patients with AF at rest and during exercise.[146] The heart rate at rest and at 10 minutes after exercise did not differ between the three groups (sotalol alone, digoxin alone, or combination of digoxin plus sotalol). However, the heart rate during maximal exercise was significantly lower in patients receiving sotalol (either alone or in combination with digoxin) than in patients receiving digoxin alone ($p<0.01$ and $p<0.01$, respectively) suggesting that further study of the impact of sotalol on heart rate may be needed. The heterogeneity in agents, study duration, and findings led us to conclude that the evidence was insufficient to support conclusions about the comparative effectiveness of beta blockers versus digoxin for ventricular rate control.

Beta Blockers Versus Calcium Channel Blockers

The beta blocker metoprolol was compared with the calcium channel blocker diltiazem in patients with AF who presented at the emergency room with heart rate ≥120 bpm in one study.[139] The success rate of ventricular rate control (defined as ventricular rate <100 bpm or decrease in ventricular rate by 20% from baseline and at least less than 120 bpm or conversion to sinus rhythm) at 20 minutes was similar between patients receiving diltiazem and metoprolol (90% vs. 80%; $p>0.05$). However, the success rate of ventricular control at 2 minutes was greater in patients receiving diltiazem than in patients receiving metoprolol (50% vs. 15%; $p<0.05$). The mean percentage decrease in ventricular rate at 2, 5, 10, 15, and 20 minutes were all greater in patients receiving diltiazem (25.6, 30.7, 33.6, 34.5, and 35.9) than in patients receiving metoprolol (17.5, 20.4, 24.3, 25.9, and 28.9). There was no significant difference between the two treatment groups in the decrease of blood pressure, and none of the patients developed hypotension. The small size and quality of the one study, as well as the imprecision of the findings, led us to conclude that the evidence was insufficient to support conclusions about the comparative effectiveness of beta blockers versus calcium channel blockers for ventricular rate control (insufficient strength of evidence)

Beta Blockers Versus Calcium Channel Blockers in Patients Taking Digoxin

One study compared beta blockers (bisoprolol, atenolol, or metoprolol) with the calcium channel blocker verapamil in patients with chronic AF taking digoxin.[150] Two-thirds of the patients using beta blockers were using bisoprolol. When compared with digoxin, beta blockers increased the minimum heart rate and decreased the maximum heart rate (although the changes did not reach statistical significance in either case [$p<0.1$]) and overall did not change the mean heart rate. Verapamil significantly increased the minimum heart rate and mean heart rate when compared with digoxin. Verapamil prolonged exercise duration when compared with digoxin ($p<0.05$), whereas beta blockers did not. Beta blockers did not affect quality of life scores (Medical Outcomes Study 36-Item Short Form Health Survey [SF-36]) when compared with digoxin. Verapamil, however, improved the role function-physical score on the SF-36 and the

variety and frequency of AF symptoms when compared with digoxin. This one study included only 29 patients and was considered to provide insufficient evidence of these conclusions.

Sotalol Versus Metoprolol in Patients Taking Digoxin

One study compared two beta blockers (metoprolol versus sotalol) in patients with chronic AF receiving digoxin.[142] Both beta blocker agents were effective at reducing heart rate at 24 hours. Patients receiving sotalol presented a lower mean heart rate at submaximal exercise than patients receiving metoprolol (116 vs. 125 bpm; $p<0.001$; insufficient strength of evidence). During isometric exercise, similar results were seen where sotalol produced a lower mean maximum heart rate than did metoprolol (113 vs. 129 bpm). Finally, patients receiving sotalol presented a lower mean heart rate than patients receiving metoprolol during the daytime. The QT interval in patients receiving sotalol was longer than in patients receiving metoprolol ($p<0.001$), but no clinical side effects or adverse outcomes were reported or associated with the use of sotalol.

Amiodarone Versus Calcium Channel Blockers

Three studies compared amiodarone with calcium channel blockers.[138,143,144] In the first,[144] both amiodarone and diltiazem significantly reduced the ventricular rate and mean heart rate from baseline to 1 month prior to cardioversion; however, there was no comparison between study arms. In the second study,[138] ventricular rate was compared in patients receiving diltiazem (25 mg IV bolus followed by continuous infusion for 24 hours) and amiodarone for 15 minutes (300 mg in bolus only) and 24 hours (300 mg bolus followed by continuous infusion for 24 hours). The number of patients with >30 percent reduction in heart rate within 4 hours was similar across the three arms (14, 11, and 15, respectively; $p=0.38$). However, the number of patients with a heart rate less than 120 bpm within 4 hours was significantly higher in patients receiving amiodarone in both arms (9 and 1, respectively) when compared with patients receiving diltiazem (0; $p=0.00016$). In the third study, sustained ventricular rate control (<90 bpm) within 24 hours was compared between patients receiving diltiazem or amiodarone.[143] In contrast to the other two studies, patients receiving diltiazem in this third study were more likely to achieve sustained heart rate control (90%) when compared with patients receiving amiodarone (74%; $p=0.047$). The median time to ventricular rate control was also significantly shorter in patients receiving diltiazem (3 hours) than in patients receiving amiodarone (7 hours; $p<0.0001$). Patients receiving diltiazem had lower mean ventricular rate after the first hour of drug administration compared with patients receiving amiodarone ($p<0.05$). Based on these three studies, amiodarone was comparable to the calcium channel blocker diltiazem for rate control, but given the inconsistency and imprecision of these findings, the strength of evidence was reduced (low strength of evidence).

Amiodarone Versus Digoxin

Three studies compared amiodarone with digoxin.[140,143,149] In one,[149] the ventricular heart rate control (<100 bpm) was significantly better with amiodarone than with digoxin at 30 minutes and 3 hours ($p=0.02$ and $p=0.02$, respectively). In the second study,[140] the mean heart rate at 30 minutes was significantly lower in patients receiving amiodarone than in patients receiving digoxin (104 vs. 116 bpm, respectively; $p=0.02$). Similar results were seen at 60 minutes (94 versus 105 bpm, respectively; $p=0.03$). In the third study, sustained ventricular rate (<90 bpm) within 24 hours was compared between patients receiving digoxin or amiodarone.[143]

There was no difference in sustained ventricular rate control between arms (74% vs. 74%). The median time to ventricular rate control was also similar between arms (6 vs. 7 hours, respectively). In summary, based on these three studies, amiodarone controlled ventricular rate better than digoxin, but the inconsistency across studies and the imprecision of these findings reduced the strength of evidence (low strength of evidence).

Calcium Channel Blockers Plus Digoxin Versus Digoxin Alone

The calcium channel blocker diltiazem in combination with digoxin was compared with digoxin alone in patients with AF and rapid ventricular response in one study.[151] Successful rate control was defined as ventricular rate <100 bpm persisting for at least 1 hour or conversion to sinus rhythm. All patients achieved successful rate control at 12 hours. The ventricular rates were comparable in both treatment arms throughout the study period (insufficient strength of evidence). The time taken to achieve successful rate control was shorter in patients receiving diltiazem plus digoxin than in patients receiving digoxin alone although was not statistically significant (p=NS). The loss of rate control in the combination treatment arm was significantly less than in the diltiazem alone arm (14 episodes vs. 39; p=0.05). Among patients with episodes of loss of rate control, the combination treatment caused less loss of rate control when compared with digoxin alone (2 episodes vs. 3.5; p=0.04). The only adverse event observed was an episode of sinus pause for 2.5 seconds in one patient who received the combination treatment.

Calcium Channel Blockers Versus Digoxin

Four studies compared calcium channel blockers with digoxin.[143,145,147,148] In one,[145] verapamil was compared with digoxin in patients undergoing elective cardioversion. At 2 weeks after inclusion, the mean heart rate was comparable between patients receiving verapamil and digoxin (82 vs. 82 bpm). In order to obtain adequate rate control, more patients in the digoxin arm were treated with additional beta blocker therapy than in the verapamil arm (60% vs. 38%; p=0.01). In the second study,[143] sustained ventricular rate (<90 bpm) within 24 hours was compared between patients receiving digoxin or diltiazem. Patients receiving diltiazem were more likely to achieve sustained heart rate control (90%) than patients receiving digoxin (74%; p=0.047). The median time to ventricular rate control was also significantly shorter in patients receiving diltiazem (3 hours) than in patients receiving digoxin (6 hours; p<0.0001). Patients receiving diltiazem had lower mean ventricular rate after the first hour of drug administration compared with patients receiving digoxin (p<0.05). In a third study,[147] patients were more like to have a ventricular rate >90 bpm at 4 weeks when receiving digoxin (15 patients) than when receiving verapamil (5 patients; p<0.05). Importantly, five patients in the verapamil group required concomitant use of digoxin to reach ventricular rate control. Finally, in the last study,[148] digoxin was compared with the calcium channel blocker verapamil in patients with new onset AF with rapid ventricular response. The mean reduction in heart rate over 6 hours was 52.1 bpm in the digoxin arm and 41.8 bpm in the verapamil arm (p=0.55). At 6 hours, there was no difference in the rates of sinus rhythm between the two groups (p=0.962; insufficient strength of evidence). Conversion to sinus rhythm tended to be achieved more quickly in the digoxin group than in the verapamil group, although this difference was not statistically significant. Among patients remaining in AF, the reduction in heart rate was greater in patients receiving digoxin (mean reduction 47 bpm) than in patients receiving verapamil (mean reduction 21.6 bpm; p=0.035). Patients receiving verapamil had a greater reduction in heart rate compared with patients receiving digoxin at 0.5 hours (p=0.007) and 1 hour (p=0.027), but no differences were

seen between groups at 2, 3, or 4 hours. There were no clear adverse events related to the treatments in this study. Some of the symptoms that were reported, such as lightheadedness and palpitations, seem to have been related to AF and not to the study treatments.

In summary, there was a consistent benefit of verapamil or diltiazem compared with digoxin across studies (high strength of evidence).

Results in Specific Subgroups of Interest

One study compared combined treatment with the beta blocker carvedilol plus digoxin with carvedilol alone and with digoxin alone in patients with AF and heart failure in one study.[141] The combination of digoxin plus carvedilol was superior to digoxin alone for rate control at 4 months. At 6 months, there was no difference in rate control between digoxin alone and carvedilol alone. The improvement of AF symptoms was greater in patients receiving combined treatment than in patients receiving digoxin alone.). The included studies did not allow a direct comparison of these findings with those in other populations. Other subgroups of interest were not specifically evaluated.

Strength of Evidence

Our review of rate-control drugs explored the comparative effectiveness of beta blockers, calcium channel blockers, digoxin, and other antiarrhythmics in controlling ventricular rate. The 14 included studies varied in terms of the drugs involved, and the lack of multiple studies exploring similar comparisons decreased our ability to quantitatively synthesize their findings. Our findings highlight the lack of definitive data on the superiority of one beta blocker over another or against calcium channel blockers. Our findings underscore the importance of conducting studies comparing the effectiveness, tolerability and safety of different beta blockers and calcium channel blockers and in different patient populations. Based on a limited number of comparative studies, our analysis suggests that either a calcium channel blocker (verapamil or diltiazem) or amiodarone is beneficial compared with digoxin for rate control. Evidence exploring adverse events and safety and effectiveness of the available agents in specific subgroups of interest was insufficient. Table 4 summarizes the strength of evidence for the studied rate-control drugs and outcomes of interest. In general, the limited number of studies exploring specific comparisons, along with the various metrics used to assess outcomes of interest, reduced our confidence in the findings.

Table 4. Strength of evidence domains for rate-control drugs

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Beta Blockers vs. Digoxin						
Ventricular Rate Control	1 (47)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Beta Blockers vs. Calcium Channel Blockers						
Ventricular Rate Control	1 (40)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Beta Blockers vs. Calcium Channel Blockers in Patients Taking Digoxin						
Ventricular Rate Control	1 (29)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Exercise Capacity	1 (29)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Quality of Life	1 (29)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Sotalol vs. Metoprolol in Patients Taking Digoxin						
Ventricular Rate Control	1 (23)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Amiodarone vs. Calcium Channel Blockers						
Ventricular Rate Control	3 (271)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** Amiodarone is comparable to the calcium channel blocker diltiazem for rate control
Amiodarone vs. Digoxin						
Ventricular Rate Control	3 (390)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** Amiodarone controlled ventricular rate better than digoxin across 2 studies (both p=0.02) but did not demonstrate a difference in a third study
Calcium Channel Blockers Plus Digoxin vs. Digoxin Alone						
Ventricular Rate Control	1 (52)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Calcium Channel Blockers vs. Digoxin						
Ventricular Rate Control	4 (422)	RCT/Low	Consistent	Direct	Precise	**SOE=High** Consistent benefit of verapamil or diltiazem compared with digoxin (p<0.05 across studies)

Abbreviations: CI=confidence interval; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 2. Strict Versus Lenient Rate-Control Strategies

KQ 2: What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Key Points

- Based on one RCT and one observational study (both good quality) involving 828 patients, there was low strength of evidence to support a decrease in strokes for patients on lenient rate control. This decrease was statistically significant in the RCT, but not in the observational study.
- There was insufficient strength of evidence to support comparisons between strict and lenient rate control for other outcomes, specifically for all-cause and cardiovascular mortality, cardiovascular hospitalizations, heart failure symptoms, control of AF symptoms, quality of life, and composite measures.

Description of Included Studies

Three studies—one RCT[17] and two observational studies[152,153] representing secondary analyses of RCTs—were included in our analyses. We also included data from a separately published subgroup analysis[154] of the one RCT directly included in our analysis[17] (Appendix Table F-2). All studies included outpatients from multiple centers, and all were performed in Europe. Of the included studies, two were of good quality[17,152] and one was of fair quality.[153] All reported multiple funding sources; these included industry,[17,152,153] government,[153] and nonindustry/nongovernment sources.[17,152,153] Studies enrolled patients between 1998 and 2007. The number of patients included in studies ranged from 214[152] to 1,091,[153] with some overlap in patient populations across studies; a total of approximately 1,705 unique patients were included, with 1,177 deemed "strict" and 528 deemed "lenient." The mean age of study participants ranged from 68–69 years. The proportion of male patients included ranged from 59–66 percent. None of the studies reported data on race or ethnicity of subjects. Study durations ranged from 2.3 years[152] to 3 years.[17,154]

Study populations were composed entirely of patients with persistent[153] or permanent[17,152] AF. Included studies used varying definitions of "strict" and "lenient" rate control. The single included RCT[17] used a resting heart rate <80 bpm as the definition of strict rate control and resting heart rate <110 bpm as the definition of lenient rate control, and this definition was accordingly also used by the secondary analysis of this study that examined quality of life.[154] One observational study[153] compared patients from the rate-control arms of two prior RCTs; one of these RCTs[155] used a resting rate-control goal of <80 bpm, and the other[156] used a resting rate-control goal of <100 bpm; for the purposes of the observational study included here, the cohort with the resting rate-control goal of <80 bpm was deemed "strict" and the cohort with the resting rate-control goal of <100 bpm was deemed "lenient."[153] A second observational study[152] examined data from the rate-control arm of a prior RCT[156] and established post hoc definitions of strict (<80 bpm) and lenient (>80 bpm) rate control.

The protocols for the studies included in this analysis all utilized beta blockers, non-dihydropyridine calcium channel blockers, and digoxin, either alone or in combination, to achieve strict and lenient rate-control goals. Detailed information on agents used was provided in all but one of the studies.[153] Patients in all studies also received antithrombotic therapy (vitamin K antagonists or aspirin, primarily the former) appropriate to their level of thromboembolic risk as determined by the presence of known thromboembolic risk factors.

Detailed Synthesis

Overview

This analysis addressed the comparative effectiveness of strict versus lenient rate control on a variety of relevant outcomes in patients with AF. Because the included studies used different definitions of strict and lenient rate control, no available data were deemed appropriate for meta-analysis.

Ventricular Rate Achieved

As noted above, the included studies each had distinct definitions of strict and lenient rate control. Accordingly, strict and lenient rate-control patients achieved different mean heart rates in different studies. The levels of rate control achieved in each group are presented in Table 5. The "lenient" group from one observational study that compared patients from the rate-control arms of two prior RCTs[153] appeared to have tighter heart rate control than the other two relevant studies.[153] These differences should be taken into account when interpreting study outcomes.

Table 5. Ventricular rate achieved

Study	Strict Rate Control (bpm±SD)	Lenient Rate Control (bpm±SD)	P Value for Comparison
Van Gelder, 2010[17] (RCT)	76±12	93±9	<0.001
Groenveld, 2009[152]	76.1	83.4	<0.0001
Van Gelder, 2006[153]	72±5	90±8	<0.001

Abbreviation: bpm=beats per minute; RCT=randomized controlled trial; SD=standard deviation

All-Cause and Cardiovascular Mortality

The RCT[17] and one observational study[153] examined incidence of all-cause mortality among patients receiving strict and lenient rate control. Incidence of all-cause mortality ranged from 4–6.6 percent among strict rate-control patients, and from 2–5.6 percent among lenient rate-control patients. The RCT showed a nonsignificant HR of 0.91 (90% CI, 0.52 to 1.59).[17] No statistically significant difference in the incidence of all-cause mortality between strict and lenient rate control was observed in either study (insufficient strength of evidence).

The RCT[17] and a different observational study[152] examined incidence of cardiovascular mortality among patients receiving strict and lenient rate control. Incidence of cardiovascular mortality ranged from 3.9–7 percent among strict rate-control patients, and from 2.9–7 percent among lenient rate-control patients. The RCT showed a HR of 0.79 (90% CI, 0.38 to 1.65), demonstrating a potential benefit of lenient rate control which did not reach statistical significance.[17] No statistically significant difference in the incidence of cardiovascular mortality between strict and lenient rate control was observed in either of the included studies (insufficient strength of evidence).

Cardiovascular Hospitalizations

The RCT[17] and one observational study[153] provided details on hospitalizations among patients receiving strict and lenient rate control. With respect to cardiovascular hospitalizations (expressed as a percentage reflecting the number of patients with a hospitalization divided by the total N), numbers ranged from 5.6–28 percent among strict rate-control patients, and from 7.7–22 percent among lenient rate-control patients. Another observational study indicated that "hospitalization for heart failure, thromboembolic complications, and bleeding occurred in similar proportions in both groups," but did not provide detailed data.[152] Ultimately, no statistically significant differences in the incidence of cardiovascular hospitalization between patients receiving strict and lenient rate control were observed in either study (insufficient strength of evidence).

Heart Failure Symptoms

The RCT[17] and one observational study[152] examined incidence of heart failure symptoms among patients receiving strict and lenient rate control. Incidence of heart failure symptoms ranged from 4.1–5 percent in the strict rate-control groups, and from 2–3.8 percent in the lenient rate-control groups. The RCT showed a nonsignificant HR of 0.97 (90% CI, 0.48 to 1.96).[17] No statistically significant difference in the incidence of heart failure symptoms between strict and lenient rate control was observed in either study (insufficient strength of evidence).

Quality of Life

A secondary analysis[154] of the RCT[17] and one other observational study[152] provided data on patient quality of life as assessed by the SF-36. No significant differences were observed on any of the eight subscales between patients in the strict and lenient rate-control groups in either study (insufficient strength of evidence).

Thromboembolic Events

The RCT[17] and one observational study[152] examined incidence of thromboembolic events (stroke and systemic embolism) among patients receiving strict and lenient rate control. Incidence of thromboembolic events ranged from 3.9–7 percent among strict rate-control patients, and from 1.6–5 percent among lenient rate-control patients. Although favoring lenient control, no statistically significant difference in rate of thromboembolic events was seen in the observational study (absolute difference of 1.6; 95% CI, -5.3 to 8.6).[152] For the RCT, significance data were presented separately for stroke and systemic embolism; a statistically significant difference in stroke rate was observed, with a HR of 0.35 (90% CI, 0.13 to 0.92) in the direction of lenient rate control, with 0.3 percent of patients in the lenient rate-control group suffering a systemic embolism compared with no patients in the strict rate-control group.[17] However, although it was a good quality study, this RCT used a prespecified 90 percent CI, and it is not clear whether this conclusion of noninferiority for stroke would be equally valid using a statistical significance of $p<0.05$ (low strength of evidence).

Bleeding Events

The RCT[17] and one observational study[152] examined incidence of bleeding events among patients receiving strict and lenient rate control. Incidence of bleeding events ranged from 4.5–7 percent among strict rate-control patients, and from 4–5.3 percent among lenient rate-control patients. The RCT showed a nonsignificant HR of 1.12 (90% CI, 0.60 to 2.08).[17] No statistically

significant difference in the incidence of bleeding events between strict and lenient rate control was observed in either study (insufficient strength of evidence).

Composite Outcomes

The included studies examined a variety of composite outcomes as primary outcomes. As described in the articles, these included: (1) death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, major bleeding, arrhythmic events (including syncope), sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate-control drugs, and implantation of a pacemaker or cardioverter-defibrillator;[17] (2) all-cause death, cardiovascular hospitalization, and myocardial infarction;[153] and (3) cardiovascular death, heart failure, thromboembolic complications, bleeding, severe adverse effects of antiarrhythmic drugs, and pacemaker implantations.[152]

Composite outcome incidence ranged from 14.9–34 percent among strict rate-control patients, and from 12.9–25 percent among lenient rate-control patients. The single available RCT showed a nonsignificant hazard ratio (HR) of 0.84 (90% CI, 0.58 to 1.21) for a reduction in the composite outcome.[17] No statistically significant difference in composite primary outcome between strict and lenient rate control was observed in any of the included studies, despite the use of distinct composite outcomes and unique definitions for strict and lenient rate control.

Other Outcomes

Other outcomes were reported infrequently. The RCT reported that 46.0 percent of the strict-control group and 45.6 percent of the lenient rate-control group had experienced symptoms associated with AF by the end of the study (p=0.92), including dyspnea, fatigue, and palpitations.[17] Additionally, 1.4 percent of strict rate-control patients and 0.8 percent of lenient rate-control patients required pacemaker implantation for refractory AF symptoms (p=NS). Two observational studies also reported data on pacemaker implantation for patients with refractory rate control; one reported an incidence of pacemaker implantation of 11 percent in the strict rate-control group and 1 percent in the lenient rate-control group (p=0.0001),[153] while the other reported an incidence of 0 percent in the strict rate-control group and 2 percent in the lenient rate-control group (p=NS).[152] One observational study reported data on myocardial infarction, with an incidence of 2 percent in the strict rate-control group and 1 percent in the lenient rate-control group (p=NS).[153]

Adverse Events

Reporting of adverse events attributable to rate-controlling drugs was inconsistent across studies. The RCT reported an adverse event rate of 23.8 percent among patients receiving strict rate control and 19.9 percent among patients receiving lenient rate control (p=0.2; reported events included dizziness, fatigue, and dyspnea), with 0.7 percent of the strict rate-control group and 1.1 percent of the lenient rate-control group experiencing a “life-threatening adverse effect of rate-control drugs.”[17] One observational study reported a single severe adverse event attributable to rate-control drugs in each group (atrioventricular nodal escape rhythm due to digoxin intoxication in the strict rate-control group, and symptomatic bradycardia with atrioventricular nodal escape rhythm during beta blocker therapy in combination with digoxin in the lenient rate-control group),[152] but otherwise no other study reported adverse events (insufficient strength of evidence).

Results in Specific Subgroups of Interest

No results were reported for outcomes of interest in specific subgroups of interest.

Strength of Evidence

Our review identified only one RCT and two observational studies representing secondary analyses of RCTs exploring the comparative safety and effectiveness of strict versus lenient rate-control strategies. In general, these studies were consistent in showing no significant difference between strict and lenient rate control with respect to mortality, cardiovascular hospitalizations, heart failure symptoms, quality of life, thromboembolic events, bleeding events, and composite outcomes. However, the RCT differed from the observational studies in showing a statistically significantly lower stroke rate with lenient rate control. By emphasizing the limitations in the available data and the paucity of data on lenient versus strict rate control, our findings highlight the need for more research in this area. Table 6 summarizes the strength of evidence for the outcomes of interest and illustrates how the current evidence base is insufficient to provide conclusive estimates of the effect of strict and lenient rate-control strategies. Note that because the one RCT was powered as a noninferiority trial the risk of bias was estimated to be moderate rather than low.

Table 6. Strength of evidence domains for strict versus lenient rate-control strategies

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
All-Cause Mortality	1 (614)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
CV Mortality	2 (828)	RCT/ Moderate Observa-tional/ Moderate	Consistent	Direct	Imprecise	**SOE=Insufficient**
CV Hospitaliza-tions	2 (1,705)	RCT/Moder ate Observa-tional/ Moderate	Consistent	Direct	Imprecise	**SOE=Insufficient**
Heart Failure Symptoms	2 (828)	RCT/ Moderate Observa-tional/ Moderate	Consistent	Direct	Imprecise	**SOE=Insufficient**
Quality of Life	2 (828)	RCT/ Moderate Observa-tional/ Moderate	Consistent	Direct	Imprecise	**SOE=Insufficient**
Thrombo-embolic Events	2 (828)	RCT/ Moderate Observa-tional/ Moderate	Consistent	Direct	Precise	**SOE=Low** HR 0.35 (90% CI, 0.13 to 0.92) in RCT favoring lenient control; while also favoring lenient control, the observational study did not demonstrate a statistically significant difference (absolute difference of 1.6; 95% CI -5.3 to 8.6)
Bleeding Events	2 (828)	RCT/ Moderate Observa-tional/ Moderate	Consistent	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: CI=confidence interval; CV = cardiovascular; HR=hazard ratio; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 3. Rate-Control Procedures Versus Drugs or Versus Other Procedures in Patients for Whom Initial Pharmacotherapy Was Ineffective

KQ 3: What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared

with pharmacological agents in patients with atrial fibrillation for whom initial pharmacotherapy was ineffective? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Key Points

Procedures versus drugs:

- Based on 3 studies (1 good, 2 poor quality) involving 175 patients, patients undergoing a procedural intervention had a significantly lower heart rate at 12 months than those receiving a primarily pharmacological intervention (moderate strength of evidence).
- There was no difference by treatment arm in all-cause mortality (2 studies [1 good, 1 fair quality], 201 patients); cardiovascular mortality (1 study [good quality], 102 patients); or exercise capacity (2 studies [1 good, 1 fair quality], 135 patients) (all low strength of evidence).
- There was insufficient strength of evidence to support findings for other outcomes, including quality of life.

One procedure versus another:

- Based on 1 study (fair quality) involving 40 patients, there was no difference in ventricular rate control between those assigned to an anterior versus posterior ablation approach (low strength of evidence).
- Based on 1 study (fair quality) involving 184 patients, there was no significant difference in all-cause mortality between those receiving biventricular pacing versus those receiving right ventricular (RV) pacing (low strength of evidence).
- Based on 1 study (fair quality) involving 184 patients, there were significant improvements in exercise capacity for those in the biventricular pacing group compared with those receiving RV pacing (low strength of evidence).
- There was insufficient strength of evidence to support findings of other outcomes, including quality of life.

Description of Included Studies

Six RCTs (2 good, 3 fair, and 1 poor quality) involving a total of 537 patients met the inclusion criteria for KQ 3 (Appendix Table F-3), evaluating the comparative effectiveness of a procedural intervention versus a primarily pharmacological intervention for rate control of AF,[157-160] or comparing two primarily procedural interventions.[161,162] We also included data from a separately published subgroup analysis[163] of one of the RCTs.[160] One study each was based in the UK,[158] continental Europe,[159] and Asia;[161] one was a multicenter trial based in Australia (Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial [AIRCRAFT]);[160] one was a multicenter trial in the United States and Canada;[162] and one did not specify the geographical location.[157] All studies were unblinded due to the nature of the interventions, although one was described to be patient-blinded.[162] Four studies recruited patients with only one specific type of AF, either permanent[158,160,162] or persistent;[159] one study recruited patients with "resistant chronic" AF;[157] and one study recruited patients with permanent or paroxysmal AF.[161] These studies, however, evaluated and compared different types of treatments, preventing conclusions about whether effectiveness varied by type of AF. Treatment

arms ranged in size from 18–103 patients. Three studies reported outcomes at 6 months.[158,160,162] Three studies reported outcomes at 12 months;[157,158,160] for one of these,[160] outcomes were also reported for a subgroup of the original study population at approximately 5 years.[163] One study[159] reported outcomes with a mean followup period of approximately 26 months. Finally, one study reported outcomes at an unclear time point, which is presumed to be immediately after the procedure was completed, as well as at 14 months.[161] Three studies reported their funding source, which was from industry for two studies,[160,162] and at least partially from a governmental organization in the other.[161]

In line with our a priori definition of rate-control procedures, all studies included at least one treatment arm with radiofrequency ablation of either the atrioventricular node (AVN) or His bundle, most often in conjunction with pacemaker placement. The comparison arms included a pharmacological intervention whose main purpose was to control ventricular heart rate rather than converting the underlying rhythm of AF, based on the description of outcomes; this was combined with a procedure in some studies. One study compared AVN ablation plus pacing of the His bundle area versus treatment with amiodarone at a dose of 200–400 mg a day.[157] Another study compared AVN ablation plus ventricular demand rate-responsive (VVIR) pacing versus a pharmacological intervention for ventricular rate control, including digoxin, beta blockers, and calcium channel blockers, alone or in combination, as selected by the treating health care provider.[160] In one study, all patients had placement of a VVIR-programmed pacemaker, followed by randomization to either a His bundle ablation or pharmacological treatment to assist with ventricular heart rate control, with medications including calcium channel blockers, digoxin, or beta blockers.[158]

In two studies, all patients had AVN ablation, but were randomized to different types of pacing strategies. In one of these studies, all patients underwent AVN ablation for chronic AF and were randomized to chronic biventricular pacing versus right ventricular (RV) pacing.[162] In the other study, in addition to AVN ablation, participants were randomized to dual chamber demand rate-responsive (DDDR) pacing in conjunction with antiarrhythmic therapy with medicines such as propafenone, sotalol, or amiodarone, versus VVIR pacing with no additional antiarrhythmic therapy.[159] Finally, one study compared anterior and posterior approaches to AVN ablation for rate control.[161]

Detailed Synthesis

Ventricular Rate Control

Four studies reported outcomes related to ventricular rate control based on 24-hour Holter monitor,[157,158,160,161] but only three of these presented actual measures of heart rates achieved with the different treatments (Table 7).[158,160,161] Three studies compared a primarily procedural intervention with a primarily pharmacological intervention;[157,158,160] one compared two primarily procedural interventions with one another.[161]

Table 7. Heart rate results (24-hour Holter monitor)

Study	Sample Size (N)	Timing of Outcome	Interventions	Minimum Heart Rate[a]	Mean Heart Rate[a]	Maximum Heart Rate[a]
Procedures vs. drugs						
Levy, 2001[158]	36	1 month	VVIR pacing + His bundle ablation	60 (programmed)	71±6[b]	113±17
			VVIR pacing + rate-control medications	70 (programmed)	83±8	116±19
Weerasooriya, 2003[160]	99	1 month	VVIR pacing+ AVN ablation	80±12[c]	87±9[c]	117±14[c]
			Rate-controlling medications	44±14	76±12	147±44
Weerasooriya, 2003[160]	99	12 months	VVIR pacing + AVN ablation	70±9[c]	76±7[c]	117±16[c]
			Rate-control medications	39±9	71±11	152±37
Lim, 2007[163]	99	4-6 years (subgroup)	VVIR pacing + AVN ablation	60±9[c]	79±6	108±12[c]
			Rate-control medications	44±13	72 ±11	132±29
One procedure vs. another						
Lee, 2000[161]	40	14 months	Anterior approach for AVN ablation	63±10	82±11	128±14
			Posterior approach for AVN ablation	66±11	86±10	131±16

[a]Results given in beats per minute (bpm), mean ± standard deviation (SD).
[b]$p<0.01$ versus comparator.
[c]$p<0.05$ versus comparator.
Abbreviations: AVN=atrioventricular node; VVIR=ventricular demand rate-responsive

Procedures Versus Drugs

Three studies found that patients in the primarily procedural intervention arm had a significantly lower heart rate at 12 months than those receiving the primarily pharmacological intervention (moderate strength of evidence). The studies used different measures based on 24-hour Holter monitor—either maximal heart rate or mean heart rate. One study comparing AVN ablation plus pacing of the His bundle area versus amiodarone found that after 3 weeks of treatment, 100 percent of the patients who had undergone AVN ablation with pacemaker achieved a normal ventricular rate, defined as 50–90 bpm, compared with only 57.9 percent of those receiving amiodarone.[157] Also, none of the patients who received AVN ablation with pacemaker had an uncontrolled heart rate, defined as >90 bpm at rest or >130 bpm on exertion, while 42.1 percent of patients receiving amiodarone did have uncontrolled heart rate by these parameters ($p<0.001$). In this same study, 100 percent of patients who had undergone AVN ablation with pacemaker achieved a normal ventricular rate at 12 months, compared with only 33.6 percent of those receiving amiodarone. Also, none of the patients who received AVN ablation with pacemaker had an uncontrolled heart rate at 12 months, while 66.4 percent of patients receiving amiodarone did have uncontrolled heart rate (no statistical results given).

In the study comparing VVIR pacing plus His bundle ablation versus VVIR pacing plus rate-control medications, at 1-month followup, those receiving the ablation had a lower mean heart rate over 24 hours, based on 24-hour Holter recordings, with a mean heart rate of 71±6 bpm compared with 83±8 bpm in the medication arm ($p<0.01$).[158] Mean heart rates were described as being similar to these values through 1 year of followup. Resting heart rates also differed between groups, but this difference was thought to be due to the fact that the lower heart rate was programmed on the pacemakers differently in the two groups, with the ablation group having the lower heart rate set at 60 bpm and the medication group having the lower heart rate set at 70 bpm. The maximum heart rate, as measured on the 24-hour Holter recordings, did not differ significantly between the two groups.

In another study, at 12 months, based on 24-hour ambulatory electrocardiograms (ECGs), those receiving AVN ablation plus VVIR pacing compared with those on medication alone had significantly higher minimum heart rates (70±9 vs. 39±9 bpm; $p<0.05$) and mean heart rates (76±7 vs. 71±11 bpm; $p<0.05$).[160] However, those receiving the ablation had significantly lower maximum heart rates compared with those on medication alone on 24-hour tapes (117±16 vs. 152±37 bpm; $p<0.05$).

For the last study described above,[160] longer term outcomes were reported separately[163] for a subgroup of the original study population comprising 48 participants from two of the study sites, representing about 48 percent of the original study population. For this subgroup, investigators reported that at approximately 5 years of followup, minimum heart rate (assessed by 24-hour Holter monitor) was still higher in those receiving AVN ablation plus VVIR pacing than in those receiving medication alone (60±9 bpm vs. 44±13; $p<0.05$). Mean heart rates were not significantly different, but maximum heart rate was again lower in those receiving ablation plus VVIR pacing than in those receiving medication alone (108±12 vs. 132±29 bpm; $p<0.05$).

One Procedure Versus Another

The study that compared two different approaches for performing AVN ablation—an anterior approach and a posterior approach—defined immediate success of the procedure with reference to heart rate parameters including a heart rate of approximately 120–130 bpm during infusion of isoproterenol (4 mcg/min) or an average ventricular rate of approximately 70–75 percent of the

baseline ventricular rate during infusion of isoproterenol (4 mcg/min).[161] Seventy-eight percent of patients receiving the anterior approach achieved this result, compared with 64 percent receiving a posterior approach (statistical test not reported). Allowing for crossovers for those who did not achieve the outcome described above, results of 24-hour Holter monitors were compared at approximately 14 months of followup. These results found no statistically significant difference between those assigned to the anterior versus posterior approaches based on minimal, mean, or maximal heart rates (low strength of evidence).

Mortality, Cardiovascular Events, and Cardiovascular Hospitalizations

Procedures Versus Drugs

Two studies analyzed long-term clinical outcomes in patients with persistent or chronic AF,[159,160] one of which[160] reported long-term mortality separately for a subgroup of its population.[163] The primary outcome of the first study,[159] which compared AVN ablation plus DDDR pacing and antiarrhythmic therapy versus AVN ablation plus VVIR pacing alone, was the occurrence of stroke or cardiovascular mortality. Secondary outcomes included all-cause mortality, development of permanent AF, cardiovascular hospitalizations, heart failure, and myocardial ischemia. Mean followup time for both treatment arms was similar at 26 months. This study found that there was no statistically significant difference in the primary outcome between the treatment arms, with an event rate of 5.3 percent per year in patients with the VVIR pacing compared with 5.9 percent in patients with the DDDR pacing and medications (p=0.930). There was also no statistically significant difference in all-cause mortality, with event rates of 4.3 and 4.8 percent for those with the VVIR and DDDR pacing, respectively (OR 0.98; 95% CI, 0.25 to 3.53; p=0.74). Fewer patients receiving DDDR pacing plus medication developed permanent AF compared with patients receiving VVIR pacing (OR 0.06; 95% CI, 0.02 to 0.17; p<0.001). However, those patients receiving VVIR pacing had fewer cardiovascular hospitalizations compared with those receiving the DDDR pacemaker and medications, with 9 versus 31 hospitalizations, respectively (p<0.001). There was no statistically significant different in the occurrence of heart failure or myocardial ischemia between the two treatment groups.

In the study comparing AVN ablation plus VVIR pacing versus rate-control medication, there was no significant difference in all-cause mortality or cardiovascular events at 12 months. There were two deaths in the ablation arm and one death in the medication arm (p=0.617); two acute myocardial infarctions (MIs) in the ablation arm and one in the medication arm (p=0.617); and four cases of unstable angina in the ablation arm and one in the medication arm (p=0.204). Hospitalizations were not reported.[160] At a mean of 5.4±0.9 years of followup, in the subgroup of 48 patients that were reevaluated for clinical outcomes, there were 15 total deaths, with no statistically significant difference in survival between treatment groups (p=0.26).[163]

We rated the findings of no significant difference for all-cause and cardiovascular mortality as having a low strength of evidence.

One Procedure Versus Another

In a study comparing AVN ablation plus biventricular pacing versus AVN ablation plus RV pacing, total mortality was reported over a 3-year period. This study found no statistically significant difference in mortality for these two treatment groups, with 8 and 18 percent deaths (p=0.16), respectively, for those with biventricular pacing and RV pacing (low strength of evidence).[162]

Exercise Capacity

Procedures Versus Drugs

Two studies evaluated exercise capacity at 12 months using treadmill tests,[158,160] and neither showed statistically significant differences by treatment arm (low strength of evidence). In the study comparing VVIR pacing plus His bundle ablation versus VVIR pacing plus rate-control medications,[158] exercise capacity was tested using a symptom-limited treadmill exercise test. In this study, both groups had a significant improvement in exercise duration of approximately 20 and 40 percent, respectively, but the improvements were not statistically significantly different between treatment groups (full statistical results not reported in paper). In the study comparing AVN ablation plus VVIR pacing versus rate-control medication,[160] all patients also underwent treadmill exercise tests. At 12 months, neither group had any significant improvement in exercise duration, and exercise duration at baseline and at 12 months did not differ significantly between groups. The maximum heart rate achieved with exercise was significantly lower, however, in patients receiving ablation compared with those receiving medication (112±17 vs. 153±36 bpm; $p<0.05$).

One Procedure Versus Another

One study compared AVN ablation plus biventricular pacing versus AVN ablation plus RV pacing and evaluated exercise capacity based on 6-minute walk test distance.[162] This study found improvement in both arms from preablation measures to 6 months postprocedure. However, the improvement in walking distance was significantly greater among those in the biventricular pacing group at 82.9±94.7 m compared with 61.2±90.0 m for those receiving RV pacing ($p=0.04$) (low strength of evidence).[162]

Quality of Life

Procedures Versus Drugs

Two studies described outcomes related to quality of life at 6 or 12 months, but they used different measurement tools and differed in their results.[158,160] In the study comparing VVIR pacing plus His bundle ablation versus VVIR pacing plus rate-control medications,[158] the burden of cardiac symptoms was measured using a modified Karolinska Questionnaire, which has been validated for patients with pacemakers.[164] This study also administered the Nottingham Health Profile to measure general quality of life, a tool previously validated in cardiac patients.[165,166] Patients in both treatment arms had significant improvements over the 12-month followup period both in their burden of cardiac symptoms and in their general quality of life; however, there was no statistically significant difference in these improvements by treatment arm (full statistical results not provided in the paper for either measure).

In the study comparing AVN ablation plus VVIR pacing versus rate-control medications,[160] three health-related quality-of-life questionnaires were administered: the Australian Quality of Life Questionnaire (AQoL), a generic utility instrument validated for use in a wide range of illnesses and interventions;[167] the quality-of-life questionnaire used in the Cardiac Arrhythmia Suppression Trial (CAST), validated in patients with heart disease;[168] and the Sickness Impact Profile (SIP), validated for use in patients with a wide-range of illnesses and disease severities.[169] Based on two of these three measures, there was no statistically significant difference in the change in quality of life, which was minimal, between treatment groups at 12 months. However,

based on the CAST measure, those patients who received AVN ablation plus VVIR pacing had significantly improved ratings of their quality of life compared with those on medications, with a relative risk reduction in symptoms of 18 percent (p=0.004).[160]

Long-term followup on quality-of-life measures was reported separately[163] for a subgroup of participants in the second trial described above.[160] There were no statistically significant differences between groups at 5 years in the AQoL measures (no p-value given) or in SIP scores (p=0.16). Overall life satisfaction scores and psychosocial scores on the CAST questionnaire also did not differ between treatment groups (p>0.05); however, those patients who received AVN ablation plus VVIR pacing did have a reduction in certain symptoms evaluated by the CAST questionnaire compared with those on medication alone, with a reduction in symptoms of irregular heart beat (p<0.001), chest pain (p=0.02), and difficulty breathing (p=0.02).

The strength of evidence was rated as insufficient to determine the impact of the interventions on quality of life.

One Procedure Versus Another

In the study comparing AVN ablation plus biventricular pacing versus AVN ablation plus RV pacing,[162] there was reportedly no difference in quality of life at 6 months between treatment arms as measured by the SF-36 Health Status Scale (detailed results were not provided; insufficient strength of evidence).

Adverse Events

Procedures Versus Drugs

Three studies described adverse events, with one study[160] including a second publication describing long-term outcomes of the interventions.[163] In the two studies using antiarrhythmic drugs,[157,159] two patients reported adverse events, including one episode of torsade-de-points in a patient receiving sotalol and one case of heart failure in a patient receiving propafenone.[159] No adverse reactions were reported by patients receiving amiodarone.[157] One study using rate-control drugs reported adverse events,[160] finding three hematomas in the ablation arm, as well as one pulmonary embolus. During long-term followup of this study, two patients who received ablation plus pacing developed heart failure, one patient who received ablation plus pacing developed failure to capture related to malfunction of their pacemaker, and one patient in the medication arm experienced prolonged pauses with their AF and required pacemaker placement.[163]

One Procedure Versus Another

In the study comparing AVN ablation plus biventricular pacing versus AVN ablation plus RV pacing, overall numbers of complications were reported for a 3-year period and included adverse events related to pacemaker dysfunction, such as diaphragmatic stimulation, lead dislodgement, and oversensing, as well as adverse events related to pacemaker placement including pneumothorax, hematoma, and infection.[162] There was no significant difference in overall complication rates between treatment arms, with rates of 15 and 6 percent (p=0.06) for those with biventricular pacing and RV pacing, respectively.

Subgroups of Interest

Procedures Versus Drugs

One study evaluated outcomes at 1 year according to a prespecified subgroup analysis in 19 patients with left ventricular ejection fraction (LVEF) ≤45 percent who were randomized to either AVN ablation plus VVIR pacing or rate-control medication. This study found that the results of heart rate changes or exercise capacity by treatment group did not differ from the main study for this subgroup.[160]

One Procedure Versus Another

The study comparing AVN ablation plus biventricular pacing versus AVN ablation plus RV pacing also evaluated 6-month outcomes of subgroups of participants based on LVEF. This study found that among participants with an LVEF >45 percent (n=89), both treatment arms had improvements in 6-minute walk distance, and there was no significant difference between treatment groups in this improvement. However, among participants with an LVEF ≤45 percent (n=76), those participants receiving biventricular pacing had significantly greater improvements in their 6-minute walk distance compared with those receiving RV pacing, with improvements of 96.9±97.7 m and 55.9±96.1 m, respectively (p=0.04). This study also compared outcomes for patients with different functional classes of heart failure based on New York Heart Association (NYHA) symptoms. Similar to the pattern observed for patients by LVEF, those with NYHA class I symptoms demonstrated similar improvements in 6-minute walk distance (p=0.29), while those with either NYHA class II or III symptoms had significantly greater improvements in 6-minute walk distance with biventricular pacing compared with RV pacing (p=0.01).[162]

Strength of Evidence

Tables 8 and 9 summarize the strength of evidence for the various comparisons and outcomes of interest. Studies varied in the type of procedures and drugs that were tested, limiting our ability to synthesize evidence across studies. Studies that explored the impact of procedures versus drugs on ventricular rate control demonstrated a significantly lower heart rate in patients in the procedural intervention arms. Other outcomes assessed either found no differences by treatment arm (exercise capacity, mortality) or were inconsistent (quality of life). Studies that evaluated one rate-control procedure versus another did not find differences in rate control or all-cause mortality but did demonstrate an improvement in exercise capacity among those in a biventricular pacing group compared with right ventricular pacing. Our findings underscore the need for additional studies to compare rate-control procedures with rate-control drugs or other procedural interventions with in relation to these outcomes. Although based on direct and mostly consistent evidence, the low number of studies, imprecise findings, and inability to determine a summary effect given the variability in study design and population lowered our confidence in the evidence.

Table 8. Strength of evidence domains for rate-control procedures versus drugs

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ventricular Rate Control	3 (175)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** Using different metrics, all 3 studies found that patients in the procedure arm had a significantly lower heart rate at 12 months than those on drugs
All-Cause Mortality	2 (201)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** No significant difference
CV Mortality	1 (102)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No significant difference
Exercise Capacity	2 (135)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** Studies did not show significant differences between procedure and drug arms
Quality of Life	2 (135)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: CI=confidence interval; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Table 9. Strength of evidence domains for one rate-control procedure versus another

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ventricular Rate Control	1 (40)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No difference between those assigned to anterior vs. posterior approach
All-Cause Mortality	1 (184)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No significant difference among those in the biventricular pacing group compared with those receiving RV pacing (p=0.16)
Exercise Capacity	1 (184)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Improvement in walking distance significantly greater among those in the biventricular pacing group compared with those receiving RV pacing (p=0.04)
Quality of Life	1 (184)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: CI=confidence interval; NA=not applicable; RCT=randomized controlled trial; RV=right ventricular; SOE=strength of evidence

Key Question 4. Antiarrhythmic Drugs and Electrical Cardioversion for Conversion to Sinus Rhythm

KQ 4: What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Key Points

- Based on 4 RCTs (2 good, 2 fair quality) involving 411 patients, use of a single biphasic waveform is more effective in restoring sinus rhythm than use of a single monophasic waveform in patients with persistent AF (high strength of evidence).
- Based on 4 RCTs (1 good, 3 fair quality) involving 393 patients, there was no statistically significant difference in restoration of sinus rhythm with use of anterolateral versus anteroposterior positioning of cardioversion electrodes in patients with persistent AF (low strength of evidence).

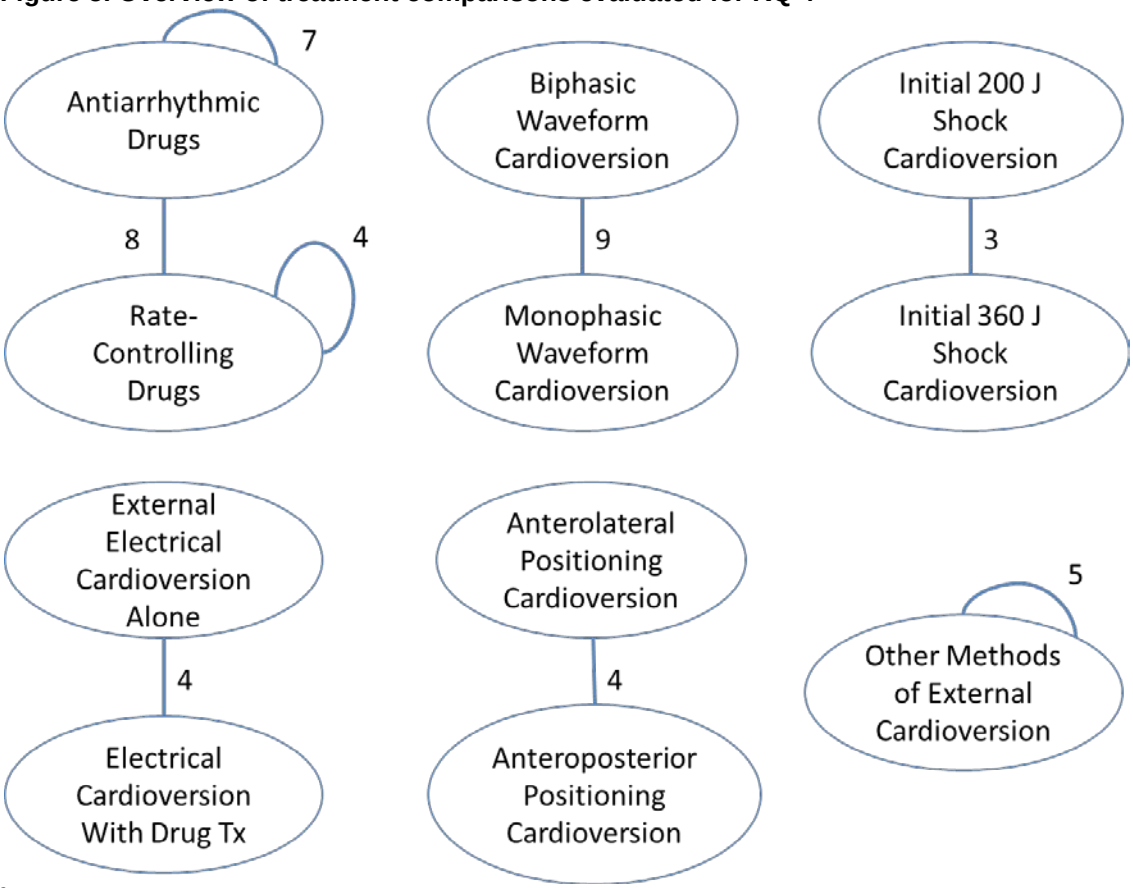
- Based on 3 studies (1 good, 2 fair quality) involving 432 patients, a 360 Joules (J) monophasic shock restores sinus rhythm more effectively than a 200 J monophasic shock (high strength of evidence).
- Although based on limited studies and use of different drugs for pretreatment, current evidence suggests that drug pretreatment does not enhance electrical cardioversion in terms of restoration of sinus rhythm (2 studies [1 good, 1 fair quality], 218 patients, moderate strength of evidence), but does increase maintenance of sinus rhythm (2 studies [1 good, 1 fair quality], 195 patients, moderate strength of evidence), and decrease recurrence of AF (1 poor-quality study, 88 patients, low strength of evidence).
- Based on 4 studies (2 good, 2 fair quality) involving 736 patients, amiodarone demonstrates a potential benefit compared with sotalol for restoring sinus rhythm, although the difference did not reach statistical significance (low strength of evidence).

Description of Included Studies

A total of 42 RCTs involving 5,780 patients were identified that assessed the use of antiarrhythmic drugs or electrical cardioversion for the conversion of AF to sinus rhythm (Appendix Table F-4). Thirteen studies were considered to be of good quality,[140,170-181] 27 of fair quality,[144,145,147,149,182-204] and 2 of poor quality.[205,206] The studies were published from the years 2000 through 2011; however, all but four studies[170,171,188,196] were published in 2007 or earlier. Eleven studies were multicenter,[145,147,171,172,179,180,189,190,197,198,206] 28 were single-center,[140,144,149,170,173-178,182-188,191-196,200-203,205] and in 3 studies the number of sites was unclear or not stated.[181,199,204] Only 7 studies included sites in the United States;[172,179,180,182,189,197,198] 25 included sites in Europe.[140,144,145,147,170,175-179,187,188,191-196,200-206] The study population consisted entirely of patients with persistent AF in 25 studies,[144,145,147,170-172,175-178,183,185-187,192-195,197-199,202-204,206] entirely of patients with paroxysmal AF in 1 study,[189] and entirely of patients for whom prior rate- or rhythm-control therapy had been ineffective in 2 studies.[174,195] Funding was unclear or not reported in 31 studies.[140,144,147,170,172,173,175,179,181,183,185-188,190-206] Seven studies used industry funding,[145,171,174,176,178,180,184] none was government-only funded, and eight were funded by nongovernment/nonindustry sources.[145,149,171,174,177,178,182,189] In the majority of studies, the setting was not reported (18 studies[145,179,181,183-187,193,195,197-203,206]). Of the remaining studies, 7 were inpatient,[140,144,174,177,182,191,205] 5 were in the emergency room,[149,170,173,189,190] 10 were outpatient,[147,171,172,175,176,178,180,192,194,204] and 2 were in more than one setting.[188,196]

Figure 5 represents the treatment comparisons evaluated for this KQ.

Figure 5. Overview of treatment comparisons evaluated for KQ 4[a]



[a]Lines running from one oval back to the same oval (e.g., "Antiarrhythmic Drugs" oval) indicate intraclass comparisons (e.g., comparison of one antiarrhythmic drug with another). Numbers refer to numbers of comparisons.
Abbreviations: KQ=Key Question; J=Joules; Tx=treatment

Twenty-one studies compared methods of external electrical cardioversion, four studies compared electrical cardioversion augmented by medications (metoprolol,[178] verapamil,[199,205] and ibutilide[195]) with electrical cardioversion alone, and eight studies evaluated the efficacy of drugs used both prior to and after external electrical cardioversion (amiodarone [five studies[144,149,180,181,204]], diltiazem [two studies[144,204]], digoxin [five studies[145,147,149,204,206]], verapamil [three studies,[145,147,206]], sotalol [three studies[149,180,181]]). Nine studies compared drugs without (or prior to) external electrical cardioversion.[140,170,177,188-193] No study compared electrical cardioversion directly with pharmacological cardioversion. Of the 42 studies, 3 had a placebo arm,[170,180,193] and 2 had a "control" arm that was not included in this review.[181,192] Excluding the placebo/control arm in these five studies, one study had four intervention arms,[198] and five studies had three intervention arms each.[149,170,172,190,204] The remaining 36 studies had 2 intervention arms each.

The primary outcome reported for this KQ was restoration of sinus of rhythm within a specified time period following the intervention. This time period ranged from immediately following the intervention to 6 weeks following the intervention. Several studies presented outcome data at multiple time points following the intervention, while others assessed time to outcome within a prespecified time frame. Only three studies did not report restoration of sinus rhythm.[194,199,205] Of these, one assessed maintenance of sinus rhythm at 1 week following electrical cardioversion or verapamil plus electrical cardioversion,[199] another reported

maintenance of sinus rhythm 1 month after electrical cardioversion,[194] and the third reported recurrence of AF within 1 week following verapamil with electrical cardioversion versus electrical cardioversion alone.[205]

Three studies reported an outcome relevant to this KQ in addition to restoration of sinus rhythm. One study reported all-cause mortality, mixed embolic events, and maintenance of sinus rhythm at 6 weeks;[185] one reported recurrence of AF within 24 hours after cardioversion;[191] and one reported recurrence of AF within 1 minute of electrical cardioversion.[202]

Detailed Synthesis

Comparisons of Various Methods for External Electrical Cardioversion

Overview

Twenty-one studies (2,996 patients) compared different methods of external electrical cardioversion. Nine studies (1,219 patients) compared a biphasic waveform with a monophasic waveform (Table 10), and 4 studies (393 patients) compared anterolateral versus anteroposterior positioning of the defibrillation electrodes (paddles in 2 studies, paddles and/or gel pads in 1 study, and pads in 1 study).[175,183,187,202] Three studies (432 patients) included a comparison of an initial 200 J shock with an initial 360 J shock.[172,185,186] The remaining five studies addressed comparisons in polarity (one study[197]), shapes of the biphasic waveform (one study[182]), composition of the cardioversion electrodes (one study[176]), and different amounts of energy delivered (two studies[171,198]).

Among the 9 studies comparing a biphasic waveform with a monophasic waveform, 8 assessed restoration of sinus rhythm at 0 or 30 minutes after cardioversion, and 1 assessed maintenance of sinus rhythm at 1 month following electrical cardioversion.[194] Only two studies included only patients with persistent AF,[194,203] and one study included only patients for whom a prior rate- or rhythm-control therapy was ineffecitve.[174] One study also included an assessment of recurrence of AF within 1 minute following initial cardioversion.[203] All but one of the studies were single-center.[179] Three studies were of good quality, and six were of fair quality. Among these nine studies, mean/median population age ranged from 55–70 years; data on AF type and heart failure prevalence were generally not reported.

Table 10. Studies evaluating biphasic versus monophasic waveform

Study	Biphasic Protocol	Monophasic Protocol	N	Outcomes Assessed
Ambler, 2006[184]	100 J, 200 J, 300 J, 360 J, 360 J	70 J, 110 J, 150 J, 200 J, 360 J	128	– Restoration of SR immediately – Restoration of SR at 30 minutes
Kawabata, 2007[173]	50 J, 100 J, 150 J, 175 J (IV amiodarone)	100 J, 200 J, 300 J, 360 J (IV amiodarone)	154	– Restoration of SR after cumulative shocks – Restoration of SR after 1st shock
Khaykin, 2003[174]	150 J, 200 J, 360 J	Single 360 J	56	– Restoration of SR
Marinsek, 2003[194]	70 J, 100 J, 150 J, 200 J	100 J, 200 J, 300 J, 360 J	83	– Maintenance of SR at 1 month
Mortensen, 2008[196]	75 J, 100 J, 150 J, 200 J	100 J, 150 J, 200 J, 300 J, 360 J	95	– Restoration of SR immediately after cumulative shocks – Restoration of SR after 1st shock
Page, 2002[179]	100 J, 150 J, 200 J, 200 J biphasic or 360 J monophasic	100 J, 150 J, 200 J, 200 J biphasic or 360 J monophasic	203	– Restoration of SR after 4 shocks – Restoration of SR after 3 shocks – Restoration of SR after 2 shocks – Restoration of SR after 1 shock
Ricard, 2001[200]	150 J, 150 J	150 J, 360 J	57	– Restoration of SR after all shocks – Restoration of SR after 1 shock
Scholten, 2003[201]	120–200 J sequence	200–360 J sequence	277	– Restoration of SR after 1st shock – Restoration of SR after 2nd shock
Siaplaouras, 2004[203]	120 J, 150 J, 200 J, 200 J	200 J, 300 J, 360 J, 360 J	216	– Restoration of SR – Recurrence of AF within 1 minute

Abbreviations: AF=atrial fibrillation; J=Joules; N=number of patients; SR=sinus rhythm

Four studies (393 patients) compared anterolateral vs. anteroposterior placement of the defibrillation electrodes during external electrical cardioversion.[175,183,187,202] One study was of good quality,[175] and three were of fair quality.[183,187,202] One study was conducted in the outpatient setting;[175] the other three did not specify the setting. All four studies included only patients with persistent AF. The mean age of patients receiving the anterolateral approach ranged from 58–68 years, and the mean age of patients receiving the anteroposterior approach ranged from 62–67 years. All four studies assessed restoration of sinus rhythm immediately after the external electrical cardioversion, all four were conducted in Europe, and all four were single-center studies. LVEF was reported only in three studies, and the mean ranged from 49–60 percent in those receiving the anterolateral approach and 49–59 percent in those receiving the anteroposterior approach.

Six studies assessed different external electrical cardioversion protocols for conversion of AF. In three of these (432 patients) there was a comparison between an initial monophasic energy of 200 J and 360 J.[172,185,186] Two of these were single-center studies,[185,186] and one was

multicenter;[172] two were conducted in Europe,[185,186] and one in the United States.[172] All three studies were composed entirely of patients with persistent AF, and all utilized monophasic waveforms with varying electrode positioning; in two, patients who did not convert with the first shock received a subsequent shock.[172,186] All three studies comparing monophasic shocks of 200 J and 360 J assessed restoration of sinus rhythm immediately after the electrical cardioversion procedure. In the other three studies assessing cardioversion protocols, different biphasic energies were evaluated.[171,182,198] In one of these, the different energy protocols also involved different biphasic wave shapes (truncated vs. rectilinear).[182] Two of the studies were composed entirely of patients with persistent AF;[171,198] the type of AF was not reported in the third study.[182]

A single study compared standard polarity to reverse polarity.[197] This was a multicenter study in the United States and included only patients with persistent AF. The study was of fair quality; however, errors in the publication prevented collection of accurate baseline characteristics. Both biphasic and monophasic waveforms were tested, and the outcome was restoration of sinus rhythm within 30 seconds; however, statistical testing was not performed on this outcome measure.

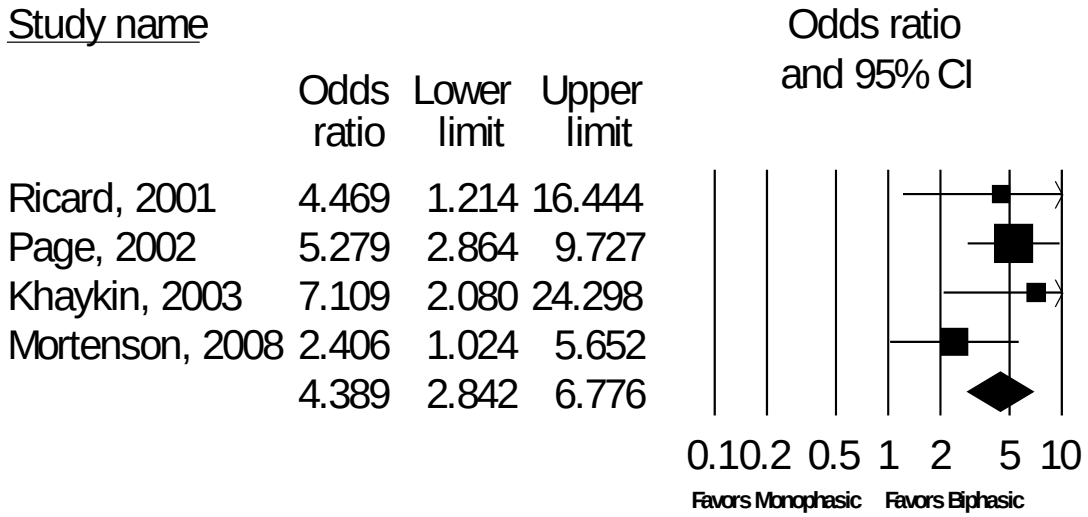
Finally, a single study compared steel paddles to adhesive pads for electrical cardioversion.[176] This study was a single-center study of good quality funded by industry and conducted in Europe. All patients were outpatients with persistent AF. A monophasic and biphasic waveform was used in both intervention arms.

Restoration of Sinus Rhythm

Biphasic Versus Monophasic Waveforms

Eight studies compared biphasic and monophasic waveforms and assessed restoration of sinus rhythm immediately or at 30 minutes after external electrical cardioversion;[173,174,179,184,196,200,201,203] none of these demonstrated a statistically significant difference between the biphasic and monophasic protocols. However, among studies with analyses looking only at the first protocol-specified shock, four studies demonstrated a statistically significant greater restoration of sinus rhythm with biphasic waveforms compared with monophasic.[174,179,196,200] A meta-analysis of these 4 studies representing 411 patients estimated an odds ratio (OR) of 4.39 (95% CI, 2.84 to 6.78) and demonstrated a large and statistically significant benefit of biphasic waveform for restoration of sinus rhythm compared with monophasic when looking only at the first protocol-specified shock (Figure 6; high strength of evidence). There was no evidence of heterogeneity. The Q-value was 2.85 for 3 degrees of freedom, p=0.416.

Figure 6. Forest plot for restoration of sinus rhythm for monophasic versus biphasic waveforms



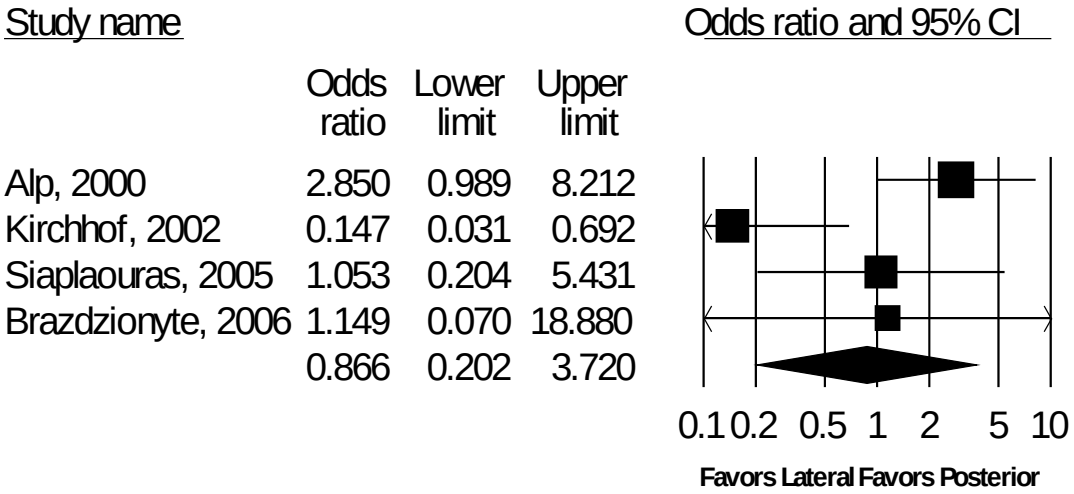
Abbreviation: CI=confidence interval

Anterolateral Versus Anteroposterior Electrical Cardioversion

In the four studies that assessed restoration of sinus rhythm in patients with persistent AF receiving external electrical cardioversion via anterolateral versus the anteroposterior electrode placement,[175,183,187,202] one[175] found a statistically significant greater rate of conversion to sinus rhythm with the anteroposterior placement (78% with anterolateral vs. 96% with anteroposterior; p=0.009), and one[183] found a greater conversion rate with the anterolateral position (60% anterolateral vs. 34% anteroposterior; p=0.048). In the other two studies, there was no statistically significant difference between the two approaches.[187,202] A meta-analysis of these 4 studies involved 393 patients and estimated an OR of 0.87 (95% CI, 0.20 to 3.72), showing no statistical difference between the two approaches (Figure 7; low strength of evidence). There was some evidence of heterogeneity (Q-value=9.60 for 3 degrees of freedom, p=0.22), reducing the overall strength of evidence.

In the two studies using monophasic waveforms,[175,183] crossover to the alternative approach was specified in the protocol[183] or allowed[175] if there was a failure of cardioversion with the initial approach. In the study in which the crossover was specified in the protocol, there was no statistically significant difference in success with the anteroposterior second shock versus the anterolateral second shock (42% vs. 21%, p=0.22).[183] In the study in which crossover to the alternative approach was allowed, 8 of 12 patients in whom the anterolateral approach failed were successfully cardioverted with the anteroposterior approach, and neither of the 2 patients in whom the anteroposterior approach failed was successfully cardioverted with the anterolateral approach.[175] No statistical testing was done to compare these results.

Figure 7. Forest plot of restoration of sinus rhythm for anterolateral versus anteroposterior electrode placement

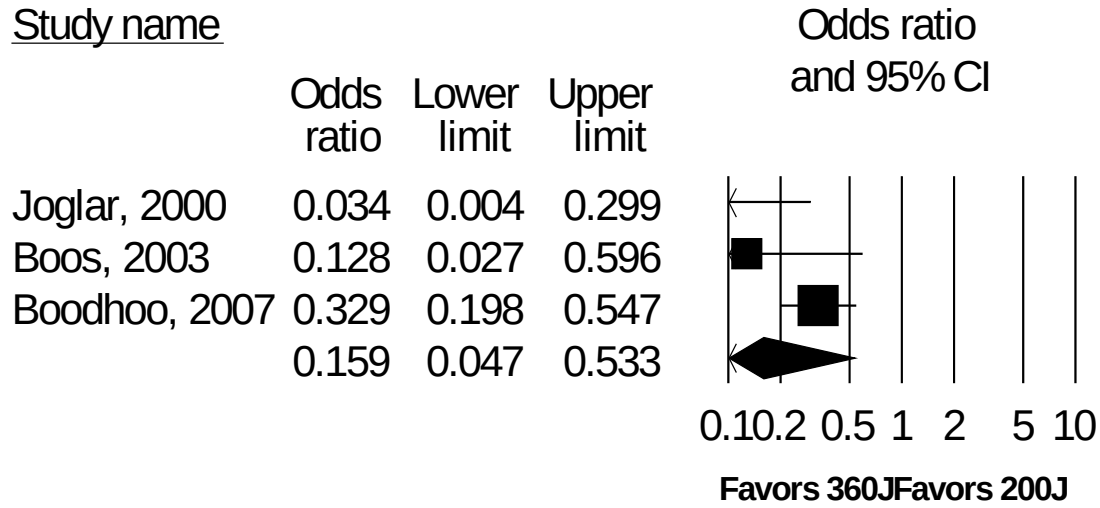


Abbreviation: CI=confidence interval

Energy and Energy Protocols for External Electrical Cardioversion

The three studies that included a comparison of a 200 J monophasic initial shock to a 360 J monophasic initial shock in patients with persistent AF[172,185,186] all showed a statistically significantly greater rate of restoration of sinus rhythm immediately after the shock in those receiving the 360 J shock versus the 200 J shock (95% vs. 39%, p<0.0001;[172] 96% vs. 75%, p=0.003;[186] and 68% vs. 42%, p<0.001[185]). A meta-analysis of these 3 studies represented 432 patients and estimated an OR of 0.16 (95% CI, 0.05 to 0.53) favoring a 360 J monophasic shock (Figure 8; high strength of evidence). There was limited evidence of heterogeneity. The Q-value was 4.99 for 2 degrees of freedom, p=0.083.

Figure 8. Forest plot of restoration of sinus rhythm for 200 J versus 360 J monophasic initial shocks



Abbreviations: CI=confidence interval; J=Joules

In two of three studies that compared different biphasic energy protocols there was no statistically significant difference between the truncated and rectilinear protocols (97% vs. 93%;

p=0.44), or between a biphasic stepped and non-stepped approach (90% vs. 88%; p=0.56) in restoration of sinus rhythm.[171,182] In the third study, a larger proportion of patients had restoration of sinus rhythm with the higher biphasic energy levels (7% with 20J, 23% with 50J, 63% with 100J, and 83% with 200J), but the study did not statistically assess that difference.[198]

In the study comparing use of standard polarity with reverse polarity using both monophasic and biphasic waveforms, 84 percent of patients with standard polarity and 78 percent with reverse polarity reverted to sinus rhythm (statistical test not provided).[197]

In the study comparing steel paddles with adhesive pads using both monophasic and biphasic waveforms, 96 percent of patients with the steel paddles compared with 88 percent of patients with the adhesive patches had restoration of sinus rhythm immediately following the cardioversion (p=0.04).[176] Cardioversion success rate was 100 percent in the biphasic shock group with paddle electrodes (56/56 patients) but 96 percent (46/48 patients) when patches were used (p=0.07).

Maintenance of Sinus Rhythm

Biphasic Versus Monophasic Waveforms

In the study that assessed maintenance of sinus rhythm at 1 month following electrical cardioversion,[194] there was no statistically significant difference between biphasic and monophasic waveforms in these patients with persistent AF (60% vs. 100%; p=0.13 for biphasic vs. monophasic; insufficient strength of evidence).

Recurrence of Atrial Fibrillation

Biphasic Versus Monophasic Waveforms

In assessing early recurrence of AF there was no statistically significant difference between the biphasic and monophasic waveform in the 1 study that assessed this outcome in patients with persistent AF (8.1% for biphasic and 9.7% for monophasic; p=NS;[203] low strength of evidence).

Results in Specific Subgroups of Interest

Thirteen (62%) of the 21 studies that compared different methods of external electrical cardioversion included only patients with persistent AF (2 of 9 studies comparing biphasic with monophasic waveforms,[194,203] all 4 studies comparing anterolateral vs. anteroposterior placement of the defibrillation electrodes,[175,183,187,202] all 3 studies comparing 200 vs. 360 J monophasic shock,[172,185,186] 2 of the 3 studies comparing different biphasic protocols,[171,198], the 1 study comparing standard polarity to reverse polarity,[197] and the 1 study comparing steel paddles to adhesive pads[176]). As expected, methods of external electrical cardioversion would be most relevant to patients with persistent AF, and therefore, the majority of studies focused primarily on this subgroup of interest. The results of these studies therefore may not be applicable to patients with permanent AF and are potentially applicable only to subsets of patients with paroxysmal AF. Of the eight studies that were not categorized as including only patients with persistent AF, seven did not provide information on type of AF,[173,174,179,182,184,196,201] and one[200] had seven percent of patients with paroxysmal AF; the proportion of patients with other types of AF were not reported. Therefore, comparisons in results by type of AF could not be made.

Drug Enhancement of External Electrical Cardioversion

Overview

Four studies evaluated the use of external electrical cardioversion alone in comparison with external electrical cardioversion augmented by drug treatment (metoprolol,[178] verapamil,[199,205] and ibutilide[195]). The general objective of these studies was to determine if drug pretreatment improves the outcome of external electrical cardioversion. A total of 329 patients were included in these studies; 3 studies included only patients with persistent AF.[178,195,199] One study was rated as good quality,[178] two were fair quality,[195,199] and one was poor quality.[205] All four studies were conducted in Europe, and three were single-center;[178,195,205] the number of sites was not reported in the fourth study.[199] In the two studies using verapamil, verapamil was given 3 days before and 3 days after electrical cardioversion.[199,205] Ibutilide was given about 20 minutes before electrical cardioversion,[195] and metoprolol was titrated over an unspecified time period prior to electrical cardioversion.[178] Placebo was administered to patients in the electrical cardioversion arm only in the study that assessed metoprolol pretreatment.[178] Mean age of patients ranged from 60–69 years in the drug-enhanced arms and from 60–68 years in the electrical cardioversion only arms. LVEF was reported in three studies[178,195,205] and ranged from 49–53 percent in the drug arms and from 50–53 percent in the electrical cardioversion alone arm. Restoration of sinus rhythm immediately after electrical cardioversion was reported in two studies.[178,195] Maintenance of sinus rhythm 1 week after electrical cardioversion was assessed in two studies,[178,199] and recurrence of AF at 1 week was reported in one poor-quality study.[205]

Restoration of Sinus Rhythm

Two of the four studies included a measure of restoration of sinus rhythm following the electrical cardioversion procedure. Both studies included only patients with persistent AF. One compared external electrical cardioversion with ibutilide pretreatment versus electrical cardioversion without ibutilide pretreatment.[195] In this study 100 percent of patients in both groups had sinus rhythm restored immediately after electrical cardioversion. Adverse events were not reported. In a second study,[178] restoration of sinus rhythm immediately after cardioversion was compared among patients receiving metoprolol pretreatment and patients receiving placebo pretreatment. Ninety-five percent of patients with metoprolol pretreatment converted to sinus rhythm compared with 93 percent of patients without metoprolol pretreatment (no p-value reported; moderate strength of evidence).

Maintenance of Sinus Rhythm

Two of the four studies assessed maintenance of sinus rhythm at 1 week following external electrical cardioversion. In one study comparing metoprolol pretreatment with no pretreatment,[178] a greater proportion of patients with metoprolol pretreatment maintained sinus rhythm at 1 week than did patients without metoprolol pretreatment (55% vs. 40%; p=0.04). Two patients in the metoprolol group developed bradycardia, and 10 percent and 9 percent, respectively, developed vertigo or dizziness in the metoprolol and no metoprolol groups. In the second study,[199] verapamil pretreatment was compared with no verapamil pretreatment in 23 patients with persistent AF. Eight of 9 patients (89%) receiving verapamil pretreatment maintained sinus rhythm at 1 week compared with 6 of 14 patients (43%) not receiving verapamil pretreatment (p=0.027). There was significant benefit for patients given verapamil or metoprolol pretreatment (moderate strength of evidence). Adverse events were not reported.

Recurrence of Atrial Fibrillation

One poor-quality study reported recurrence of AF within the first week after electrical cardioversion in patients with and without verapamil pretreatment.[205] In this study 3 percent of patients with verapamil pretreatment compared with 11 percent without verapamil pretreatment had recurrent AF within 1 week following cardioversion (p=0.02; low strength of evidence). Adverse events were not reported.

Results in Specific Subgroups of Interest

As described above, three of the four studies included patients with only persistent AF. As with the overall results, no definitive conclusions can be drawn for this subgroup of interest because of the small number of patients and different drug treatments used in the studies. Other specific subgroups of interest were not explored within the included studies.

Comparison of Drugs for Pharmacologic Cardioversion

Overview

Seventeen studies including 2,455 patients compared 2 or more rate- or rhythm-control drugs and assessed conversion of AF to sinus rhythm.[140,144,145,147,149,170,177,180,181,188-193,204,206] Six studies were multicenter,[145,147,180,189,190,206] nine were single-center,[140,144,149,170,177,188,191-193] and in two the number of sites was not reported.[181,204] Twelve studies were conducted in Europe,[140,144,145,147,170,177,188,191-193,204,206] two in Australia/New Zealand,[149,190] one in the UK,[181] and two in the United States.[180,189] Five studies were of good quality,[140,170,177,180,181] 11 of fair quality,[144,145,147,149,188-193,204] and 1 of poor quality.[206] Three studies were conducted in an inpatient setting,[140,144,177] three in an outpatient setting,[147,180,192] four in the emergency room,[149,170,189,190] one in multiple settings,[188] and in six the setting was not reported.[145,181,191,193,204,206] Two studies received industry funding,[145,180] 1 received government funding,[180] 4 were funded by nongovernment, nonindustry sources,[145,149,177,189] and 12 did not report funding source.[140,144,147,170,181,188,190-193,204,206] Nine studies included only patients with persistent AF,[144,145,147,170,177,192,193,204,206] and one included only patients with paroxysmal AF.[189]

Only seven of the studies included a comparison between two or more antiarrhythmic drugs (Table 11).[149,170,177,180,181,190,191] The most common comparison was between amiodarone and sotalol (four studies). Amiodarone was compared with ibutilide in one study and with flecainide and propafenone in one study, and ibutilide was compared with propafenone plus ibutilide in one study. Three of the studies included placebo[170,180] or control[181] arms which were not included in our analyses. Two of these studies also included an additional intervention arm that evaluated the use of digoxin.[149,190] In four studies, electrical cardioversion was not part of the study protocol, while in the remaining three the effect of the drugs was evaluated before and after external electrical cardioversion. Restoration of sinus rhythm was assessed prior to electrical cardioversion within 12 hours of drug administration in 1 of these 3 studies,[149] within 28 days in the second study,[180] and within 6 weeks of drug initiation in the third.[181] In the studies without use of electrical cardioversion, restoration of sinus rhythm was assessed at 48 hours in one study and within 24 hours in the other three studies. In addition, one study assessed recurrence of AF within 24 hours.[177] Two of the studies were conducted primarily in an emergency room setting,[149,170] two in an inpatient setting,[177,191] and three in an outpatient setting.[180,181,190]

Table 11. Studies including comparisons between antiarrhythmic drugs

Study	Sample Size (N)	Arm 1	Arm 2	Arm 3	Timing of Outcome Assessment Prior to or Without DCC	Assessment of Conversion Post-DCC?
Thomas, 2004[149]	140	Amiodarone (IV then oral)	Sotalol (IV then oral)	Digoxin (IV then oral)	Within 12 hours	Yes
Vijayalakshmi, 2006[181]	94	Amiodarone (oral)	Sotalol (oral)	Control[a]	Within 6 weeks	Yes
Singh, 2005[180]	665	Amiodarone (oral)	Sotalol (oral)	-	28 days	Yes
Joseph, 2000[190]	115	Amiodarone (IV then oral)	Sotalol (IV then oral)	Digoxin (IV then oral)	48 hours	No
Balla, 2011[170]	160	Amiodarone (oral)	Flecainide (oral)	Propafenone (oral)	Within 24 hours	No
Kafkas, 2007[191]	152	Amiodarone (IV)	Ibutilide (IV)	-	Within 24 hours	No
Korantzopoulos, 2006[177]	100	Ibutilide (IV)	Propafenone (oral) + ibutilide (IV)	-	Within 24 hours Also assessed recurrence within 24 hours post-conversion	No

[a]Not included in analyses.
Abbreviations: DCC=direct current cardioversion

In 8 studies (including 2 from Table 11), an antiarrhythmic drug (amiodarone, sotalol, or ibutilide) was compared with a rate-controlling drug (digoxin, diltiazem, carvedilol, or esmolol). Among these, restoration of sinus rhythm was assessed both before and after electrical cardioversion in three studies.[144,149,204] In the remaining five studies, external electrical cardioversion was not part of the study protocol.[140,188,190,192,193] In those studies, restoration of sinus rhythm was assessed from 30 minutes to 48 hours following drug initiation. In addition, 1 of the studies reported recurrence of AF within 24 hours of drug treatment and electrical cardioversion.[144]

In four studies, rate-controlling drugs were used in both study arms, and the study assessed restoration of sinus rhythm. In three of these, restoration of sinus rhythm was assessed before and after electrical cardioversion.[145,147,206] In the remaining study, restoration of sinus rhythm was assessed during the period of drug infusion (esmolol vs. digoxin).[189] In addition, one of the studies also assessed recurrence of AF at 1 month following conversion.[206]

Restoration of Sinus Rhythm

Results for comparisons between antiarrhythmic drugs are shown in Table 12. No statistically significant differences among the drugs were seen except between amiodarone versus ibutilide in one study and between ibutilide plus propafenone versus ibutilide alone in one study. Few adverse events were reported in any of the studies.

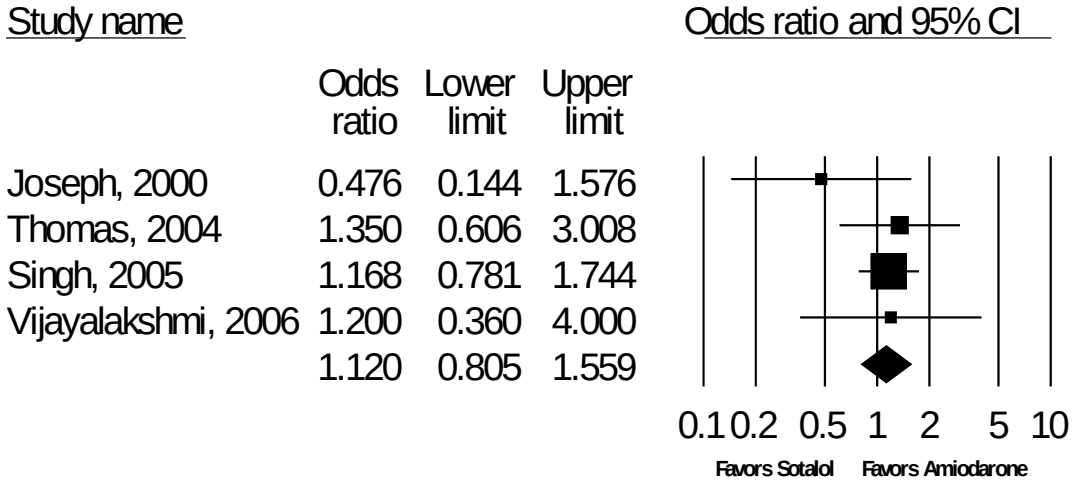
Table 12. Comparisons of antiarrhythmic drugs for restoration of sinus rhythm

Study	Sample Size (N)	Time Frame for Assessment	Restoration of SR pre-DCC (or Without DCC)	P Value	Restoration of SR Post-DCC	P value
Thomas, 2004[149]	140	12 hours	Amiodarone: 27/52 (52%) Sotalol: 20/45 (44%) Digoxin: 21/42 (50%)	NS	Amiodarone: 22/25 (88%) Sotalol: 23/25 (92%) Digoxin: 20/21 (95%)	NR
Vijaya-lakshmi, 2006[181]	94	6 weeks	Amiodarone: 7/27 (26%) Sotalol: 7/31 (23%)	0.5	Amiodarone: 15/20 (75%) Sotalol: 26/28 (93%)	NS
Joseph, 2000[190]	115	48 hours	Amiodarone: 30/39 (77%) Sotalol: 35/40 (88%) Digoxin: 21/36 (58%)	<0.01, sotalol vs. digoxin; NR between other drugs	NA	NA
Singh, 2005[180]	665	28 days	Amiodarone: 70/258 (27%) Sotalol: 59/244 (24%)	0.45	Amiodarone: 72% Sotalol: 74%	NR
Balla, 2011[170]	160	24 hours	Amiodarone: 85% Flecainide: 88% Propafenone: 85%	NS	NA	NA
Kafkas, 2007[191]	152	24 hours	Amiodarone: 42/73 (58%) Ibutilide: 63/79 (80%)	0.005	NA	NA
Korantzo-poulos, 2006[177]	100	24 hours	Ibutilide: 21/51 (41%) Propafenone + ibutilide: 35/49 (84%)	0.004	NA	NA

Abbreviations: DCC=direct current cardioversion; N=number of participants; NA=not applicable; NR=not reported; NS=not statistically significant; SR=sinus rhythm

We performed a meta-analysis of the four studies that compared amiodarone and sotalol.[149,180,181,190] These studies represented 736 patients and estimated an OR of 1.12 (95% CI, 0.81 to 1.56), demonstrating a potential benefit of amiodarone compared with sotalol which did not reach statistical significance (Figure 9; low strength of evidence). There was no evidence of heterogeneity. The Q-value was 2.22 for 3 degrees of freedom, p=0.527.

Figure 9. Forest plot for restoration of sinus rhythm for amiodarone versus sotalol



Abbreviation: CI=confidence interval

Eight studies compared an antiarrhythmic drug to a rate-controlling drug (one study compared an antiarrhythmic drug to the same antiarrhythmic drug used with a rate-controlling drug[188]) and assessed restoration of sinus rhythm from 30 minutes to 6 weeks after drug initiation (Table 13). Two of these included a second antiarrhythmic drug arm.[149,190] Three studies reported a statistically significantly greater restoration in sinus rhythm with amiodarone versus a rate-controlling drug, three studies showed no statistically significant difference between amiodarone and the rate-controlling drug, and one did not report a statistical analysis comparing amiodarone with a rate-controlling drug. One study showed that sotalol was better than digoxin at restoring sinus rhythm (88% vs. 58%; p<0.01), and another showed that esmolol plus ibutilide was better than ibutilide alone (OR 2.50; 95% CI, 1.04 to 5.84). Three studies evaluated differences between an antiarrhythmic drug and rate-controlling drug in rates of conversion after an electrical cardioversion. In 1 study amiodarone had a greater rate of conversion than diltiazem or digoxin (91% for amiodarone, 76% for diltiazem, and 67% for digoxin) which was statistically significant, but the other 2 studies either found no statistically significant difference or did not report a statistical analysis.

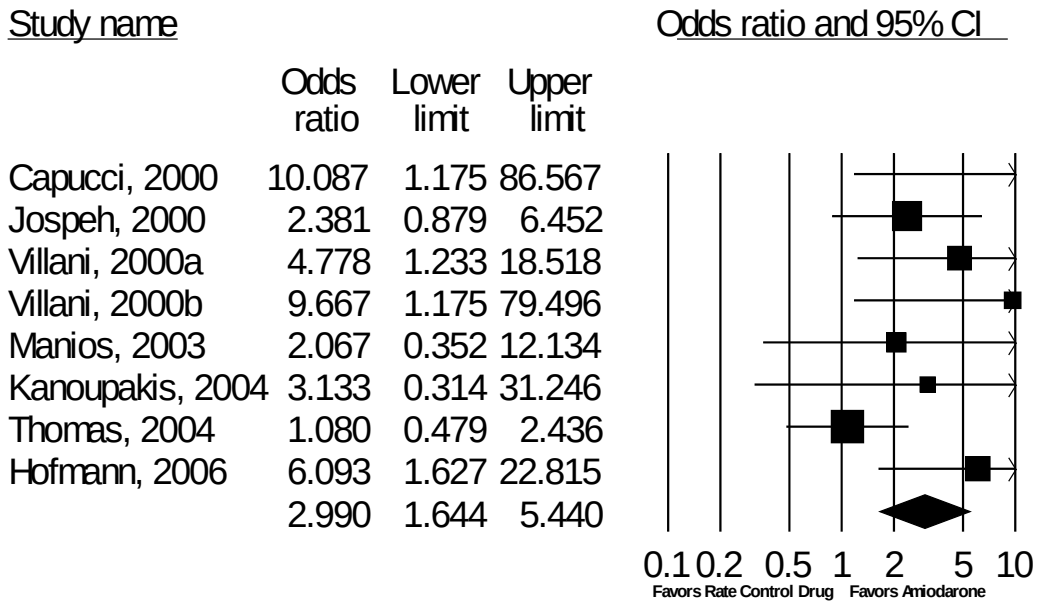
Table 13. Studies including comparisons of an antiarrhythmic drug with a rate-controlling drug

Study	Sample Size (N)	Time Frame for Assessment	Restoration of SR pre-DCC (or Without DCC)	P Value	Restoration of SR Post-DCC	P Value
Thomas, 2004[149]	140	12 hours	Amiodarone: 27/52 (52%) Sotalol: 20/45 (44%) Digoxin: 21/42 (50%)	NS	Amiodarone: 22/25 (88%) Sotalol: 23/25 (92%) Digoxin: 20/21 (95%)	NR
Joseph, 2000[190]	115	48 hours	Amiodarone: 30/39 (77%) Sotalol: 35/40 (88%) Digoxin: 21/36 (58%)	<0.01, sotalol vs. digoxin; NR between other drugs	NA	NA
Capucci, 2000[144]	61	1 month	Amiodarone: 25% Diltiazem: 3%	0.005	Amiodarone: 20/23 (87%) Diltiazem: 19/29 (66%)	NS
Villani, 2000[204]	120	1 month	Amiodarone: 25% Diltiazem: 6% Digoxin: 3%	0.005, amiodarone vs. digoxin	Amiodarone: 91% Diltiazem: 76% Digoxin: 67%	0.05, amiodarone vs. diltiazem and amiodarone vs. digoxin
Manios, 2003[193]	106	6 weeks	Amiodarone: 4/34 (12%) Diltiazem: 2/33 (6%)	NR	NA	NA
Kanoupa-kis, 2004[192]	142	4 weeks	Amiodarone: 3/48 (6%) Carvedilol: 1/48 (2%)	NR	NA	NA
Hofmann, 2006[140]	100	30 minutes	Amiodarone: 28% Digoxin: 6%	0.003	NA	NA
Fragakis, 2009[188]	90	90 minutes	Ibutilide + esmolol vs. Ibutilide alone	OR: 2.50 (95% CI, 1.04 to 5.84)	NA	NA

Abbreviations: CI=confidence interval; DCC=direct current cardioversion; N=number of participants; NA=not applicable; NR=not reported; NS=not statistically significant; OR=odds ratio; SR=sinus rhythm

We performed a meta-analysis of the 7 studies that compared amiodarone with a rate-controlling drug. This analysis of 613 patients estimated an OR of 2.99 (95% CI, 1.64 to 5.44), demonstrating a statistically significant benefit of amiodarone compared with rate-controlling drugs for restoration of sinus rhythm (Figure 10; high strength of evidence). There was no evidence of heterogeneity. The Q-value was 9.99 for 7 degrees of freedom, p=0.189. This finding is unsurprising given that rate-controlling agents would not be expected to terminate sinus rhythm.

Figure 10. Forest plot for restoration of sinus rhythm for amiodarone versus rate-control drugs



Abbreviation: CI=confidence interval

Four studies compared a rate-controlling drug with another rate-controlling drug and assessed restoration of sinus rhythm. In three of the studies, a comparison between drugs was also made after an external electrical cardioversion procedure.[145,147,206] Three of the studies compared verapamil to digoxin for 2–4 weeks,[145,147,206] and one compared IV esmolol to digoxin[189] during the infusion period. In three of the studies no difference was found between the drugs in the proportion of patients converting to sinus rhythm.[145,189,206] In 1 study, 14 percent of patients receiving verapamil converted to sinus rhythm compared with 0 percent receiving digoxin, a difference that was statistically significant ($p<0.05$).[147] In the three studies that also assessed outcomes after electrical cardioversion, only one found a statistically significant difference between the treatment arms; this favored digoxin over verapamil (65% of patients receiving verapamil vs. 88% of patients receiving digoxin converted to sinus rhythm; $p<0.05$).[147]

Recurrece of Atrial Fibrillation

Recurrence of AF within 24 hours of drug initiation was reported in 1 study that compared antiarrhythmic drugs (amiodarone vs. ibutilide).[191] In this study, 7.1 percent of patients receiving amiodarone versus 7.9 percent of patients receiving ibutilide had recurrence of AF with 24 hours (p=NS; low strength of evidence).

Results in Specific Subgroups of Interest

No results were reported for outcomes of interest in specific subgroups of interest.

Strength of Evidence

Our review identified 42 studies exploring the use of antiarrhythmic drugs and electrical cardioversion for conversion to sinus rhythm. These studies demonstrated that a single biphasic waveform is more effective than monophasic waveform in patients with persistent AF. Conversely, the included studies did not identify a significant difference in restoration of sinus rhythm with use of an anterolateral versus anteroposterior positioning of cardioversion electrodes. Although the strength of this evidence was rated as low, this finding is potentially clinically helpful, as health care providers often debate the superiority of one positioning of cardioversion electrodes over another. Studies demonstrated a benefit of drug pretreatment for restoration and maintenance of sinus rhythm, although data were inconclusive as to whether specific drugs were more beneficial as compared to other pharmacological alternatives. This finding challenges the assumption that one antiarrhythmic medication is clearly superior to others and underscores the need for more studies comparing the effectiveness and safety of different antiarrhythmic medications in enhancing restoration of sinus rhythm. Table 14 summarizes the strength of evidence for the outcomes of interest comparing antiarrhythmic drugs and electrical cardioversion methods. For those comparisons where the number of studies was sufficient to estimate a summary effect we were able to have greater confidence in our findings.

Table 14. Strength of evidence domains for antiarrhythmic drugs versus electrical cardioversion

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Comparison of Various Methods for External Electrical Cardioversion (Biphasic vs. Monophasic Waveforms)						
Restoration of Sinus Rhythm	4 (411)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 4.39 (95% CI, 2.84 to 6.78) favoring biphasic waveform
Maintenance of Sinus Rhytm	1 (83)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Recurrence of AF	1 (216)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No difference
Comparison of Various Methods for External Electrical Cardioversion (Anterolateral vs. Anteroposterior Cardioversions)						
Restoration of Sinus Rhythm	4 (393)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 0.87 (95% CI, 0.20 to 3.72) showing potential benefit of anterolateral electrode placement which did not reach statistical significance

Table 14. Strength of evidence domains for antiarrhythmic drugs versus electrical cardioversion (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Comparison of Various Methods for External Electrical Cardioversion (Energy Protocols)						
Restoration of Sinus Rhythm	3 (432)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 0.16 (95% CI, 0.05 to 0.53) favoring 360 J vs. 200 J monophasic shock
Drug Enhancement of External Electrical Cardioversion (vs. No Drug Enhancement)						
Restoration of Sinus Rhythm	2 (218)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** No significant benefit for patients given ibutilide or metoprolol pretreatment (p values NR)
Maintenance of Sinus Rhytm	2 (195)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** Significant benefit for patients given verapamil or metoprolol pretreatment (p values of 0.04 and 0.027 in the 2 studies)
Recurrence of AF	1 (88)	RCT/ Moderate	NA	Direct	Precise	**SOE=Low** Significant benefit of verapamil pretreatment (p=0.02)
Comparison of Drugs for Pharmacological Cardioversion (Amiodarone vs. Sotalol)						
Restoration of Sinus Rhythm	4 (736)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 1.12 (95% CI, 0.81 to 1.56) demonstrating a potential benefit of amiodarone which did not reach statistical significance
Comparison of Drugs for Pharmacological Cardioversion (Amiodarone vs. Rate-Control Drugs)						
Restoration of Sinus Rhythm	7 (613)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 2.99 (95% CI, 1.64 to 5.44) demonstrating a significant benefit of amiodarone
Recurrence of AF	1 (152)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No difference between amiodarone vs. ibutilide within 24 hours

Abbreviations: AF=atrial fibrillation; CI=confidence interval; OR=odds ratio; NA=not applicable; NR=not reported; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 5. Rhythm-Control Procedures and Drugs for Maintenance of Sinus Rhythm

KQ 5: What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents (either separately or in combination with each other) for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Key Points

Procedural therapies:

- ***Transcatheter pulmonary vein isolation (PVI) versus antiarrhythmic drugs***
  - Based on 8 RCTs (5 good, 3 fair quality) involving 921 patients, transcatheter PVI is superior to antiarrhythmic drugs for maintenance of sinus rhythm over 12 months of followup in patients with paroxysmal AF (high strength of evidence). This evidence is strongest in younger patients with little to no structural heart disease, and with no or mild enlargement of the left atrium.
  - Based on 2 RCTs (both good quality) involving 268 patients, transcatheter PVI is superior to antiarrhythmic medications in reducing cardiovascular hospitalizations (moderate strength of evidence).
- ***Transcatheter PVI with complex fractionated atrial electrogram (CFAE) ablation versus transcatheter PVI without CFAE ablation***
  - Based on 9 RCTs (6 good, 3 fair quality) involving 817 patients, CFAE ablation done in addition to transcatheter PVI showed a potential benefit in the maintenance of sinus rhythm at 12 months compared with PVI alone which did not reach statistical significance (low strength of evidence).
- ***Surgical Maze versus standard of care (mitral valve surgery)***
  - Based on 7 RCTs (1 good, 6 fair quality) involving 361 patients, surgical Maze at the time of other cardiac surgery (specifically mitral valve surgery) is superior to mitral valve surgery alone for maintenance of sinus rhythm over at least 12 months of followup in patients with persistent AF (moderate strength of evidence).
- ***PVI done at the time of cardiac surgery versus cardiac surgery alone or cardiac surgery in combination with antiarrhythmic drugs (AADs) or catheter ablation***
  - Based on 8 RCTs (5 good, 3 fair quality) involving 532 patients, PVI done at the time of cardiac surgery is superior to cardiac surgery alone or cardiac surgery in combination with AADs or catheter ablation for maintenance of sinus rhythm over 12 months of followup in patients with persistent AF (high strength of evidence).
- ***All comparisons***
  - There are insufficient data on the effect of rhythm control with PVI or surgical Maze on final outcomes such as all-cause mortality, stroke, heart failure, and LVEF, and on the safety and durability of the effectiveness of these procedures beyond 12 months.

Pharmacological therapies:

- Based on 9 studies (1 good, 8 fair quality) involving 2,095 patients, amiodarone appears better than sotalol but no different from propafenone in maintaining sinus rhythm (low strength of evidence).
- Based on 10 studies (4 good, 6 fair quality) involving 3,223 patients, amiodarone appears better than dronedarone or sotalol but no different from propafenone in reducing AF recurrence (low strength of evidence).
- Only 1 fair-quality study, a substudy of the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study involving 256 patients, systematically assessed differences in all-cause mortality between AADs; it found no statistically significant difference after a mean followup of 3.8 years between those receiving amiodarone versus sotalol (insufficient strength of evidence).
- Based on 1 good-quality study of 403 patients, amiodarone lowered AF hospitalizations compared with sotalol or propafenone (low strength of evidence) but did not demonstrate a benefit in control of AF symptoms (low strength of evidence).
- Based on 2 good-quality studies involving 1,068 patients, there was no difference among agents in impact on quality of life (low strength of evidence).

Overall Description of Included Studies

A total of 83 studies met our inclusion criteria and assessed the comparative safety and effectiveness of new procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents for the maintenance of sinus rhythm in patients with AF (Appendix Table F-5). Studies began enrollment from 1994 to 2007 and enrolled between 22 and 665 patients per study, resulting in a total of 11,014 patients. All were RCTs, with 36 rated as being of good quality,[178,180,181,207-239] 43 fair quality,[144,145,240-280] and 4 poor quality.[205,281-283]

A majority of studies (53 [64%]) were single-center trials,[144,178,205,207,210,211,213,214,216-219,221,226,229,231,233,234,240,242-248,250,252,254,255,257-271,274-278,280,281,283] while 23 were multicenter trials,[145,180,208,209,212,215,220,222-225,227,228,230,232,235,236,241,249,253,256,272,273] and 7 were not clear regarding the number of study sites.[181,237-239,251,279,282] A majority of studies (54 [65%] included sites in Europe,[144,145,178,181,205,207-215,219-228,232-237,242,244,245,247,249-251,253-256,258-261,265,269,270,273-275,280-282] 22 included sites in North America,[180,215-218,220,223-225,228-230,236,241,253,256,266,267,271,276,277,279] 10 included sites in Asia,[224,231,238,246,257,262-264,278,283] 5 included sites in South America,[224,240,243,248,268] 2 included sites in Australia;[224,252] and 2 studies did not report a location.[239,272] A majority of studies (51 [61%]), did not report their source of funding.[144,181,205,207,208,210,211,213-216,220,222,223,226,229,231,234,238-240,242,244,245,248-253,255-261,268-272,274-277,279-283] Fourteen report that at least a component of their funding came from industry,[145,178,180,209,217,218,224,228,232,236,237,241,265,273] and 10 reported that part of their funding came from government sources;[180,212,221,227,230,241,243,263,264,278] 15 reported other funding sources including primarily nongovernmental agencies.[145,178,209,219,225,227,233,235,243,246,247,254,262,266,267]

Six of the 83 included studies[145,180,214,226,228-230] had secondary publications with additional relevant data which we used. Three of these six studies were multicenter trials; the other three were single-center trials. Linked/secondary papers used in the analyses below were:

- Atwood, 2007;[284] Batcher, 2007;[285] and Singh, 2009[286] – all linked to Singh, 2005[180] (SAFE-T)

- Dorian, 2003;[287] Dorian, 2002;[288] and Lumer, 2002[289] – all linked to Roy, 2000[230] (Canadian Trial of Atrial Fibrillation)
- Khargi, 2001[290] – linked to Deneke, 2002[214]
- Leong-Sit, 2011[291] – linked to Roux, 2009[229] (5A)
- Pappone, 2011[292] – linked to Pappone, 2006[226] (APAF)
- Reynolds, 2010[293] – linked to Wilber, 2010[228] (ThermoCool AF)]

Below we provide an overview and then detailed syntheses stratified by the comparisons evaluated in the 83 studies.

Procedural Therapies for Rhythm Control

Description of Studies

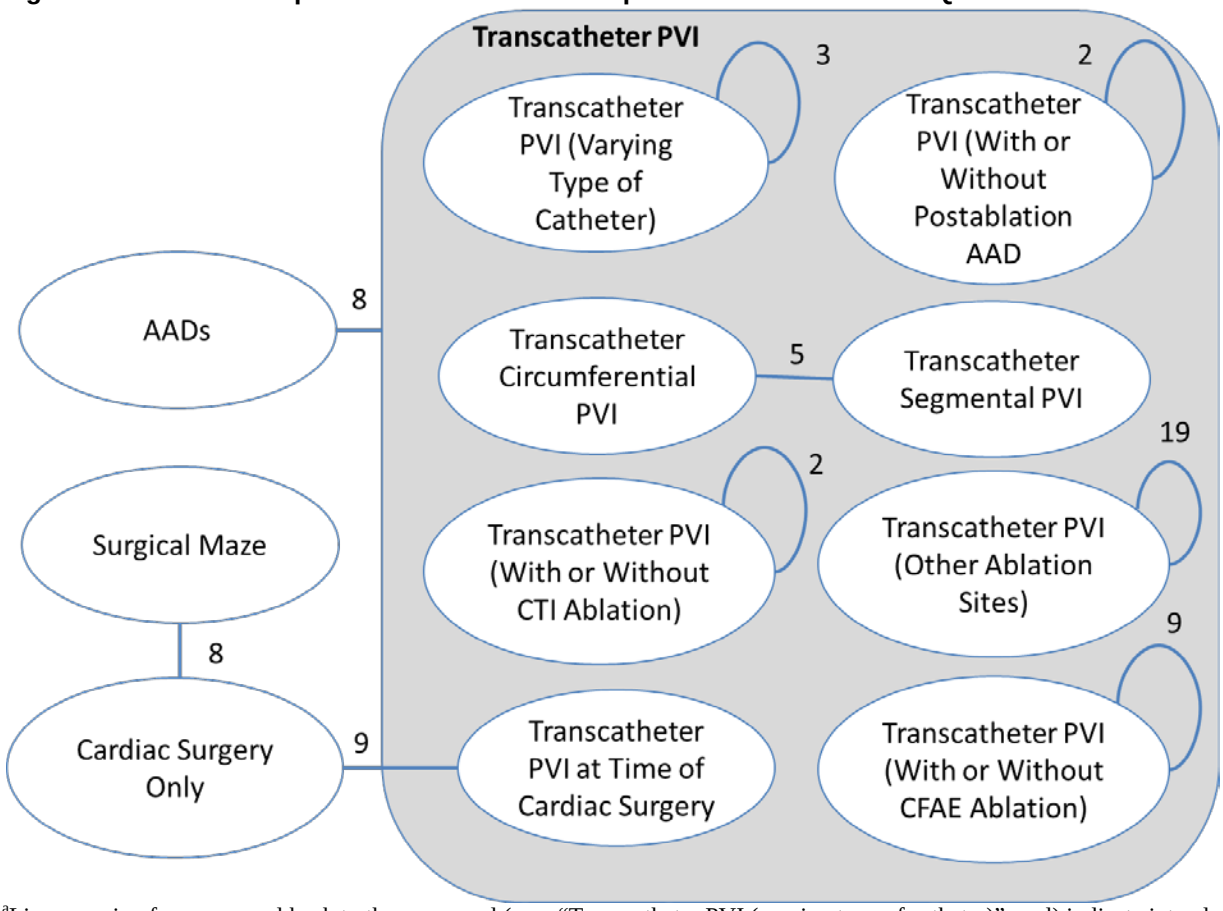
We identified 65 studies of procedural therapies for rhythm control. All were RCTs published between 2000 and 2012. They enrolled 6,739 patients across 5 continents, with the majority (36 studies) including sites in Europe. Thirty-one studies were rated as good quality,[207-223,225-229,231-239] 32 as fair quality,[240,242-244,246-248,250-255,257,262-268,270-280] and 2 as poor quality.[282,283] Sixteen studies were multicenter,[208,209,212,215,220,222,223,225,227,228,232,235,236,253,272,273] 43 were single-center,[207,210,211,213,214,216-219,221,226,229,231,233,234,240,242-244,246-248,250,252,254,255,257,262-268,270,271,274-278,280,283] and 6 did not specify the number of sites.[237-239,251,279,282] The majority of studies (39 [59%]) did not report their funding source.[207,208,210,211,213-216,220,222,223,226,229,231,234,238-240,242,244,248,250-253,255,257,268,270-272,274-277,279,280,282,283] Five were reported as exclusively government funded;[212,221,263,264,278] 2 were a combination of government and nongovernment/non-industry funded;[227,243] and 10 were reported as nongovernment/nonindustry funded alone.[219,225,233,235,246,247,254,262,266,267] Eight studies were exclusively industry funded,[217,218,228,232,236,237,265,273] and one study reported both industry and nongovernment funding.[209] The majority of studies (38 [58%]) did not report the clinical setting.[207,209,211,213-222,227,231-234,238,239,243,244,246-248,250,264,266,270-274,277,279,280,282,283] Thirteen studies were conducted in an inpatient setting,[208,212,229,235,237,240,242,254,263,265,267,268,275] nine were conducted in an outpatient setting,[210,226,251-253,255,257,276,278] and five were both inpatient and outpatient.[223,225,228,236,262]

Fourteen studies included patients from the United States,[215-218,220,223,225,228,229,266,267,271,276,277] four included the UK,[219,223,237,254] six included Canada,[215,220,223,228,236,253] nine included Asia,[231,238,246,257,262-264,278,283] four included South America,[240,243,248,268] and one included Australia/New Zealand;[252] three studies did not report their locations.[239,272,279] Thirty-six studies included patients from Europe.[207-215,220-223,225-228,232-236,242,244,247,250,251,253,255,265,270,273-275,280,282]

Several studies focused on specific populations. Eleven included only patients with long-standing persistent AF,[208,214,219,220,231,238,243,248,268,276,277] 17 included only patients with paroxysmal AF,[210,213,215,217,218,221,226,242,246,251,253,255,257,278-280,283] and 4 included only patients with persistent AF.[212,216,225,240] Finally, two studies enrolled only patients with comorbid heart failure.[240,264]

Figure 11 represents the treatment comparisons evaluated for this KQ.

Figure 11. Overview of procedural treatment comparisons evaluated for KQ 5[a]



[a]Lines running from one oval back to the same oval (e.g., "Transcatheter PVI (varying type of catheter)" oval) indicate intraclass comparisons (e.g., comparison of one transcatheter PVI catheter with another). Numbers refer to numbers of comparisons.
Abbreviations: AAD(s)=antiarrhythmic drug(s); CFAE=complex fractionated atrial electrogram; CTI=cavotricuspid isthmus; KQ=Key Question; PVI=pulmonary vein isolation

Thirty-eight studies compared one type of transcatheter ablation/PVI procedure with another.[207,210,211,213,215-218,220,221,223,227,233,236,238,239,244,246,247,250-252,255,257,264-267,271,272,275-280,282,283] An additional eight studies compared transcatheter ablation/PVI with antiarrhythmic drugs (AADs).[222,225,226,228,232,253,262,273] Finally, two studies compared AADs after PVI with no AADs after PVI.[229,234] Seventeen studies focused on surgical procedures for rhythm control: nine of these compared concomitant surgical ablation versus cardiac surgery without ablation;[208,209,212,219,235,237,268,270,274] and eight compared concomitant surgical Maze procedure versus surgery without Maze or versus transcatheter/PVI ablation.[214,231,240,242,243,248,254,263]

The most commonly reported outcome in the included studies was maintenance of sinus rhythm: 46 studies reported this outcome.[207-210,212-223,225,226,229,233,235,236,238,240,242-244,247,250-255,257,263-265,271,274-277,279,280,282] The second most commonly reported outcome (20 studies) was recurrence of AF.[210,211,216,221,222,227,232,234,239,243,246,248,257,262,264,266,268,270,272,273] Fifteen studies reported on restoration of sinus rhythm.[212,214,215,219,220,231,237,238,243,266-268,278,279,283] Other outcomes reported were all-cause mortality in 12 studies,[212,214,218,221,225,231,238,240,242,243,248,274] and cardiovascular mortality in 1 study.[219] Five studies reported incidence of stroke,[217,220,238,239,248] five reported mixed embolic events,[216,222,242,273,275] and three reported bleeding events including hemorrhagic stroke.[212,243,273] AF symptom control was reported in eight studies,[214,228,253-

[255,262,271,275] and heart failure symptom control in one study.[214] Cardiovascular hospitalization was reported in two studies,[222,226] and hospitalization related to AF in two studies.[229,273] Finally, quality of life and functional status were reported in 10 studies.[219,222,223,226,228,235,242,254,262,273] Control of ventricular rate was reported in one study.[253] Three studies reported composite outcomes.[212,213,229]

Detailed Synthesis

Transcatheter PVI Versus Antiarrhythmic Drugs

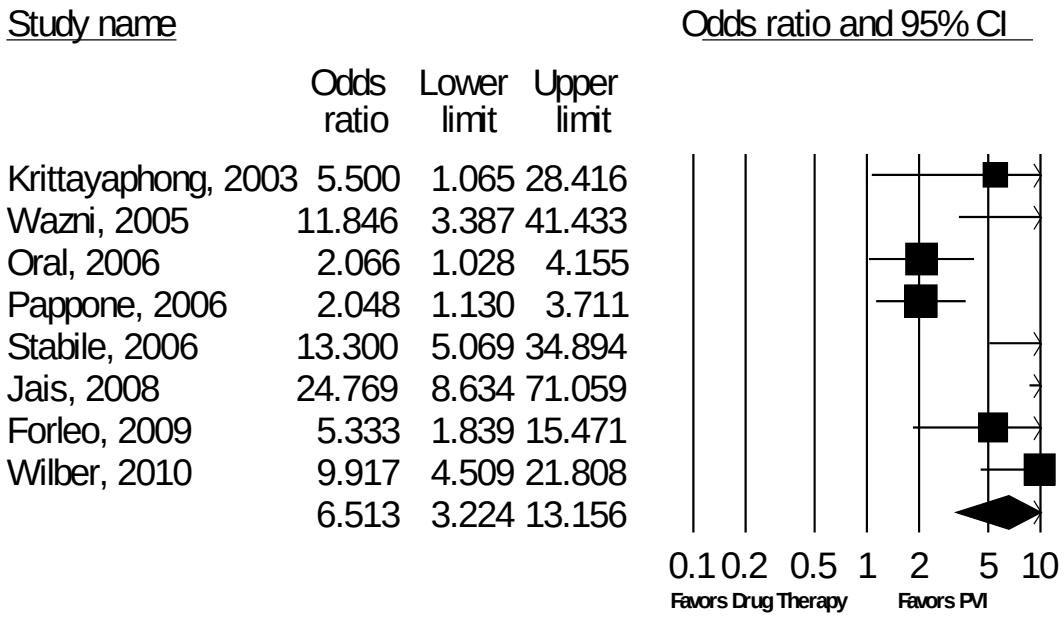
Overview

We identified eight RCTs for this comparison,[222,225,226,228,232,253,262,273] and the available data were deemed appropriate for a meta-analysis only for only the maintenance of sinus rhythm outcome. Results for other outcomes are described qualitatively below.

Maintenance of Sinus Rhythm

All eight studies evaluated this outcome.[222,225,226,228,232,253,262,273] A meta-analysis of these 8 studies included 921 patients and estimated an OR of 6.51 (95% CI, 3.22 to 13.16) favoring transcatheter PVI over antiarrhythmic drugs in the maintenance of sinus rhythm (Figure 12; high strength of evidence). There was significant heterogeneity. The Q-value was 32.36 for 7 degrees of freedom, $p<0.001$. The consistency of the findings in terms of the benefit of transcatheter PVI, however, reduced our concern with this heterogeneity, and we therefore did not reduce our strength of evidence rating.

Figure 12. Forest plot of maintenance of sinus rhythm for PVI versus drug therapy



Abbreviations: CI=confidence interval; PVI=pulmonary vein isolation

All-Cause Mortality

Only one study reported on all-cause mortality.[225] During 12 months of followup, 1 out of 69 (1.4%) patients in the PVI arm died versus no patients in the AAD arm (insufficient strength of evidence).

CV Hospitalizations

Two studies reported generally on CV hospitalizations during 12 months of followup.[222,226] In one,[226] 24 CV hospitalizations occurred in the 99 patients who underwent PVI versus 167 in the 99 patients who received AADs ($p<0.001$). In the second,[222] 8.6 percent of patients who underwent PVI were hospitalized for a CV cause vs. 34.3 percent of patients who received an AAD ($p=0.01$) (moderate strength of evidence).

One study reported more specifically on AF hospitalizations.[273] During 12 months of followup the rate of AF hospitalization was significantly higher in the AAD arm (15 out of 35) than in the PVI arm (3 out of 32; $p<0.001$) (insufficient strength of evidence).

Quality of Life/Functional Status

Six studies evaluated the impact of transcatheter PVI versus antiarrhythmic drugs on quality of life or functional status.[222,226,253,262,273,293] The metrics for assessing these outcomes were too variable to allow quantitative synthesis, but of the six studies, four demonstrated a statistically significant better quality of life or functional status in the PVI group.[222,253,273,293] The other two studies, which represented both the smallest (30 patients) and largest (198 patients) studies, did not demonstrate significant differences.[226,262] Given the inconsistency in metrics and findings amongst the good-quality studies,[222,226,293] we were unable to estimate the direction of impact of transcatheter PVI versus antiarrhythmic drugs on quality of life or functional status (insufficient strength of evidence).

Mixed Embolic Events Including Stroke

Only two studies[222,273] reported on mixed embolic events including stroke. In both studies, no embolic events occurred in the PVI arm or the AAD arm during 12 months of followup (low strength of evidence).

Bleeding Events

Only one study reported on bleeding events.[273] During 1 year of followup, there was no significant difference in the rate of bleeding between the PVI group (2 out of 32) and the AAD arm (1 out of 35; $p=0.60$) (insufficient strength of evidence).

Other Outcomes

None of these studies reported on cardiovascular mortality, or restoration of sinus rhythm, cardiovascular mortality, or heart failure symptoms.

Adverse Events

In one study,[262] PVI resulted in one stroke and one groin hematoma, while amiodarone caused the following adverse effects in 7 patients (46.7%): GI adverse effects (mostly nausea) in 6 patients, corneal deposits in 2 patients, hypothyroidism in 2 patients, abnormal liver enzymes in 2 patients, hyperthyroidism in 1 patient, and sinus node dysfunction in 1 patient.

In one study,[273] there were no thromboembolic events (defined as transient ischemic events, stroke, deep vein thrombosis, or pulmonary embolism) in either treatment group. Bleeding rates

were similar in both groups. Incidence of documented bradycardia was higher in the AAD group (3 [8.6%] of 35 patients vs. none in the PVI group). Asymptomatic moderate (50%–70%) pulmonary vein (PV) stenosis was documented in 1 (3%) of 32 patients in the PVI group, affecting only one vein; no patient developed severe (>70%) PV stenosis.

In one study,[226] there were no serious adverse events in the PVI arm. Significant adverse events leading to permanent drug withdrawal occurred in 23 patients. Proarrhythmia developed in 3 patients in the flecainide group (hypotensive wide QRS tachycardia in 2 patients and 1:1 atrial flutter in 1); thyroid dysfunction occurred in 7 patients in the amiodarone group requiring drug discontinuation; and sexual impairment in 11 patients in the sotalol group.

In one study,[225] there were no complications in either group.

In one study,[232] 3 (4.4%) major complications were related to ablation: one patient had a stroke during left atrium ablation and died 9 months later of brain hemorrhage; another suffered transient phrenic paralysis; and a third had a pericardial effusion which required pericardiocentesis. There was no PV stenosis reported. In the AAD arm, one patient had a TIA, two patients had cancer (one died), and one patient died suddenly.

In one study,[253] a total of 155 ablation procedures were performed. Two episodes of cardiac tamponade requiring pericardiocentesis and two groin hematomas were reported; one in each group (one crossover patient), with a favorable outcome in all. A stenosis of the left superior PV that required dilatation and stent implantation occurred in one crossover patient, with an uneventful course thereafter. One case of hyperthyroidism was observed in the AAD group, as well as two deaths that were not deemed related to AADs (acute myeloid leukemia and myocardial infarction).

In one study,[222] no serious procedure-related complications were observed except for an access site hematoma severe enough to require a prolongation of hospitalization, which did not require blood transfusion and resolved without any sequelae. Six patients in the AAD group (17.1%) developed significant drug adverse effects. Symptomatic bradycardia requiring a dosage reduction or a change to an alternative drug occurred in five patients, all known to have hypertension. One of the patients underwent implantation of a dual-chamber pacemaker for symptomatic sinus nodal dysfunction. Another patient developed 1:1 atrial flutter while on flecainide.

In one study,[228] within 30 days following the intervention, major treatment-related adverse events occurred in 5 patients (1 pericardial effusion, 1 pulmonary edema, 1 pneumonia, 1 vascular complication, and 1 heart failure) in the catheter ablation group (5/103 [4.9%]) and 5 patients (2 with life-threatening arrhythmias and 3 with disabling drug intolerance requiring discontinuation) in the AAD group (5/57 [8.8%]). One patient in the catheter ablation group who had undergone PV isolation alone died 284 days after the procedure due to acute myocardial infarction deemed unrelated to the procedure.

Transcatheter PVI Using Different Types of Ablation Catheters

Overview

Although we identified three studies comparing types of catheter, these were deemed inappropriate for a meta-analysis given that each study compared different types of catheter, making heterogeneity insurmountable. One study[217] compared an 8 mm tip catheter with a cooled tip catheter. A second study[210] compared a multipolar circular ablation catheter with point-by-point PVI using an irrigated-tip ablation catheter. One study[207] compared a new circular

ablation catheter with point-by-point conventional ablation catheter. Results for outcomes of interest are accordingly described qualitatively below.

Maintenance of Sinus Rhythm (SR)

One study[217] showed that within 6 months and on no AADs, 25 out of 42 patients in the 8 mm tip catheter arm maintained SR versus 20 out of 40 patients in the cooled tip catheter arm (p=0.321). In another study[210] and within 6 months, 87.2 percent of patients in whom a multiple circular ablation catheter was used maintained SR compared with 81.5 percent of patients in whom point-by-point PVI with an irrigated tip ablation catheter was used. In another study,[207] SR was maintained by 72 percent of patients in the circular ablation catheter arm versus 68 percent of patients in the point-by-point conventional ablation catheter arm (p=0.48) (low strength of evidence).

Recurrence of AF

For one study,[210] during a mean of 221 days, 12 of 51 patients in whom a multipolar circular ablation catheter was used had recurrent AF versus 15 of 51 patients in whom point-by-point PVI with an irrigated tip ablation catheter was used (p=0.8; low strength of evidence).

Stroke

Within 6 months of followup, one study[217] reported that the stroke risk was 0 in the 8 mm tip catheter arm versus 1 out of 40 in the cooled tip catheter arm (insufficient strength of evidence).

Other Outcomes

None of the studies examined restoration of SR, all-cause or cardiovascular mortality, CV hospitalizations, heart failure symptoms, control of AF symptoms, quality of life, mixed embolic events including stroke, or bleeding events.

Adverse Events

In one study,[207] no major intraprocedural complications occurred. One patient in the circular ablation catheter group had transient asymptomatic ST-segment elevation in the inferior leads, which was completely reversible within 5 minutes and probably due to air embolism. In the point-by-point conventional ablation catheter group, one patient developed a femoral hematoma, which prolonged hospital stay but did not require surgical revision. Another patient had a deep venous femoral thrombosis without sequelae on followup.

In one study,[217] two serious adverse events were observed. One patient randomized to the cooled tip catheter developed transient left-sided weakness 45 minutes after completion of the ablation procedure. CT scan was suggestive of a small right subcortical thromboembolic stroke, and the weakness recovered completely within 24 hours without any intervention. One patient randomized to 8-mm tip catheter developed an LA esophageal fistula that resulted in death.

In one study,[210] no serious adverse events were noted in either study group.

Transcatheter Circumferential PVI Versus Transcatheter Segmental PVI

Overview

We identified 5 RCTs on circumferential vs. segmental PVI,[215,221,264-266,275] and the available data were deemed appropriate for a meta-analysis for the maintenance of sinus rhythm. Results for other outcomes are described qualitatively below.

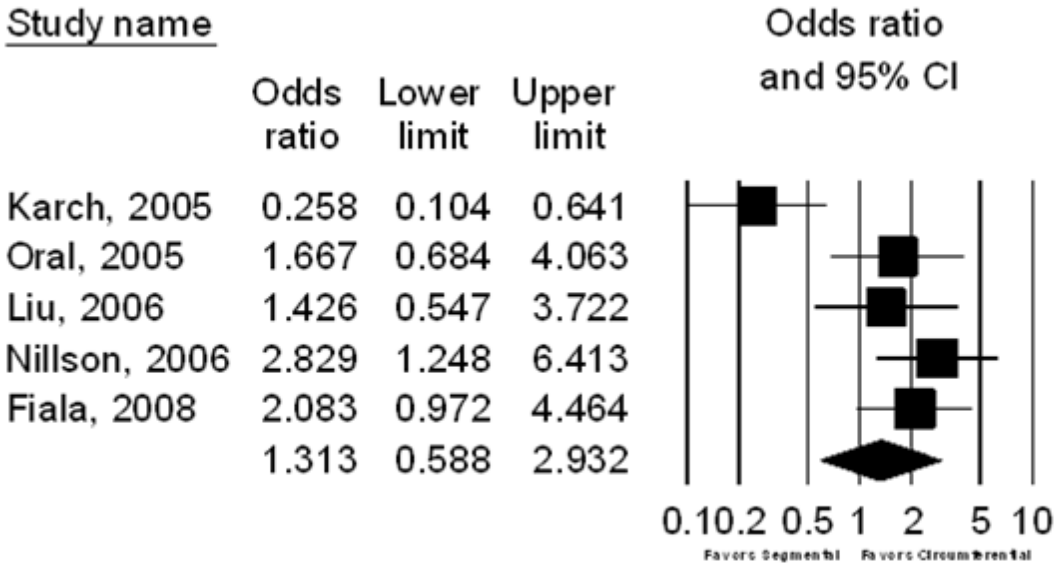
Restoration of SR

One study examined restoration of SR immediately post-ablation.[266] Not counting the effect of ibutilide and/or cardioversion, SR was restored in 11 out of 40 patients who underwent circumferential PVI versus 7 out of 40 patients who underwent segmental PVI (p=0.40) (insufficient strength of evidence).

Maintenance of Sinus Rhythm

A meta-analysis of 5 studies[221,264-266,275] included 500 patients and estimated an OR of 1.31 (95% CI, 0.59 to 2.93; Figure 13), demonstrating a potential benefit of circumferential PVI compared with segmental PVI which did not reach statistical significance (low strength of evidence). There was significant heterogeneity. The Q-value was 17.29 for 4 degrees of freedom, p=0.002. Given the wide confidence interval, the heterogeneity, and the fact that this finding did not reach statistical significance, this conclusion should be viewed with caution. The study by Karch and colleagues,[275] which appears inconsistent with the other studies, was a fair-quality study from a single center and had a shorter duration of followup (6 months) than the other included studies, which ranged from 9–48 months of followup, and therefore was not necessarily comparable.

Figure 13. Forest plot of maintenance of sinus rhythm for circumferential transcatheter PVI versus segmental transcatheter PVI



Abbreviations: CI=confidence interval; PVI=pulmonary vein isolation

All-Cause Mortality

One study[221] reported that after a mean followup of 48 months, no death occurred in either arm (low strength of evidence).

Other Outcomes

None of the studies reported on cardiovascular mortality, CV hospitalizations, heart failure symptoms, control of AF symptoms, quality of life, stroke, mixed embolic events including stroke, or bleeding events.

Adverse Events

In one study,[275] the composite outcome of periprocedural pericardial tamponade, thromboembolic complications, and PV stenosis was encountered in 6 patients (12%) in the circumferential PV ablation group and in 7 patients (14%) in the segmental PV ablation group (p=0.77). Mild pericardial effusion (3 to 8 mm) was observed in 22 patients in the circumferential PV ablation group versus 5 patients in the segmental PV ablation group (p<0.01). This did not lead to cardiac tamponade in any of the patients, and percutaneous drainage was never needed. Thromboembolic complications occurred as transient ischemic attacks in 2 patients after circumferential PV ablation and in 1 patient after segmental PV ablation. One stroke with a persistent sensorimotor defect was noted in a patient after circumferential PV ablation. PV stenosis occurred after both ablation strategies. However, it was more frequent after segmental PV ablation (6 patients with 7 affected PVs versus 3 patients with 3 affected PVs after circumferential PV ablation). None of the patients with PV stenosis was symptomatic during followup.

In one study,[266] no complication occurred in either arm.

In one study,[264] three patients from the segmental PVI group and four from the circumferential PVI group developed subcutaneous hematoma and one patient from the segmental PVI group required a blood transfusion. Asymptomatic right superior PV stenosis was detected in one patient in each arm.

In 1 study,[265] 4 patients in 173 procedures had a systemic embolic event (2.3%), all within the first 2 days after ablation. Of these patients, one stroke and one episode of transient cerebral ischemia occurred in each group. Five patients complained of respiratory symptoms after ablation. All had a normal magnetic resonance angiography, except in 1 patient, with a narrowing of the left inferior PV (30%) with no hemodynamic significance approximately 3 months after the procedure.

In one study,[221] there were no atrial esophageal fistulae, embolic complications, or significant pericardial effusion (>5 mm) associated with the first ablation procedure. One patient had a femoral arterial pseudoaneurysm which was cured by pressure. No clinically significant PV stenosis occurred.

Transcatheter PVI With Cavotricuspid Isthmus (CTI) Ablation Versus Transcatheter PVI Without CTI Ablation

Overview

Because we identified only two studies of transcatheter PVI with CTI ablation versus without CTI ablation,[227,272] the data were deemed inappropriate for meta-analysis. Results for outcomes of interest are accordingly described qualitatively below.

Recurrence of AF

Two studies reported AF recurrence.[227,272] In one study,[272] during 2 months of followup AF recurred in 32.6 percent of patients who underwent PVI with CTI compared with 30.5 percent of patients who underwent PVI without CTI (p=NS). In another study,[227] AF recurred in 31 percent of patients who had PVI with CTI compared with 24 percent of patients who had PVI without CTI versus (p=0.07) (insufficient strength of evidence).

Other Outcomes

None of the studies reported on restoration of SR, maintenance of SR, all-cause or cardiovascular mortality, CV hospitalizations, heart failure symptoms, control of AF symptoms, stroke, mixed embolic events including stroke, quality of life, or bleeding events.

Adverse Events

In one study,[227] no adverse events were reported. In the second study,[272] none of the patients had thromboembolic complications. There was no occurrence of severe PV stenosis (>70%). One patient in each group had moderate (50% to 70%) asymptomatic PV stenosis.

Transcatheter PVI With CFAE Ablation Versus Transcatheter PVI Without CFAE Ablation

Overview

We identified nine studies on transcatheter PVI with CFAE ablation versus without CFAE ablation,[213,215,216,220,223,236,246,267,276] and the available data were deemed appropriate for a meta-analysis for the maintenance of sinus rhythm. Results for other outcomes are described qualitatively below.

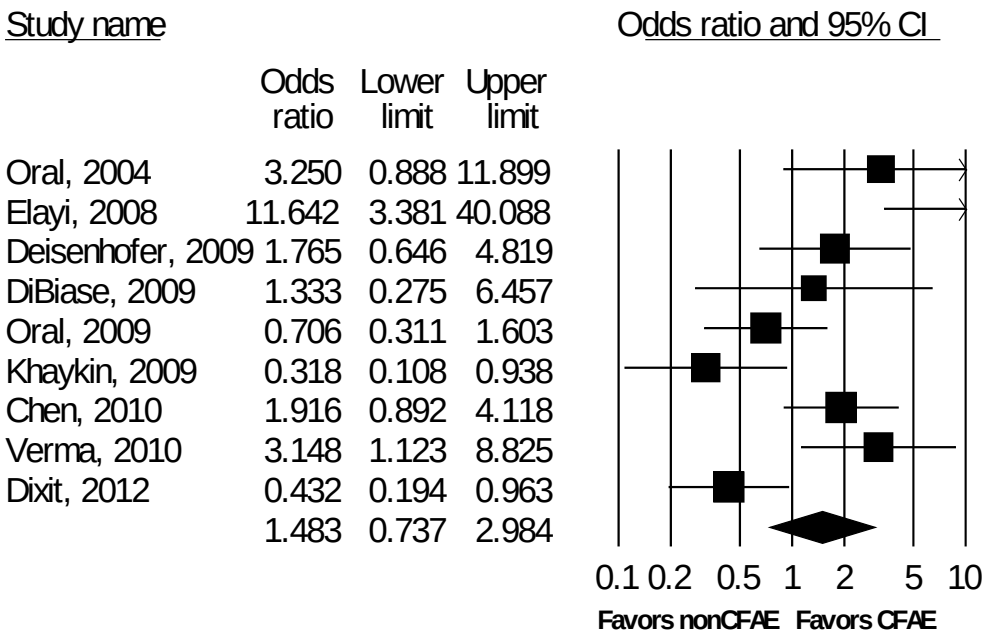
Restoration of SR

One study reported on restoration of SR immediately after the ablation procedure.[220] SR was restored in 13 percent of patients when a circumferential PVI using a 3.5 mm tip irrigated catheter versus 44 percent of patients who underwent PVAI using an open irrigation catheter versus 74 percent of patients in whom CFAE and PVAI were performed. Another study[215] demonstrated 65 percent of patients being restored to SR with CFAE while 60 percent was seen in the non-CFAE group (low strength of evidence).

Maintenance of Sinus Rhythm

A meta-analysis of 9 studies[213,215,216,220,223,236,246,267,276] included 817 patients and estimated an OR of 1.48 (95% CI, 0.74 to 2.98); although there is a potential benefit of CFAE ablation, this finding did not reach statistical significance (Figure 14). We concluded that CFAE ablation in addition to PVI did not increase maintenance of sinus rhythm compared with PVI only (low strength of evidence). There was significant heterogeneity, reducing our confidence in this finding and the strength of evidence rating. The Q-value was 34.06 for 8 degrees of freedom, $p<0.001$.

Figure 14. Forest plot of maintenance of sinus rhythm for transcatheter PVI with or without CFAE ablation



Abbreviations: CFAE=complex fractionated atrial electrogram; CI=confidence interval; PVI=pulmonary vein isolation

Quality of Life/Functional Status/Control of AF Symptoms

In one study[223] and during 6 months of followup, there was no significant difference in 8 quality-of-life and functional status parameters between the 2 arms of the study (insufficient strength of evidence).

Stroke

During a mean followup of 16 months, 1 study[220] showed no stroke in the circumferential PVI with a 3.5 mm tip irrigated catheter arm, the PVAI with an open irrigation catheter arm, or the CFAE and PVAI arm (low strength of evidence).

Composite Outcomes

One study[213] reported on the composite outcome of mixed embolic events including stroke, PV stenosis, and other procedural complications. It showed no significant difference in this outcome between the 2 arms (1 out of 48 patients who underwent PVI vs. 1 out of 50 patients who underwent PVI with CFAE ablation).

Other Outcomes

None of the studies reported on all-cause or cardiovascular mortality, CV hospitalizations, heart failure symptoms, or bleeding events. One study[216] reported on mixed embolic events including stroke, but it did not specify the arm(s) in which these events occurred.

Adverse Events

In one study,[216] serious adverse events were observed in 7 patients (5%) and were distributed across the 3 study arms (2% in Arm1, 4% in Arm 2 and 8% in Arm 3, p=0.304). These included groin access complications in three patients (pseudo-aneurysm in one, arterio-venous fistula in one, and large hematoma in one), cerebrovascular events in two patients (transient ischemic

attack in one and left cortical micro-embolic stroke in one), pericardial tamponade in one patient and significant PV stenosis requiring stenting.

In one study,[213] one pericardial effusion requiring pericardiocentesis occurred in the PVI + CFAE group. A patient in the PVI +CFAE group experienced a prolonged asystole during removal of the venous sheaths 3 hours after the procedure requiring temporary cardiopulmonary resuscitation. Asymptomatic PV stenosis <50 percent (left inferior PV) was detected in 1 patient of the PVI group on the followup MRI scan.

In one study,[215] no major complications occurred in either arm.

In 1 study,[246] major adverse events were observed in 4 patients (3.4%): 1 patient developed cardiac perforation with cardiac tamponade during the procedure; 1 patient had massive pericardial effusion after the procedure requiring pericardiocentesis; and 2 patients had hemothorax resulting in chest tube insertion. Two patients developed pseudoaneurysms that were managed conservatively. There was no occurrence of significant PV stenosis, system thromboembolism, atrial esophageal fistula, or death.

In one study,[236] adverse events occurred in eight patients overall including both initial and repeat procedures. Two cardiac perforations occurred, resulting in cardiac tamponade. Four patients had minor bleeding related to the procedure (three femoral hematomas and one hematuria from urinary catheter insertion), none requiring transfusion or intervention. One patient had a vascular complication (pseudoaneurysm) that was managed with local injection, and 1 patient had minor (30%) PV stenosis of one vein (left inferior). There were no occurrences of significant PV stenosis, embolic complication, stroke, atrial-esophageal fistula, or death.

In one study,[223] one of the patients randomly assigned to PVAI had an intraprocedural pericardial effusion that was drained in the electrophysiology laboratory. No patient had PV stenosis in excess of 20 percent. There were no thromboembolic events or strokes. One of the patients was started on amiodarone after an early recurrence and continued it until 9 months after ablation. Although this patient had no further AF recurrences during this period, the outcome was classified as ablation failure, based on study definitions.

In one study,[220] two pericardial effusions were seen in group 3; one was treated with percutaneous drainage, and the other one required surgical drainage. Two patients had asymptomatic PV stenosis on the computed tomography scan assessment after ablation that remained stable over time (1 patient from group 3, 30% to 40% in the left inferior PV [LIPV], and 1 patient from group 2, 40% in the right inferior PV [RIPV]). No esophageal fistulae or strokes occurred.

In 1 study that involved 157 ablation procedures performed on 119 patients,[276] 2 patients developed transient pericarditis, and 1 patient had a small pericardial effusion without tamponade. Two vascular complications occurred, including a self-limited extraperitoneal bleed and a femoral arteriovenous fistula.

Transcatheter PVI Versus Transcatheter PVI With Ablation Sites Other Than CTI and CFAE and Transcatheter PVI Involving all Four PVs Versus Transcatheter PVI Involving Arrhythmogenic PVs only

Overview

Although we identified 19 studies examining ablation sites other than CTI and CFAE,[211,218,233,238,239,244,247,250-252,255,257,271,277-280,282,283] these were deemed inappropriate for a meta-analysis because each study compared different ablation site(s). One study specifically

focused on transcatheter PVI involving arrhythmogenic PVs only.[294] Results for outcomes of interest are accordingly described qualitatively below.

Restoration of SR

Restoration of SR was only reported by two studies.[238,277] One[238] showed restoration of sinus rhythm in 79.9 percent of the left atrial group patients and 76 percent restoration in the biatrial group of patients (p=0.49). In another study[277] of 85 patients undergoing ablation, AF converted to sinus rhythm in 8 (9%) and to atrial tachycardia/flutter in 11 (13%) during left atrial ablation (insufficient strength of evidence).

Maintenance of SR

Fifteen studies reported on maintenance of SR.[218,233,238,244,247,250-252,255,257,271,277,279,280,282] In four studies,[244,250,251,280] maintenance of SR was significantly higher in the group that underwent additional ablation sites to PVI. In one study,[247] superior vena cava isolation in addition to PVI improved maintenance of SR only in patients with paroxysmal AF. In one study,[218] isolation of the arrhythmogenic veins was as efficacious as empiric isolation of all veins in achieving long-term control of AF. In nine studies,[233,238,252,255,257,271,277,279,282] additional ablation sites to PVI did not enhance maintenance of SR (insufficient strength of evidence).

Recurrence of AF

Although 6 studies involving 572 patients evaluated recurrence of AF, the findings were inconsistent and imprecise, resulting in an insufficient strength of evidence rating.

Specifically, in one study,[211] during a mean followup of 14 months, AF recurred in 39 percent of patients in the left atrial ablation group and in 15 percent of patients in the biatrial ablation group (p=0.022).

In another study[257] and during a mean followup of 23 months, AF recurrence was not significantly different between the PVI only group and the PVI with additional ablation sites group.

In a third study,[239] AF recurrence was significantly lower in the PVI + substrate modification consisting of a roofline connecting both left superior and right superior PV and LA isthmus ablation between left inferior PV and mitral annulus than in the PVI only group (44% vs. 77% within 1 month, p=0.002 and 31% vs. 80% within 12 months, p=0.0001).

In another (poor-quality) study,[283] after the initial ablation procedure, there was no statistically significant difference in AF recurrence between the two groups of PVI vs. PVI and superior vena cava isolation.

In another study,[278] the early AF recurrence rate within 3 months of the procedure was not significantly different among patients randomized to PVI vs. PVI + left atrial roof line ablation vs. PVI + left atrial roof line ablation + linear ablation at the posterior inferior left atrial wall (p=0.384).

One study[279] showed that after a mean followup period of about 16 months and after 1 ablation procedure, 19 (58%) patients in the segmental PVI group were free of atrial arrhythmias off all antiarrhythmic therapy, as compared with 17 (52%) patients in the PVI and left atrial linear ablation group (p=0.62; insufficient strength of evidence).

All-Cause Mortality

In one study[218] and within 1 year of followup, 1 out of 53 patients in the all PVI group died compared with 0 out of 52 patients in the selected (arrhythmogenic) PVI group. In another

study,[238] the 4-year actuarial survival was 98.7±1.1 percent in the biatrial group and 100 percent in the left atrial group (p=0.50) (insufficient strength of evidence).

Quality of Life/Functional Status/Control of AF Symptoms

In one study,[255] there was no significant difference in the control of AF symptoms between the single PVI vs. all PVI group. In another study[271] and within 9 months of followup, there was no significant difference in the control of AF symptoms between the PVI group and the PVI + two linear lesions (one between the superior PVs and one from the left inferior PV to the mitral valve annulus) (low strength of evidence).

Stroke

In one study,[238] the 1- and 3-year actuarial survival free from stroke rates were both 100 percent in the left atrial group, and 98.7±3.5 percent and 93.6±5.7 percent in the biatrial group, respectively (p=0.50).

In another study,[239] 1 out of 32 patients had a stroke in the PVI + substrate modification vs. 0 of 30 patients in the PVI group (insufficient strength of evidence).

Other Outcomes

None of the studies reported on cardiovascular mortality, CV hospitalizations, heart failure symptoms, mixed embolic events including stroke, bleeding events, or other adverse events.

Transcatheter PVI Alone Versus Transcatheter PVI Plus Postablation Antiarrhythmic Drugs

Overview

Two studies compared PVI alone with PVI plus postablation AADs.[229,234] Results for outcomes of interest are described qualitatively below.

Recurrence of AF

In one study[234] and during 12 months of followup, AF recurred in 18 out of 53 patients who received no AAD postablation compared with 16 out of 54 patients who received an AAD postablation (p=0.63). The other study[229] showed that within 6 weeks post-PVI, AF recurred significantly more in the group of patients who received no AAD after ablation than the group of patients who received an AAD after ablation (15/57 vs. 2/53, p=0.0012). Given the inconsistency in findings and varying followup times, we determined the strength of evidence to be insufficient.

CV Hospitalizations

No study reported generally on CV hospitalizations. One reported specifically on AF hospitalizations.[229] This study showed no significant difference between the AAD arm and no AAD arm (low strength of evidence).

Composite Outcomes

One study[229] examined a composite outcome of (1) atrial arrhythmias lasting >24 hours; (2) atrial arrhythmias associated with severe symptoms requiring hospital admission, cardioversion, or initiation/modification of AAD therapy; and (3) intolerance to antiarrhythmic agent requiring

drug cessation or change. Within 6 weeks, the rate of this outcome was significantly lower in the AAD arm than in the no AAD arm (10/53 vs. 24/57, p=0.005).

Other Outcomes

Neither study reported on restoration of SR, all-cause or cardiovascular mortality, heart failure symptoms, control of AF symptoms, quality of life, stroke, mixed embolic events including stroke, or bleeding events,.

Adverse Events

One study[234] did not report any adverse events. In the second study[229] three patients in the AAD group experienced side effects, presumably related to the antiarrhythmic agent, requiring drug cessation. These side effects consisted of a skin rash, severe fatigue, and recurrent severe headaches.

Surgical Maze Versus Standard of Care (Mitral Valve Surgery)

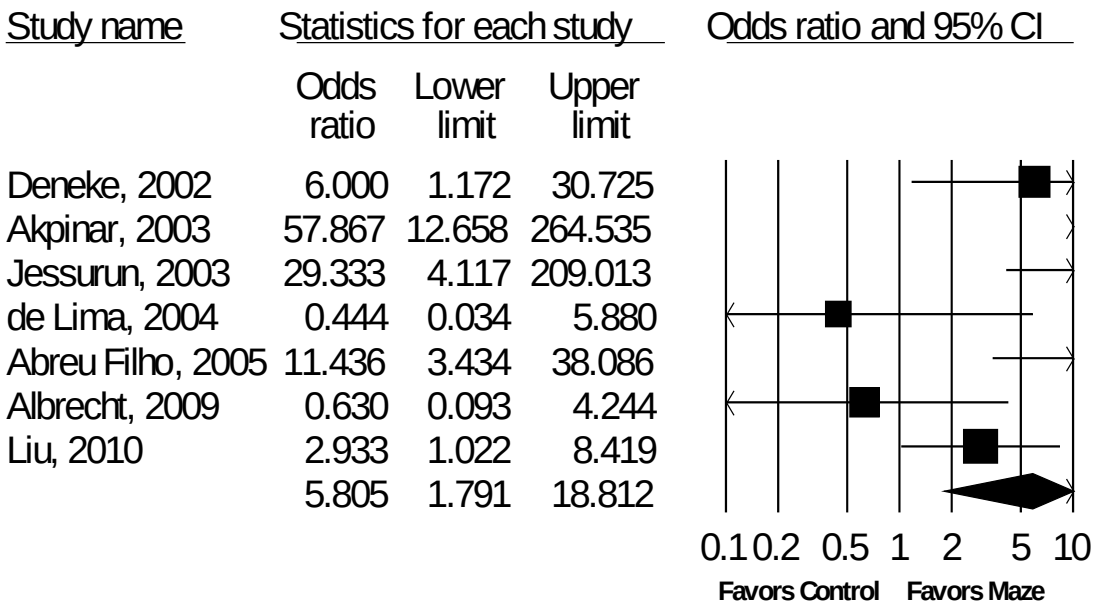
Overview

We identified eight RCTs for this comparison,[214,231,240,242,243,248,254,263] and the available data were deemed appropriate for a meta-analysis for the following outcomes: maintenance of sinus rhythm and all-cause mortality. Results for other outcomes are described qualitatively below.

Maintenance of Sinus Rhythm

Seven studies evaluated maintenance of sinus rhythm in patients undergoing surgical Maze versus standard of care (specifically mitral valve surgery).[214,240,242,243,248,254,263] A meta-analysis of these 7 studies included 361 patients and estimated an OR of 5.80 (95% CI, 1.79 to 18.81), demonstrating a large and statistically significant benefit of the Maze procedure compared with mitral valve surgery for maintenance of sinus rhythm (Figure 15; moderate strength of evidence). There was significant heterogeneity, which—despite the large estimated benefit—reduced our strength of evidence rating. The Q-value was 23.15 for 6 degrees of freedom, p=0.001. Although the two outlier studies[243,248] were both fair-quality studies where the randomization and reason for exclusion of specific patients from either randomization or analysis were unclear, the other five studies were also variable in quality (four fair- and one good-quality study) with small samples, and unclear methods.

Figure 15. Forest plot of maintenance of sinus rhythm for Maze procedure versus standard of care (mitral valve surgery)



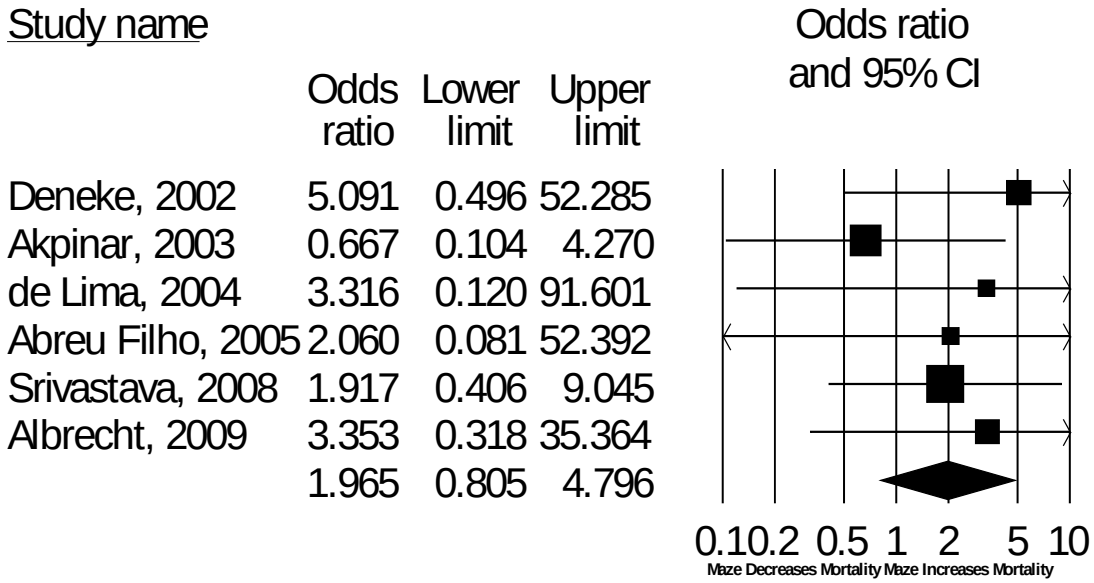
Abbreviation: CI=confidence interval

All-Cause Mortality

Six studies evaluated all-cause mortality in patients undergoing surgical Maze versus standard of care (mitral valve surgery).[214,231,240,242,243,248] A meta-analysis of these 6 studies included 387 patients and estimated an OR of 1.97 (95% CI, 0.81 to 4.80), demonstrating a potential increase in mortality associated with the Maze procedure compared with mitral valve surgery, although this finding did not reach statistical significance (Figure 16; low strength of evidence). There was no evidence of heterogeneity. The Q-value was 2.24 for 5 degrees of freedom, p=0.815. Note that the study by Akpinar and colleagues[242] was performed in Turkey and involved a small number of deaths, several of which were, according to the study authors, unrelated to the procedure or cardiovascular in nature (e.g., long-standing pulmonary infection, traffic accident).

Reviewing the timing of mortality within the Maze groups for the included studies, the mortality in one study[240] occurred from septic shock after pneumonia 17 days postprocedure; none of the deaths in another study[242] were considered related to the procedure; in a third study,[243] 1 death in the Maze group was immediate and caused by tamponade/reoperation, and 2 additional deaths occurred 57 days and 20 months postprocedure and were caused by acute renal failure/septic shock and coronary artery dissection during catheterization, respectively. In another study,[248] there was 1 hospital death on the 57th postoperative day, caused by sepsis, in a patient who underwent the Maze procedure. In another study,[214] 1 patient within the Maze group died after 40 days due to renal bleeding under standard anticoagulation as performed after prosthetic mitral valve implantation (INR 2·5 to 3·5). One patient died after 45 days from mediastinitis; 1 sudden cardiac death occurred after 4 months; and 1 death due to respiratory insufficiency followed severe lung fibrosis after 7 months. As detailed, many of these deaths in the Maze arm were most likely not related to the procedure itself.

Figure 16. Forest plot of all-cause mortality for Maze procedure versus standard of care (mitral valve surgery)



Abbreviation: CI=confidence interval

Heart Failure Symptoms

In one study[214] and during 6 months of followup, there was no significant difference in heart failure symptoms between patients who underwent the Maze procedure in conjunction with mitral valve replacement and those who did not undergo the Maze procedure in conjunction with mitral valve replacement (2.5/15 vs. 2.6/15, p=0.531) (insufficient strength of evidence).

Stroke

One study[248] examined stroke in the immediate postoperative period. It found that the rate of stoke was 0, 0, and 1 out of 10 in the PVI+mitral valve correction group, the surgical Maze plus mitral valve correction group, and mitral valve correction only group, respectively (insufficient strength of evidence).

Mixed Embolic Events Including Stroke

In one study[242] and within 1 year of followup, the risk of mixed embolic events including stroke was 0 in the mitral valve surgery plus Maze group vs. 6 percent in the mitral valve surgery only group (p=0.08) (insufficient strength of evidence).

Bleeding Events

One study[243] reported on hemorrhagic stroke. It found that during a mean followup of 35 months, this outcome occurred in 2 out of 20 patients who underwent surgical PVI versus 1 out of 20 in patients who underwent the surgical Maze versus 0 out of 20 in the control group who underwent mitral valve correction only. Patients in the control group but not in other groups also had other causes of bleeding: epistaxis (n=2), petechiae (n=1), hematuria (n=1) and lower GI bleeding (n=1) (insufficient strength of evidence).

Other Outcomes

None of these studies reported on cardiovascular mortality or CV hospitalizations.

Adverse Events

In 1 study,[214] 1 patient from the surgical Maze died after 40 days due to renal bleeding under standard anticoagulation as performed after prosthetic mitral valve implantation (INR 2·5 to 3·5).

In 1 study,[242] 1 (3%) patient in the Maze group required a pacemaker vs. 0 in the mitral valve surgery only group (p>0.05). One patient (3%) in the Maze group and 1 patient in the valve surgery only group (2.9%) required reoperation for bleeding (p>0.05). Prolonged ventilation occurred in 1 patient in the Maze group vs. 0 patients in the valve surgery only group (p>0.05). Late tamponade occurred in 1 (3%) patient in the Maze group and in 2 (6%) patients in the valve surgery only group (p>0.05). A thromboembolic event occurred in 0 patients in the Maze group versus 2 patients (6%) in the valve surgery only group (p=0.08).

In one study,[254] one patient in the Maze group had an intraoperative MI, and one patient in the control group had a stroke.

In another study,[248] there was 1 hospital death on the 57th postoperative day, caused by sepsis, in a patient who underwent the Maze procedure. One redo surgical intervention was necessary because of bleeding and hemopericardium in a patient in the control group. This patient suffered a stroke and pulmonary embolism, but exhibited a favorable clinical outcome. Four patients had previous history of stroke but only one had cerebral ischemia during the postoperative period. No patient required a permanent pacemaker during followup. There was one case of intestinal bleeding (not clear in which group), during the second postoperative week, which required surgical intervention. There were no other major complications.

In 1 study,[240] the in-hospital mortality rate was 0 in the mitral valve surgery only group and 2.3 percent in the Maze group (p>0.99). One patient in the Maze group died of septic shock after pneumonia on the 17th postoperative day. One patient (2.3%) in the Maze group and 1 patient (3.5%) in the mitral valve surgery only group received a permanent pacemaker because of symptomatic bradyarrythmia. Endocarditis occurred in one patient (3.5%) in the mitral valve surgery only group versus zero in the Maze group. Pneumonia occurred in 3 (7.1%) patients in the Maze group versus 1 (3.5%) in the mitral valve surgery only group, and mediastinitis occurred in 1 (2.3%) patient in the Maze group versus 0 patients in the mitral valve surgery only group.

In one study,[243] two hemorrhagic strokes occurred in the surgical PVI group versus one in the Maze group versus zero in the control group. One patient in the surgical PVI group had perioperative MI. One patient in the Maze group had mediastinitis, and one patient in the Maze group had immediate reoperation for bleeding. One patient in the control group had a TIA, and four patients in the control group had bleeding.

In 1 study,[263] 1 patient who had circumferential PVI 6 months after valve surgery developed major stroke with right-sided hemiplegia during the procedure. There were no femoral vein access site complication and cardiac tamponade in either group, and there was no PV stenosis during followup. One patient in the Maze procedure group (done concomitantly with valve surgery) had pericardial effusion 5 days after the operation and it disappeared 15 days after the procedure. Sternal wound infection was found in three patients in the circumferential PVI group and four patients in the Maze group, and was treated with intravenous antibiotics. Pneumonia occurred in four cases in the circumferential PVI group and three cases in the Maze group and recovered in all cases. There was no significant difference in the rates of complications between the two groups (p>0.05).

In one study,[231] two deaths were recorded in the biatrial and PVI Maze groups with no mortality in the other two groups (left atrial Maze and valve surgery only groups). Five patients required reexploration for bleeding, two each in the valve surgery only group and left atrial Maze group, and one patient in the biatrial Maze group. Three patients who underwent biatrial Maze, two patients in the left atrial Maze group and one patient in the valve surgery only group required a prolonged hospital stay for low cardiac output. One patient in the PVI Maze group developed mediastinitis.

PVI at the Time of Cardiac Surgery Versus Cardiac Surgery Alone or in Combination With Antiarrhythmic Drugs or Catheter Ablation

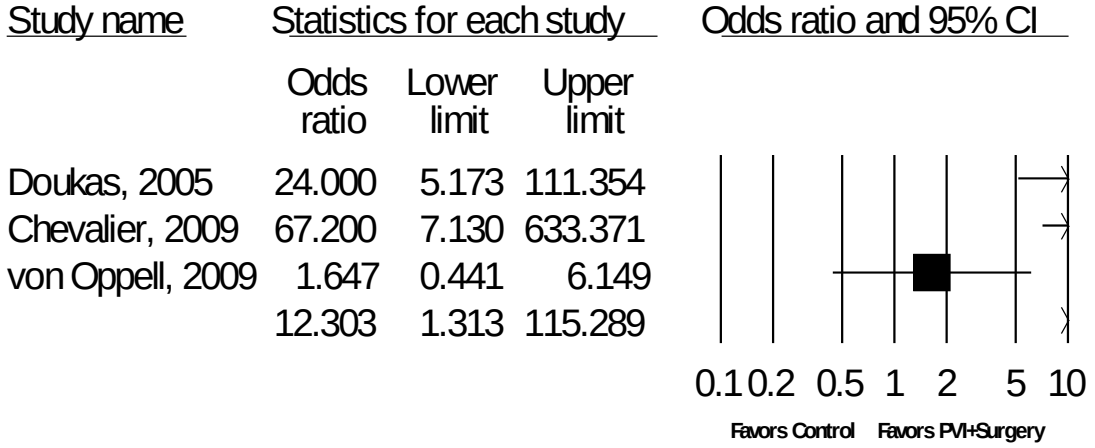
Overview

We identified 9 RCTs for this comparison,[208,209,212,219,235,237,268,270,274] and the available data were deemed appropriate for a meta-analysis for restoration and maintenance of sinus rhythm. Results for other outcomes are described qualitatively below.

Restoration of Sinus Rhythm

Four studies evaluated restoration of sinus rhythm.[212,219,237,268] Three of were combined in a meta-analysis.[212,219,237] In the fourth study,[268] all patients in both arms remained in sinus rhythm during the immediate postprocedure period; because of the lack of events, this study could not be combined quantitatively with the others. The 3 included studies involved 181 patients and estimated an OR of 12.30 (95% CI, 1.31 to 115.29), demonstrating a statistically significant benefit of PVI at the time of cardiac surgery for restoration of sinus rhythm (Figure 17; high strength of evidence). There was significant heterogeneity. The Q-value was 10.95 for 2 degrees of freedom, p=0.004. Despite the heterogeneity, the overall benefit of PVI was consistent across the studies and allowed us to assign a high strength of evidence rating.

Figure 17. Forest plot of restoration of sinus rhythm for PVI at the time of cardiac surgery versus cardiac surgery alone or in combination with antiarrhythmic drugs or catheter ablation



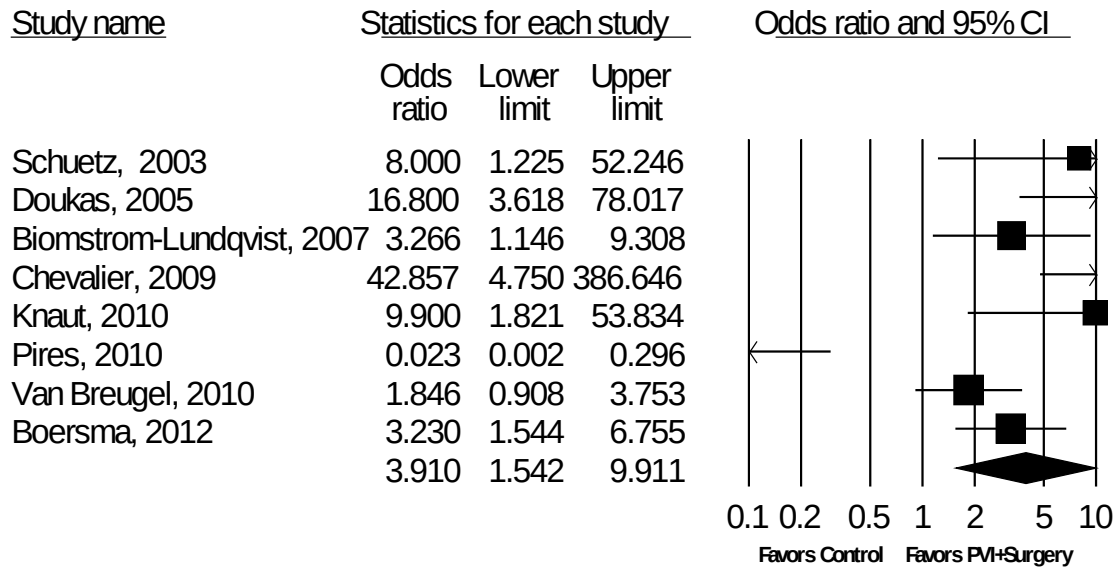
Abbreviation: CI=confidence interval; PVI=pulmonary vein isolation

Maintenance of Sinus Rhythm

Eight studies evaluated maintenance of sinus rhythm.[208,209,212,219,235,268,270,274] Meta-analysis of these 8 studies included 532 patients and estimated an OR of 3.91 (95% CI, 1.54 to 9.91), demonstrating a statistically significant benefit of PVI at the time of cardiac surgery for

maintenance of sinus rhythm (Figure 18; high strength of evidence). There was significant heterogeneity. The Q-value was 29.02 for 7 degrees of freedom, p<0.001. Note that the Pires study[268] compared surgical cut and sew versus PVI and, as such, was quite different from the other included studies. Eliminating this study from our meta-analysis did not substantially change our findings and therefore allowed us to maintain the high strength of evidence rating.

Figure 18. Forest plot of maintenance of sinus rhythm for PVI at the time of cardiac surgery versus cardiac surgery alone or in combination with antiarrhythmic drugs or catheter ablation



Abbreviations: CI=confidence interval; PVI=pulmonary vein isolation

All-Cause Mortality

In one study[212] and during 12 months of followup, 1 out of 22 patients in the ablation arm and 0 out of 22 patients in the control arm (p=NR) died. In another study,[274] within 1 year, 3 out of 22 patients died in the ablation arm versus 1 out of 21 in the control arm (p=NR) (low strength of evidence).

Cardiovascular Mortality

In one study,[219] cardiovascular mortality in the immediate postoperative period was experienced by 3 out of 45 patients in the ablation arm and 4 out of 44 patients in the control arm (p=NR) (insufficient strength of evidence).

Quality of Life/Functional Status/Control of AF Symptoms

In one study,[219] functional status was assessed by the shuttle-walk test. No significant differences in this test were found between the ablation group and the control group at 6 months; however, the distance covered at 12 months was significantly longer in the ablation group than in the control group (359 meters vs. 304 meters, p=0.02).

In one study,[235] cardiac surgery in general resulted in an overall improvement of the RAND SF-36 and the MFI-20. However, the EQ-5D showed a significant deterioration in the subscale Pain/Discomfort for both groups (p<0.001), with a significantly worse outcome for the control group (p=0.006). The authors concluded that health-related quality of life in patients with paroxysmal, permanent, and persistent AF improves after cardiac surgery, but this improvement

is presumably more affected by treating the underlying heart disease than by restoring sinus rhythm (insufficient strength of evidence).

Stroke

In one study,[219] the risk of stroke within 12 months of followup was not significantly different between the PVI group and the control group. In another study,[212] the rate of stroke within 12 months of followup was 3 out of 21 in the PVI group vs. 0 out of 22 in the control group (p=NR) There was low strength of evidence that there is no difference between PVI and control groups..

Bleeding Events

In one study,[212] significant postoperative bleeding occurred in 1 out of 21 patients in the ablation arm and 3 out of 22 patients in the control arm (p=NR) (insufficient strength of evidence).

Composite Outcomes

One study[212] reported on the composite outcome of recurrence of AF, all-cause mortality, stroke, and postprocedure complications within 1 year of followup. This outcome occurred in 16 out of 21 patients in the ablation arm versus 11 out of 22 patients in the control arm (p=0.14).

Other Outcomes

None of these studies reported on CV hospitalizations, heart failure symptoms, or mixed embolic events including stroke.

Adverse Events

In one study[209] the procedural adverse event rate was significantly higher for minimally invasive surgical ablation with 23.0 percent (14 serious adverse events [SAEs] in 14 patients) than for catheter ablation with 3.2 percent (2 SAEs in 2 patients; p=0.001). One patient in each group had a procedure-related stroke, and one patient in each group had a TIA. In the surgical ablation group, six patients had pneumothorax, one patient had hemothorax, one patient had rib fracture, one patient needed sternotomy for access to control bleeding, one patient had pneumonia, and two patients required a permanent pacemaker.

In another study,[270] two in-hospital deaths occurred. One patient (ablation group) died at postoperative day 19 due to cerebral air embolism of unknown origin. A thorough autopsy did not reveal any link to the previously performed microwave ablation therapy. The second patient (control) died because of refractory heart failure.

In 1 study,[219] operative mortality was 6.1 percent in the ablation group vs. 8.3 percent in the mitral valve surgery only group. Stroke or TIA occurred in 4 percent of patients in the ablation group and 2.1 percent of patients in the mitral valve surgery only group. Sepsis occurred in 6.1 percent of patients in the ablation group vs. 4.2 percent in the mitral valve surgery only group.

In 1 study,[208] the rate of in-hospital complications, excluding pacemaker implantations, was 11.4 percent (4 patients) in the mitral valve surgery group and 26.5 percent (9 patients) in the cryoablation group (p=0.110). Low cardiac output syndrome occurred while weaning from bypass in three patients, it was related to right heart failure and preoperative myocardial infarction in two patients, respectively, and required temporary assist by intra-aortic balloon pump in three patients. All except one patient, who died on the third postoperative day, recovered. The in-hospital mortality rate was 2.9 percent (1/34 patients) in the cryoablation

group and 0 in the mitral valve surgery alone group. The permanent pacemaker implantation rate did not differ between the two treatment groups (p=0.583).

In one study,[212] there was one death in the ablation group in a patient who developed postoperative cardiogenic shock rapidly followed by massive ischemic stroke. It was necessary to implant pacemakers in five patients (three patients in the ablation group and two patients in the control group). One patient from each group underwent a second valve replacement. Four patients presented with severe postoperative hemorrhage: one patient in the ablation group and three patients in the control group. Three patients in the ablation group had strokes. One patient had postoperative left hemiplegia due to gas embolism. During the immediate postoperative period, one patient had a TIA. In the control group, one patient presented with a TIA.

In one study,[237] no ablation device-related adverse events were reported. All significant adverse events were classified as "related to cardiac surgery" or to "pre-existing disease." Notably, there were no peri- or postoperative cerebrovascular accidents in either group.

In one study,[274] in the ablation group, no device- or procedure-related complication was observed.

In one study,[268] one patient in radiofrequency ablation group developed cardiac tamponade requiring surgical intervention. No patients died.

In one study,[235] during the postoperative in-hospital period the number of re-do thoracotomies, pulmonary complications, stroke, myocardial infarction, renal failure, and infection rate showed no significant differences between patient groups. During followup, the total number of adverse events remained equally distributed among both groups. The overall in- and out of hospital mortality rate was 5.3 percent (n=7): 5 patients in the control group versus 2 patients in the surgical ablation group.

Pharmacological Therapies for Rhythm Control

Description of Included Studies

A total of 18 studies including 4,300 patients and published between 2000 and 2010 compared the safety or effectiveness of pharmacological agents with or without external electrical cardioversion for maintaining sinus rhythm in patients with AF. Six studies were of good quality,[178,180,181,224,230,256] 10 were of fair quality,[144,145,241,245,249,258-261,269] and 2 were of poor quality.[205,281] Seven studies were multicenter,[145,180,224,230,241,249,256] 10 were single-center studies,[144,178,205,245,258-261,269,281] and in 1 study was undefined.[181] One study was conducted entirely in the United States,[180] 10 were conducted entirely in Europe[144,145,178,181,205,245,249,269,281] 5 were conducted specifically in Greece,[256,258-261] one was conducted completely in Canada,[230] and one was conducted on several continents.[224] Two studies were funded by government and industry,[180,241] one was funded solely by government,[230] two were funded by industry and nongovernment sources,[145,178] one was funded solely by industry,[224] and the funding source was unclear for 12 studies.[144,181,205,245,249,256,258-261,269,281] For eight of the studies, the setting was unclear or not reported.[145,178,181,224,230,241,245,269] Of the remaining nine studies, four included an inpatient setting,[144,205,249,281] six included an outpatient setting,[180,256,258-260,281] and four included an emergency room setting.[258-261] Four studies included patients with paroxysmal or persistent AF,[258-261] and seven studies included patients with persistent AF.[144,145,178,249,256,269,281] Sixteen studies including 3,660 patients reported the sex of study participants: 33% were female and 67% were male.[144,145,178,180,181,205,224,241,245,249,256,258-261,269]

Five studies evaluated the use of one or more pharmacological agent with external electrical cardioversion as a primary component of the tested intervention;[144,145,178,205,281] 1 study compared an AAD with a rate-controlling drug (sotalol vs. bisoprolol);[269] 1 study evaluated the effect of the addition of verapamil to either amiodarone or flecainide;[249] 1 study compared two beta blockers;[256] and 10 studies compared two or more AADs.[180,181,224,230,241,245,258-261]

Detailed Synthesis

Studies of pharmacological agents are presented in two groups: (1) those that included the use of electrical cardioversion as a key component of the study protocol (5 studies[144,145,178,205,281] and (2) those that compared pharmacological agents as the primary component of the interventions and may have included electrical cardioversion as a minor component (13 studies).[180,181,224,230,241,245,249,256,258-261,269]

Pharmacological Therapy in Which Electrical Cardioversion is a Key Component of the Treatment

Five studies involving 582 patients evaluated pharmacological therapy in which electrical cardioversion was a key component of the treatment.[144,145,178,205,281] Four of these included only patients with persistent AF.[144,145,178,281] Two studies evaluated the effect of adding a drug (verapamil[205] or metoprolol[178]) to external electrical cardioversion. Two studies compared the use of two different drugs in this context,[144,145] one of which also evaluated the use of two electrical cardioversion methods (daily monitoring resulting in acute electrical cardioversions with recurrences vs. routine monitoring potentially resulting in less frequent electrical cardioversions with recurrences).[145] One poor-quality study compared a method of giving up to two additional electrical cardioversions versus no additional electrical cardioversions in patients receiving Class Ic or Class III AADs.[281]

Maintenance of Sinus Rhythm

One good-quality study reported maintenance of sinus rhythm at 1.5, 3, and 6 months after electrical cardioversion in patients receiving metoprolol versus placebo.[178] A statistically significant greater proportion of patients maintained sinus rhythm in the metoprolol versus placebo group at all time points (1.5 months: 51% vs. 33%, p=0.02; 3 months: 47% vs. 28%, p=0.01; 6 months: 46% vs. 26%, p=0.03). The results were the same for patients who were allowed one additional electrical cardioversion (67% vs. 42% for metoprolol vs. placebo, p=0.02) and for patients who were allowed two additional electrical cardioversions (24% vs. 8%, p=0.03) Lack of studies and small sample size resulted in insufficient strength of evidence for this outcome.

Recurrence of AF

Four studies reported recurrence of AF at different time points ranging from 2–18 months.[144,145,205,281] One fair-quality study compared use of amiodarone versus diltiazem 2 months after electrical cardioversion and found that 31 percent of amiodarone patients versus 52 percent of diltiazem patients had a recurrence of AF (p<0.01).[144] A poor-quality study compared verapamil with no verapamil given for 3 days before and after electrical cardioversion; 3 months after cardioversion; 19 percent of those receiving verapamil versus 39 percent of those not receiving verapamil had a recurrence of AF (p=0.03).[205] Antiarrhythmic drugs were used in both study arms at the discretion of the physician and were not accounted for in the analysis. A third,

fair-quality study compared the use of digoxin and verapamil with different electrical cardioversion protocols.[145] There was no significant difference in recurrence of AF at 18 months between digoxin and verapamil users (36% vs. 28%, respectively; p=0.33). This study also compared the use of acute versus routine subsequent electrical cardioversions regardless of receipt of digoxin or verapamil and found no difference in the proportion of patients with recurrence of AF at 18 months (32% vs. 28 %, p=0.85). A fourth, poor-quality study compared use of two subsequent electrical cardioversions versus none in patients receiving Class Ic or III AADs.[281] There was no difference in recurrence of AF from 3 to 12 months after the initial electrical cardioversion between the groups (extra cardioversions allowed 29 percent vs. no extra cardioversions allowed 31 percent, p=0.83) Differences in followup, agents, and findings resulted in an insufficient strength of evidence rating for this outcome.

All-Cause Mortality

One good-quality study[178] reported that one patient who received metoprolol with electrical cardioversion died within 6 months compared with no patients who received placebo plus electrical cardioversion. No statistical tests were performed (insufficient strength of evidence).

Quality of Life

One fair-quality study reported no statistically significant difference in overall quality of life (SF-36) at 18 months in those receiving digoxin versus verapamil or those receiving acute versus routine subsequent electrical cardioversions.[145] Scores were not provided, and no p-values were reported for the overall quality-of-life assessment (insufficient strength of evidence).

Stroke

One good-quality study reported that one patient receiving metoprolol with electrical cardioversion versus no patients receiving placebo with electrical cardioversion had a stroke[178] (insufficient strength of evidence).

Results in Specific Subgroups of Interest

No results were reported for outcomes of interest in specific subgroups of interest.

Comparison of Pharmacological Agents

Thirteen studies with a total of 3,718 patients compared pharmacological agents (Table 15).[180,181,224,230,241,245,249,256,258-261,269] One of these studies compared an AAD with a beta-blocker (sotalol vs. bisoprolol),[269] one focused on the effect of the addition of verapamil to both amiodarone and flecainide,[249] and one compared two beta-blockers, carvedilol and bisoprolol.[256] The remaining 10 studies compared two or more AADs. Five studies included a placebo arm; results of the placebo arm were not included in this review.[180,181,245,258,260]

Table 15. Studies including comparisons of pharmacological agents

Study	Sample Size (N)	Drug Comparison	Outcomes Assessed
Kochiadakis, 2000[260]	186	Amiodarone vs. Sotalol	Composite (Recurrence of AF or Adverse drug effect): 1 month,12 months, 24 months, mean monthly progression Composite (Maintenance of SR and Free of adverse drug effects): 1 year, 2 years
Kochiadakis, 2000[261]	214	Amiodarone vs. Sotalol vs. Propafenone	Composite (Recurrence of AF or Adverse drug effect): 12 months, 24 months, mean monthly progression Recurrence of AF: 2 years, and monthly rate Composite (Maintenance of SR and Free of adverse drug effects): 1 year, 2 years
Roy, 2000[230]	403	Amiodarone vs. Sotalol/Propafenone	AF hospitalization: 12 months, All-cause mortality: mean Control of AF symptoms: 3 months Recurrence of AF at mean followup of 468 days, and time to event Quality of life Stroke
Bellandi, 2001[245]	300	Sotalol vs. Propafenone	Maintenance of SR: 1 year Recurrence of AF: 12 months, mean time
Plewan, 2001[269]	128	Sotalol vs. Bisoprolol	Maintenance of SR: 12 months Recurrence of AF: 12 months, mean days to recurrence, monthly rate of recurrence
Anonymous, 2003[241]	256	Amiodarone vs. Sotalol	All-cause mortality: 5 years Arrhythmic deaths: 5 years Maintenance of SR: 5years Recurrence (prevalence) of AF: 4 months, 1 year
De Simone, 2003[249]	324	Amiodarone vs. Flecainide vs. Amiodarone with Verapamil vs. Flecainide with Verapamil	AF-free survival at 90 days (amiodarone/flecainide vs. amiodarone/flecainide with verapamil) Recurrence of AF: 3 months Maintenance of SR: 3 months
Katritsis, 2003[256]	90	Carvedilol vs. Bisoprolol	Recurrence of AF: 1 year
Kochiadakis, 2004[258]	254	Sotalol vs. Propafenone	Composite (Recurrence of AF or Adverse drug effect): 12 months, mean monthly progression; Composite (Maintenance of SR and Free of adverse drug effects): 30 months
Kochiadakis, 2004[259]	146	Amiodarone vs. Propafenone	Composite (Recurrence or Adverse drug effect): 12 months, 24 months, mean monthly progression Recurrence of AF Composite (Maintenance of SR and Free of adverse drug effects): 1 year, 2 years
Singh, 2005[180]	665	Amiodarone vs. Sotalol	All-cause mortality at last followup Stroke (per 100 person years) Recurrence of AF: 1 year, median days to recurrence Quality of life
Vijayalakshmi, 2006[181]	94	Amiodarone vs. Sotalol	All-cause mortality: 6 months Maintenance of SR: 1.5 months, 6 months
Le Heuzey, 2010[224]	504	Amiodarone vs. Dronedarone	Composite (Recurrence or Adverse drug effect), time to event Recurrence of AF: 12 months after conversion to SR All-cause mortality

Abbreviations: AF=atrial fibrillation; N=number of participants; SR=sinus rhythm

Maintenance of Sinus Rhythm

Nine studies comparing primarily pharmacological interventions reported this outcome.[181,241,245,249,258-261,269] Four studies compared amiodarone with sotalol,[181,241,260,261] two of which reported a composite outcome of maintenance of sinus rhythm without adverse effects from medication.[260,261] In all four studies maintenance of sinus rhythm was greater with amiodarone than with sotalol, but the differences were statistically significant only in some studies and at some of the assessed time points (see Table 16).

Three studies compared propafenone with sotalol,[245,258,261] again with two of these studies reporting a composite outcome of maintenance of sinus rhythm without adverse effects from medication.[258,261] One of these studies showed no significant difference in the rate of this outcome,[245] while the other two found that the propafenone groups had rates of maintenance of sinus rhythm that were almost twice that of the sotalol groups, although statistical analyses comparing the groups were not reported.[258,261]

Two studies compared amiodarone with propafenone and evaluated a composite outcome of maintenance of sinus rhythm free from adverse effects from medication.[259,261] In both studies, at 1 year amiodarone was better than propafenone for this outcome, but at 2 years propafenone was better. In both studies, investigators described the rate of recurrence of AF as being constant throughout followup for amiodarone, but they described the rate of recurrence of AF on propafenone as being high early on during therapy and then decreasing over time.

One study compared bisoprolol with sotalol and found no significant difference in the rate of maintenance of sinus rhythm.[269] The final study found that the addition of verapamil to treatment with either amiodarone or flecainide increased the rate of AF-free survival compared with treatment with either antiarrhythmic agent alone.[249] These studies suggest that amiodarone appears to be better sotalol but no different from propafenone, but given the diversity in comparisons and the imprecision of the findings, the strength of evidence was considered low.

Table 16. Studies assessing maintenance of sinus rhythm with or without adverse effects

Study	Sample Size (N)	Time Point	Results	P-Value
Kochiadakis, 2000[261]	214	1 year[a]	Amiodarone: 70.9% Sotalol: 39.2% Propafenone: 60.4%	NR
		2 years[a]	Amiodarone: 44.7% Sotalol: 19.6% Propafenone: 60%	NR
Kochiadakis, 2000[260]	186	1 year[a]	Amiodarone: 58.46% Sotalol: 36.07%	NR
		2 years[a]	Amiodarone: 26.17% Sotalol: 12.61%	NR
Bellandi, 2001[245]	300	1 year	Propafenone:56% Sotalol: 61%	0.51
Plewan, 2001[269]	128	12 months	Bisoprolol: 55% Sotalol: 52%	NS
Anonymous, 2003[241]	256	5 years	Amiodarone vs. Sotalol Overall % without recurrences NR for cumulative time period Amiodarone had greater maintenance than Sotalol	p=0.0003
De Simone, 2003[249]	324	90 days	AF-free survival between Amiodarone/Flecainide vs. Amiodarone/Flecainide + Verapamil HR 2.17 (95% CI, 1.39 to 3.39)	p<0.001

Table 16. Studies assessing maintenance of sinus rhythm with or without adverse effects (continued)

Study	Sample Size (N)	Time Point	Results	P-Value
Kochiadakis, 2004[258]	254	30 months[a]	Propafenone: 47% Sotalol: 25%	NR
Kochiadakis, 2004[259]	146	12 months[a]	Amiodarone: 72% Propafenone: 56%	NR
		24 months[a]	Amiodarone: 42% Propafenone: 51%	NR
Vijayalakshmi, 2006[181]	94	1.5 months	Amiodarone: 67% Sotalol: 53%	p=0.3
		6 months	Amiodarone: 63% Sotalol: 39%	P=0.05

[a]In patients who had sinus rhythm and were free of adverse effects.
Abbreviations: AE=adverse event; CI=confidence interval; HR=hazard ratio; N=number of participants; NR=not reported

Recurrence of AF

Ten studies comparing primarily pharmacological interventions for AF included recurrence (or prevalence) of AF as an outcome (Table 17).[180,224,230,241,245,249,256,259,261,269] Three of these studies compared amiodarone with sotalol.[180,241,261] Of these three studies, one showed no statistically significant difference between treatment arms at 4 months or 1 year;[241] however, the other two studies reported a higher rate of recurrence of AF among those on sotalol compared with amiodarone—68 percent versus 33 percent at 2 years of followup in one study (no statistical test reported),[261] and 68 percent versus 48 percent at 1 year in the other study (p=0.001).[180]

Two studies compared sotalol with propafenone.[245,261] The rate of recurrence of AF for sotalol versus propafenone was not statistically significantly different in 1 study at 12 months (23% vs. 32%; P=NS).[245] Another study reported a higher rate with sotalol than with propafenone at 2 years (68% vs. 37.5%), but no statistical analysis was reported.[261]

Two studies compared the effects of amiodarone versus propafenone; one found a statistically significantly higher monthly rate of recurrence with propafenone;[261] the other found no significant difference in recurrence between the two drugs.[259] In line with the results of these two studies, another study evaluated the risk of recurrence of AF for amiodarone compared with either sotalol or propafenone over approximately 1 year and found a significantly lower risk among those on amiodarone, with a hazard ratio (HR) of 0.43 (95% CI, 0.32 to 0.57).[230]

Two studies compared amiodarone to different antiarrhythmic therapy.[224,249] One compared amiodarone versus flecainide, with and without verapamil added to either treatment. The rate of recurrence of AF did not differ at 3 months between amiodarone and flecainide (no statistical test reported). The addition of verapamil to flecainide reduced the rate of recurrence significantly compared with flecainide alone (21% vs. 38%, p=0.02); however, the addition of verapamil to amiodarone did not change the rate of recurrence of AF compared with amiodarone alone.[249] One study compared amiodarone with dronedarone and found a higher rate of recurrence with dronedarone, but the statistical analysis was not reported.[224]

Finally, two studies compared the beta-blocker bisoprolol with either another beta-blocker or an antiarrhythmic agent.[256,269] One study showed no significant difference between rates of recurrence at 1 year between bisoprolol and carvedilol;[256] the other showed no significant difference between rates of recurrence of AF with bisoprolol versus sotalol.[269]

These findings suggest that amiodarone appears to be better than dronedarone or sotalol, but no different from propafenone (low strength of evidence).

Table 17. Studies assessing recurrence of AF

Study	Sample Size (N)	Time Point	Results	P-Value
Kochiadakis, 2000[261]	214	2 years	Amiodarone: 33.3% Sotalol: 68% Propafenone: 37.5%	NR
		Monthly rate	Amiodarone: 1.96% Sotalol: 6.56% Propafenone: 4.73%	p=0.046 (Amiodarone vs. Propafenone)
Roy, 2000[230]	403	Mean followup 468 days	Amiodarone vs. Sotalol/Propafenone HR 0.43 (95% CI, 0.32 to 0.57)	p<0.001
Singh, 2005[180]	665	1 year	Amiodarone: 48% Sotalol: 68%	p=0.002
		Median days to recurrence	Amiodarone: 487 Sotalol: 74	p=0.002
Bellandi, 2001[245]	300	12 months	Propafenone: 32% Sotalol: 23%	p=0.16
		Mean time to recurrence	Propafenone: 105 +/- 96 days Sotalol: 109 +/- 86 days	NR
Plewan, 2001[269]380	128	12 months	Bisoprolol: 42% Sotalol: 41%	NS
		Mean days to recurrence	Bisoprolol:38 ± 74 Sotalol: 49 ± 87	NS
		Monthly rate	Bisoprolol: 3.5% Sotalol:3.4%	NS
Anonymous, 2003[241]	256	4 months	Amiodarone: 17% Sotalol: 22%	p=0.356
		1 year	Amiodarone: 12% Sotalol:19%	p=0.14
De Simone, 2003[249]	324	3 months	Amiodarone: 32% Flecainide: 38% Amiodarone + Verapamil: 20% Flecainide + Verapamil: 21%	p=0.08 (Amiodarone vs. Amiodarone + Verapamil) p=0.02 (Flecainide vs. Flecainide + Verapamil)
Katritsis, 2003[256]	90	12 months	Bisoprolol: 46% Carvedilol: 32%	p=0.486
Kochiadakis, 2004[259]	146	24 months	Amiodarone vs. Propafenone; actual rates not given	p=0.058
Le Heuzey, 2010[224]	504	12 months	Dronedarone: 36.5% Amiodarone: 24.3%	NR

Abbreviations: AF=atrial fibrillation; CI=confidence interval; HR=hazard ratio; NR=not reported; NS=not statistically significant

All-Cause Mortality

All-cause mortality was reported in 5 studies during a period of 6 months to 5 years (Table 18). Three of the studies compared amiodarone with sotalol, and statistical comparisons were either not performed or treatments were not found to be statistically significantly different.[180,181,241] In one study, amiodarone was compared with sotalol or propafenone and no statistical analyses were done.[230] In another study amiodarone was compared with dronedarone but no statistical analyses were done[224] Differences in followup, comparisons, and findings resulted in insufficient strength of evidence for this outcome.

Table 18. Studies reporting all-cause mortality as an outcome

Study	Sample Size (N)	Time Point	Results	P-Value
Roy, 2000[230]	403	Mean followup 468 days	Amiodarone: 4% Sotalol or propafenone: 4%	NR
Anonymous, 2003[241]	256	5 years (mean followup 3.84 years)	Amiodarone: 11% Sotalol: 19%	0.081
Singh, 2005[180]	665	Over 1 year	Amiodarone: 5% Sotalol: 6%	NR
Vijayalakshmi, 2006[181]	94	6 months	Amiodarone: 0% Sotalol: 0%	NR
Le Heuzey, 2010[224]	504	6 months (median treatment of 7 months)	Amiodarone: 2% Dronedarone: 0.8%	NR

Abbreviation: n=number of participants; NR=not reported

Cardiovascular Mortality

Four studies reported arrhythmic deaths as an outcome at 1–5 years of followup.[180,230,241,260] Three studies compared amiodarone with sotalol and found no difference between these treatment arms[180,241,260]. In one study, there was no statistically significant difference in arrhythmic death between those receiving amiodarone vs. sotalol (4% vs. 4%, p=0.900).[241] Another study reported 2 percent of patients in the amiodarone group had sudden death and 3 percent in the sotalol group (no statistical test reported),[180] while the third study reported no deaths in either treatment arm due to proarrhythmia or sudden death.[260] In the study comparing amiodarone with either sotalol or propafenone, 1.5 percent of patients in the amiodarone group died, presumably due to arrhythmia, while 0.5 percent of patient in the sotalol/propafenone group died due to arrhythmia (no statistical test done).[230] There was a low strength of evidence rating for there being no difference between evaluated pharmacological agents.

CV Hospitalizations

No studies reported generally on CV hospitalizations. One study[230] compared the proportion of patients with AF hospitalizations between amiodarone and either sotalol or propafenone. The rate of AF hospitalization was lower with amiodarone than with sotalol or propafenone (14% vs. 25%, p-value not reported). In addition, the mean number of days to AF hospitalization was lower with amiodarone than with sotalol/propafenone (0.47 vs.0.97, p=0.01) (low strength of evidence).

Control of AF symptoms

One study[230] assessed control of AF symptoms using the Atrial Fibrillation Severity Scale (AFSS) and found no statistically significant difference in mean scores between amiodarone versus sotalol or propafenone arms (12.8 vs. 15.3, p=NS; low strength of evidence).

Quality of Life

Two studies reported outcomes related to quality of life.[180,230] One study comparing amiodarone with sotalol found no significant changes in quality-of-life scores for any treatment group during the 1 year of followup except for a significant decrease in the mental health score for patients on amiodarone, which differed significantly from those on sotalol (p=0.005).[180] The other study[230] compared treatment with amiodarone versus treatment with either sotalol or propafenone[230] and found that all quality-of-life measures improved during 3 months of followup, but these improvements did not differ by treatment arm (low strength of evidence).

Stroke

The outcome of stroke was reported in only two studies, and in both stroke was described as an adverse event and was not evaluated as a primary or secondary outcome.[180,230] In the study comparing amiodarone with either sotalol or propafenone, patients on sotalol or propafenone experienced a greater number of strokes and intracranial hemorrhages than did those on amiodarone (9 vs.1 patient, p=0.01), and most of these patients were taking warfarin at the time of the event.[230] In a study comparing amiodarone with sotalol, there was no significant difference between treatment arms for the number of minor or major stroke episodes per person-year (0.87 with amiodarone vs. 2.03 with sotalol, p=NS)[180] (insufficient strength of evidence).

Composite Outcome (Recurrence of AF or Adverse Drug Effect)

Five studies assessed a composite outcome of recurrence of AF or adverse drug event (Table 19).[224,258-261] Two studies compared sotalol with propafenone,[258,261] two compared amiodarone with propafenone,[259,261] two compared amiodarone with sotalol,[260,261] and one compared amiodarone with dronedarone.[224] In several of these comparisons, statistical analyses were not conducted.

Both studies comparing sotalol with propafenone found that patients on propafenone had a lower rate of the composite outcome than did patients on sotalol at 12–30 months; however, statistical analyses comparing these rates were not done.[258,261] In one of these studies a statistical analysis was done to compare the mean monthly rate of progression to AF or adverse drug effects. The rate among those on propafenone was significantly lower than the rate among those on sotalol (4.93% vs.7.20%, p<0.001).[261]

In the two studies comparing amiodarone with propafenone, the proportion of patients with the composite outcome was higher in patients receiving propafenone versus amiodarone except in one study[261] at 24 months; however, statistical analyses were not done for any of these comparisons.[259,261] Both studies also assessed the mean monthly progression to AF or adverse drug effects and found a lower rate with amiodarone than with propafenone; however, the difference was not statistically significant in either study (amiodarone 3.18% vs. propafenone 3.96%, p=0.44;[259] amiodarone 3.05% vs. propafenone 4.93%, p=0.33[261]).

Two studies compared amiodarone with sotalol. Rates of the composite outcome were higher in those receiving sotalol versus amiodarone except at 1 month (see Table 19), but statistical analyses were not reported. The mean monthly rate of progression to AF or adverse drug events was statistically significantly lower for amiodarone as compared with sotalol in both studies (see Table 19).

In the study comparing amiodarone with dronedarone, there was a statistically significantly higher rate of recurrence of AF or premature drug discontinuation due to side effects or lack of efficacy at 1 year among those on dronedarone compared with amiodarone (HR 1.59; 95% CI, 1.29 to 1.98, p<0.0001).[224]

Table 19. Studies reporting a composite outcome of recurrence of AF or adverse drug effect

Study	Sample Size (N)	Time Point	Results	P-Value
Kochiadakis, 2000[260]	186	1 month	Amiodarone: 28% Sotalol: 13%	NR
		12 months	Amiodarone: 41.5% Sotalol: 64%	NR
		24 months	Amiodarone: 87.4% Sotalol: 90%	NR
		Mean monthly progression	Amiodarone: 4.9% Sotalol: 8.3%	p<0.001
		1-year event-free rate in patients free of AEs	Amiodarone: 60.3% Sotalol: 37.9%	NR
		2-year event-free rate in patients free of AEs	Amiodarone: 42.6% Sotalol: 13.3%	NR
Kochiadakis, 2000[261]	214	12 months	Amiodarone: 29.1% Sotalol: 60.8% Propafenone: 39.6%	NR
		24 months	Amiodarone: 55.3% Sotalol: 80.4% Propafenone: 40%	NR
		Mean monthly rate	Amiodarone: 3.05% Sotalol: 7.2% Propafenone: 4.93%	p=0.33 (Amiodarone vs. Propafenone p<0.001 (Amiodarone vs. Sotalol) p<0.001 (Sotalol vs. Propafenone)
Kochiadakis, 2004[258]	254	12 months	Sotalol: 50% Propafenone: 59%	NR
		Mean monthly progression	Sotalol: 5.26% Propafenone: 3.13%	NR
Kochiadakis, 2004[259]	146	12 months	Amiodarone: 28% Propafenone: 55%	NR
		24 months	Amiodarone: 44% Propafenone: 58%	NR
		Mean monthly progression	Amiodarone: 3.18% Propafenone: 3.96%	0.44
Le Heuzey[224]	504	Time to event (12 months)	Dronedarone vs. Amiodarone HR 1.59 (95% CI, 1.29 to 1.98)	p<0.0001

Abbreviations: AE=adverse event; CI=confidence interval; HR=hazard ratio; N=number of participants; NR=not reported

Adverse Events

Of the 13 studies primarily assessing pharmacological agents for maintaining sinus rhythm, 11 (85%) provided some information on adverse drug events in 2,647 patients.[180,181,224,230,241,245,258-261,269] Arrhythmic death (including sudden cardiac arrest) and all-cause mortality are described above as separate outcomes. Of these 11 studies, 5 incorporated adverse drug events resulting in drug discontinuation into a composite outcome with recurrence of AF to assess the effectiveness of the drug(s).[224,258-261] These studies had a more robust method of collecting adverse drug event information than other studies. The method of collecting adverse drug events and the definitions of adverse drugs varied between studies, making comparison between studies and summaries of studies challenging.

In the 11 studies, 1,093 patients received amiodarone, 813 received sotalol, 326 received propafenone, 249 received dronedarone, 64 received bisoprolol, and 202 received either sotalol or propafenone. In these 2,747 patients, only 7 proarrhythmias were reported (1 in a patient receiving propafenone and 6 in patients receiving sotalol).[245,258,269] Tachycardia was reported in 3 patients (2 receiving propafenone, and 1 receiving either sotalol or propafenone).[230,259] Bradycardia was one of the more commonly reported adverse drug reactions, reported in 161 patients in 9 studies (73 on dronedarone, 61 on amiodarone, 15 on sotalol, 2 on propafenone, 3 on bisoprolol, and 7 on either sotalol or propafenone).[224,230,241,245,258-261,269] Hypothyroidism or hyperthyroidism were reported in 5 studies that included 668 patients with amiodarone, 138 patients with propafenone, 136 with sotalol, 249 with dronedarone, and 202 with either sotalol or propafenone.[224,230,259-261] Hypothyroidism was reported in 29 patients with amiodarone and 2 patients with dronedarone. Hyperthyroidism was reported in 20 patients with amiodarone.

Results in Specific Subgroups of Interest

Six studies report outcomes by treatment arm for subgroups of patients based on characteristics such as age, sex, type of AF, duration of AF, left atrial size, and presence of heart disease.[180,230,258-261] With few exceptions, the results of primary outcomes did not change by subgroup. Four studies compared amiodarone with sotalol.[180,230,260,261] In one of these, the probability of remaining in sinus rhythm continued to be significantly greater among patients without ischemic heart disease on amiodarone compared with sotalol ($p<0.001$), but this probability was not statistically significantly different among patients with a history of ischemic heart disease (0.53).[180] In the other three subgroup analyses comparing amiodarone with sotalol, there was no such difference between patients with and without a history of heart disease.[230,260,261] In one of three studies comparing amiodarone with sotalol and reporting subgroup analyses by age, there was a higher rate of recurrence of AF or adverse effects from the medication among those patients taking sotalol who were >65 years of age compared with those who were ≤65 years of age ($p=0.04$).[260] Finally, in the study comparing the effect of amiodarone with propafenone on the outcome of the recurrence of AF alone, there was a statistically significant lower rate of recurrence among women on amiodarone compared with women on propafenone, but this difference was not seen among males.[259]

Strength of Evidence

Our review identified 83 studies that evaluated the comparative safety and effectiveness of rhythm-control procedures and drugs for maintenance of sinus rhythm. These studies demonstrated that among patients with AF, there is high strength of evidence that rhythm control using transcatheter PVI is superior to rhythm control using antiarrhythmic medications in reducing recurrent AF over 12 months of followup in patients with paroxysmal AF. This evidence is strongest in younger patients with little to no structural heart disease, and with no or mild enlargement of the left atrium. The evidence also suggested that the duration of AF is an important predictor of response to PVI. Our findings support the findings of prior reviews. Our review also examined whether complex fractionated atrial electrogram (CFAE) ablation in addition to PVI increases the odds of maintaining sinus rhythm during followup compared with PVI only. Based on data from 9 RCTs, we found that CFAE ablation in addition to PVI did not demonstrate a statistically significant increase in maintenance of sinus rhythm compared with PVI only. By combining data from nine RCTs, our review is the largest to date to address this question. Unlike prior reviews, our review showed a potential benefit, but this finding did not

reach statistical significance, and we therefore concluded that CFAE ablation in addition to PVI did not increase maintenance of sinus rhythm compared with PVI alone. This difference is largely driven by the inclusion of two recent studies[216,223] not included in prior reviews which did not demonstrate a benefit of CFAE. This finding could inform clinical decision making regarding the extent of ablation during a PVI procedure, especially given the potential for reduced atrial mechanical function from more scarring with CFAE. The low strength of evidence rating for this comparison and outcome underscores the importance of conducting well-powered and designed RCTs to address this issue definitively. Our review also evaluated surgical Maze and determined that there is moderate evidence that rhythm control using surgical Maze at the time of other cardiac surgery (specifically, mitral valve surgery) is superior to mitral valve surgery alone in reducing AF recurrence. We also found that there is strong evidence that rhythm control using PVI at the time of cardiac surgery is superior to cardiac surgery alone or in combination with antiarrhythmic drugs (AADs) or with catheter ablation in reducing AF recurrence over 12 months of followup in patients with persistent AF. Our findings support exploring these interventions further with regard to their effect on final outcomes and in different patient populations.

Despite the wide range of antiarrhythmic drugs available in the United States, our review identified only 18 comparative studies eligible for inclusion. Amiodarone, sotalol, and propafenone were the most commonly used antiarrhythmic drugs in RCTs assessing the pharmacological maintenance of sinus rhythm. Only one study (a substudy of the AFFIRM study) systematically assessed differences in all-cause mortality between antiarrhythmic drugs and found no statistically significant difference between amiodarone and sotalol. With regard to maintaining sinus rhythm or decreasing recurrences of AF, amiodarone did not appear to be different from propafenone in the two studies of fair quality that reported results on this comparison. Comparisons of other antiarrhythmic drugs were infrequent and often led to conflicting results. The superiority of one antiarrhythmic medication over another has been debated for years and there has been a long-standing need to review and synthesize the evidence surrounding the comparative effectiveness of different antiarrhythmic medications at maintaining sinus rhythm. However, due to the number of studies, small number of patients enrolled in the studies, and heterogeneity across studies in terms of both patient populations and treatments, the results are inconclusive.

Overall, across the included studies additional evidence is needed to explore the impact of available interventions on final clinical outcomes (e.g., all-cause mortality, stroke, heart failure, and LVEF) as well as long-term outcomes beyond 12 months. Finally, the evidence base is limited in terms of the exploration of subgroups of interest.

Tables 20 and 21 summarize the strength of evidence for the outcomes of interest comparing rhythm-control procedures and drugs for maintenance of sinus rhythm. For those comparisons where the number of studies was sufficient to estimate a summary effect, we were able to have greater confidence in our findings.

Table 20. Strength of evidence domains for rhythm-control procedures

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Transcatheter PVI vs. AADs						
Maintenance of Sinus Rhythm	8 (921)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 6.51 (95% CI, 3.22 to 13.16) favoring transcatheter PVI
All-Cause Mortality	1 (69)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
CV Hospitalizations	2 (268)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** Both studies demonstrated significant increase in CV hospitalizations in the AAD arm vs. PVI
AF Hospitalizations	1 (67)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Quality of Life	6 (647)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Mixed Embolic Events Including Stroke	2 (140)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** No embolic events in either the PVI or AAD arm
Bleeding Events	1 (67)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Transcatheter PVI Using Different Types of Ablation Catheters						
Maintenance of Sinus Rhythm	3 (264)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** No difference between different types of ablation catheters
Recurrence of AF	1 (102)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No difference between a multipolar circular ablation catheter and a point-by-point PVI with an irrigated tip ablation catheter (p=0.8)
Stroke	1 (82)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Transcatheter Circumferential PVI vs. Transcatheter Segmental PVI						
Restoration of Sinus Rhythm	1 (80)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**

Table 20. Strength of evidence domains for rhythm-control procedures (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Maintenance of Sinus Rhythm	5 (500)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 1.31 (95% CI, 0.59 to 2.93) demonstrating a potential benefit of circumferential PVI which did not reach statistical significance
All-Cause Mortality	1 (110)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No events in either arm after 48 months
Transcatheter PVI With CTI ablation vs. Transcatheter PVI Without CTI ablation						
Recurrence of AF	2 (257)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Transcatheter PVI With CFAE Ablation vs. Transcatheter PVI Without CFAE Ablation						
Restoration of Sinus Rhythm	2 (247)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** 2 studies showing significant benefit of CFAE arm
Maintenance of Sinus Rhythm	9 (817)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 1.48 (95% CI, 0.74 to 2.98) showing a potential benefit of CFAE which did not reach statistical significance
Quality of Life	1 (60)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Stroke	1 (144)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No events in any arm after 16 months
Transcatheter PVI vs. Transcatheter PVI With Additional Ablation Sites Other Than CTI and CFAE and Transcatheter PVI Involving all Four PVs vs. Transcatheter PVI Involving Arrhythmogenic PVs Only						
Restoration of Sinus Rhythm	2 (384)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Insufficient**
Maintenance of Sinus Rhythm	15 (1,926)	RCT/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Recurrence of AF	6 (572)	RCT/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
All-Cause Mortality	2 (405)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Quality of Life	2 (152)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** No significant difference between arms in 2 studies
Stroke	2 (361)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**

Table 20. Strength of evidence domains for rhythm-control procedures (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Transcatheter PVI Alone vs. Transcatheter PVI Plus Postablation AADs						
Recurrence of AF	2 (217)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
AF Hospitalizations	1 (110)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No difference between arms
Surgical Maze vs. Standard of Care (Mitral Valve Surgery)						
Maintenance of Sinus Rhythm	7 (361)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** OR 5.80 (95% CI, 1.79 to 18.81) demonstrating large and significant benefit of Maze
All-Cause Mortality	6 (387)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 1.97 (95% CI, 0.81 to 4.80) demonstrating potentially greater mortality with Maze which did not reach statistical significance
Heart Failure Symptoms	1 (30)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Stroke	1 (30)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Mixed Embolic Events Including Stroke	1 (67)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Bleeding Events	1 (60)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
PVI at the Time of Cardiac Surgery vs. Cardiac Surgery Alone or in Combination with AADs or Catheter Ablation						
Restoration of Sinus Rhythm	3 (181)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 12.30 (95% CI, 1.31 to 115.29) demonstrating statistically significant benefit of PVI at time of cardiac surgery
Maintenace of Sinus Rhythm	8 (532)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 3.91 (95% CI, 1.54 to 9.91) demonstrating statistically significant benefit of PVI at time of cardiac surgery

Table 20. Strength of evidence domains for rhythm-control procedures (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
All-Cause Mortaltiy	2 (88)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** 2 studies showing no difference between groups
CV Mortality	1 (97)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**
Quality of Life	2 (229)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Stroke	2 (140)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** 2 studies showing no difference between groups
Bleeding Events	1 (43)	RCT/ Moderate	NA	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: AAD(s)=antiarrhythmic drug(s); AF=atrial fibrillation; CFAE=complex fractionated atrial electrogram; CI=confidence interval; CTI=cavotricuspid isthmus; CV=cardiovascular; NA=not applicable; OR=odds ratio; PV(s)=pulmonary vein(s); PVI=pulmonary vein isolation; RCT=randomized controlled trial; SOE=strength of evidence

Table 21. Strength of evidence domains for pharmacological rhythm-control therapies

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Pharmacological Therapy in Which Electrical Cardioversion is a Key Component of the Treatment						
Maintenance of Sinus Rhythm	1 (168)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**
Recurrence of AF	4 (414)	RCT/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
All-Cause Mortality	1 (168)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**
Quality of Life	1 (144)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**
Stroke	1 (168)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**
Comparison of Pharmacological Agents						
Maintenance of Sinus Rhythm	9 (2,095)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** Amiodarone appears better than sotalol, but no different from propafenone
Recurrence of AF	10 (3,223)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** Amiodarone appears better than dronedarone or sotalol, but no different from propafenone
All-Cause Mortality	5 (2,076)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
CV Mortality	4 (1,664)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** No difference between study arms in arrhythmic deaths

Table 21. Strength of evidence domains for pharmacological rhythm-control therapies (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
AF Hospitalizations	1 (403)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Rate and mean length of stay of AF hospitalization were lower with amiodarone than with sotalol/ propafenone
Control of AF Symptoms	1 (403)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** No difference between amiodarone versus sotalol or propafenone
Quality of Life	2 (1,068)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** No significant difference in either study
Stroke	2 (1,068)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: AF=atrial fibrillation; CI=confidence interval; CV=cardiovascular; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 6. Rate- Versus Rhythm-Control Therapies

KQ 6: What are the comparative safety and effectiveness of rate-control therapies compared with rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Key Points

- Based on evidence from 3 RCTs (2 good, 1 fair quality) involving 439 patients, pharmacological rate-control strategies with antiarrhythmic medications are superior to rhythm-control strategies in reducing cardiovascular hospitalizations (high strength of evidence).
- Among patients with AF, there is evidence that pharmacological rate-control strategies are comparable in efficacy to rhythm-control strategies with antiarrhythmic medications with regard to their effect on the following outcomes:
  - Cardiovascular mortality: Based on data from 5 RCTs (all good quality) involving 2,405 patients (moderate strength of evidence)
  - Stroke: Based on data from 8 RCTs (5 good, 2 fair, 1 poor quality) involving 6,424 patients (moderate strength of evidence)
  - All-cause mortality: Based on data from 8 RCTs (5 good, 2 fair, 1 poor quality) involving 6,372 patients (moderate strength of evidence)
- With regard to heart failure symptoms, there is evidence showing a potential benefit of rhythm-control strategies with antiarrhythmic medications compared with pharmacological rate-control strategies, which did not reach statistical significance. This

finding is based on evidence from 4 RCTs (2 good, 2 fair quality) involving 1,700 patients (low strength of evidence).

- Not surprisingly, based on evidence from 7 RCTs (4 good, 2 fair, 1 poor quality) involving 1,473 patients, rhythm-control strategies with antiarrhythmic medications are significantly more efficacious at maintaining sinus rhythm than pharmacological rate-control strategies (high strength of evidence).
- There was insufficient strength of evidence about outcomes comparing a rhythm-control strategy that involved PVI with a rate-control strategy that involved AVN ablation and implantation of a pacemaker (one good-quality study) or rate-controlling medications (one poor-quality study).

Description of Included Studies

A total of 14 RCTs were included in our analysis (Appendix Table F-6), 12 that explored a rhythm-control strategy using pharmacological therapy versus a rate-control strategy,[155,156,159,295-303] and 2 that compared a rhythm-control strategy with PVI versus a rate-control strategy that involved AVN ablation and implantation of a pacemaker in one case[304] and rate-controlling medications in the other (poor-quality) study.[305] Ten studies were multicenter RCTs. Eleven included outpatients,[155,156,159,295,296,299-302,304,305] one included inpatients,[298] and two did not report information on setting.[297,303] Ten studies were conducted in Europe;[156,159,295-300,303,305] one was conducted in the United States and Canada only;[155] one was conducted in Asia only;[302] one was conducted in the United States, Canada, South America, and Israel;[301] and one did not report the location.[304] Nine studies were of good quality,[155,156,159,296,297,299-301,304] three were of fair quality,[295,298,302] and two were of poor quality.[303,305] The funding source was the government for three studies,[155,299,305] industry for three studies,[295,297,302] government and industry for three studies,[156,301,304] and not reported for five studies.[159,296,298,300,303] Studies enrolled patients between 1995 and 2009. The number of patients included ranged from 41[305] to 4,060[155] for a total of 7,556 patients across the 14 studies. The mean age of study participants ranged from 39 years[302] to 72 years.[300] When reported, study duration varied from 2 years to 6 years.[155,295,299,301,302]

Five studies included only patients with persistent AF,[156,159,298-300] one included only patients with paroxysmal AF,[295] two included both patients with paroxysmal and those with persistent AF,[301,304] and six studies did not explicitly report type of AF.[155,296,297,302,303,305] Duration of AF at baseline ranged from 103 days[297] to 3,285 days.[295] Four studies included only patients with heart failure.[300,301,304,305] None of the remaining studies was limited to a special population.[155,156,159,295-299,302,303]

Regarding interventions, one study mandated the use of diltiazem as a rate-controlling medication versus amiodarone as a rhythm-controlling medication.[297] Six studies allowed different rate-controlling medications in the rate-control strategy (usually digoxin, beta blockers and calcium channel blockers), and different antiarrhythmic medications, along with electrical cardioversion when needed, in the rhythm-control strategy. The latter strategy restricts the use of some of these antiarrhythmic medications based on the presence of absence of structural heart disease like heart failure and/or coronary artery disease.[155,156,296,299,301,303] Two studies mandated AVN ablation and pacemaker as the rate-controlling strategy and allowed different antiarrhythmic medications for rhythm control.[159,295] In one of these two studies, AVN ablation with VVIR pacing was specified as the rate-control strategy, and AVN ablation with DDDR pacing and use of antiarrhythmic medication was specified as the rhythm-control strategy.[159] One study specified using amiodarone with or without electrical cardioversion in the rhythm-control

group versus digoxin or metoprolol in the rate-control group.[298] One study specified using placebo versus amiodarone in the rhythm-control group, with or without cardioversion, and diltiazem in the rate-control group.[302] One study specified using digoxin or beta blockers in the rate-control group versus amiodarone with or without electrical cardioversion in the rhythm-control group.[300] One study compared PVI as the rhythm-control strategy with AVN ablation and pacemaker as the rate-control strategy.[304] Finally, one poor-quality study compared PVI as the rhythm-control strategy versus rate-controlling medications.[305]

Detailed Synthesis

Comparison 1: Rate-Control Strategy Versus Rhythm-Control Strategy Using Antiarrhythmic Drugs

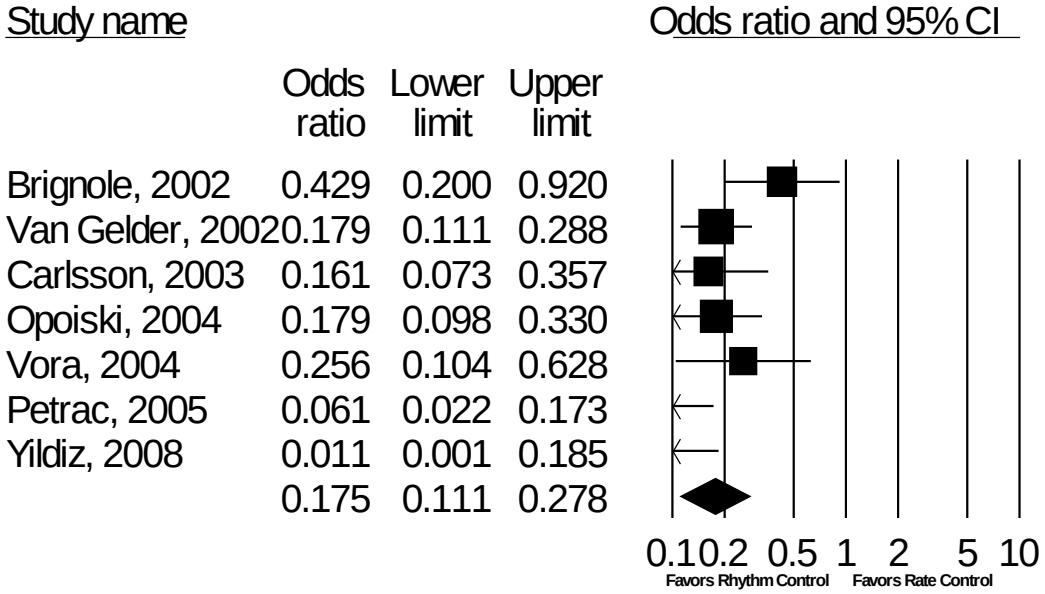
Quantitative Analysis

This analysis addressed the comparative safety and effectiveness of a rate-control strategy versus a rhythm-control strategy using pharmacological agents. We identified 12 RCTs for this comparison, and the available data were deemed appropriate for meta-analysis for the following outcomes: maintenance of sinus rhythm, all-cause mortality, cardiovascular mortality, cardiovascular hospitalizations, heart failure symptoms, stroke, mixed embolic events including stroke, and bleeding events.

Maintenance of Sinus Rhythm

Seven studies representing 1,473 patients were included in our meta-analysis of maintenance of sinus rhythm.[156,159,295,296,299,302,303] Figure 19 shows that the OR of rate control versus rhythm control for maintenance of sinus rhythm was 0.18 (95% CI, 0.11 to 0.28), demonstrating a statistically significant greater ability of patients on rhythm-control strategies to be maintained in sinus rhythm as compared with those on rate-control strategies (high strength of evidence). There was evidence of heterogeneity; however, the demonstration of a benefit of rhythm-control strategies was consistent, and therefore this heterogeneity did not reduce the strength of evidence rating. The Q-value was 213.49 for 3 degrees of freedom, p=0.036.

Figure 19. Forest plot of maintenance of sinus rhythm for rate- versus rhythm-control strategies



Abbreviation: CI=confidence interval

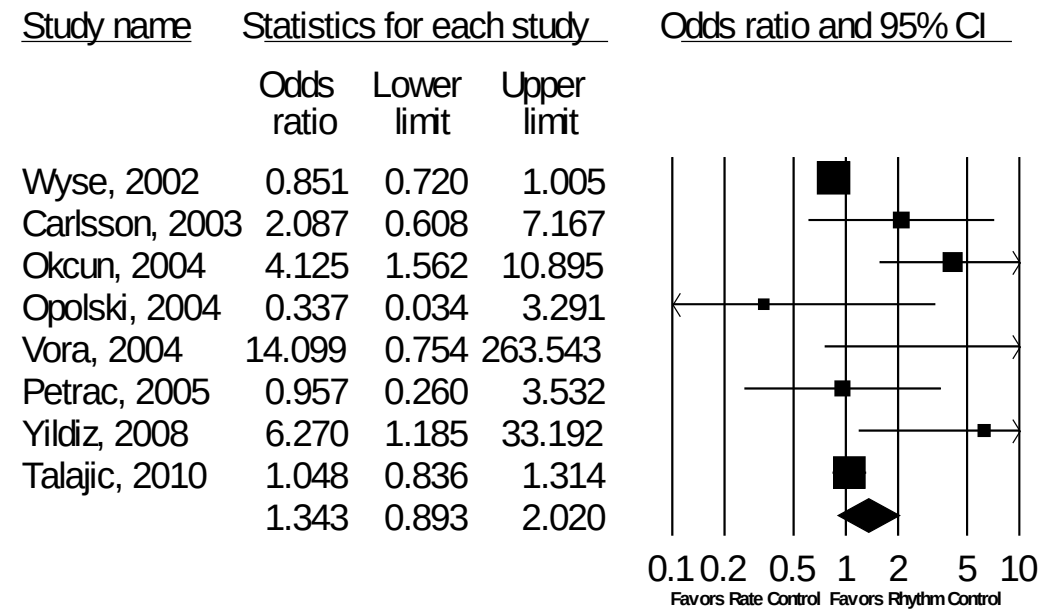
Ventricular Rate Control

Control of ventricular rate was reported by two studies.[156,299] In one,[299] ventricular rate control was significantly better in the rhythm-control group than in the rate-control group (mean±SD, 79.1±8.6 bpm vs. 85.8±7.5 bpm; $p<0.003$). In the other study,[156] the mean heart rate in the resting state was significantly better during rhythm control (73±18 bpm) than during rate control (82±16 bpm) (low strength of evidence).

All-Cause Mortality

Eight studies representing 6,413 patients were included in our meta-analysis of all-cause mortality.[155,159,296,298,299,301-303] Figure 20 shows that the OR of rate control versus rhythm control for all-cause mortality was 1.34 (95% CI, 0.89 to 2.02), demonstrating a potential benefit of a rhythm-control strategy which did not reach statistical significance. In addition, 6 of the 8 studies had ORs that crossed 1, including 6,069 (95%) of the patients. There was also significant heterogeneity. The Q-value was 21.71 for 7 degrees of freedom ($p=0.003$). We therefore assessed these eight studies as demonstrating comparable efficacy between rate and rhythm control strategies for all-cause mortality (moderate strength of evidence).

Figure 20. Forest plot of all-cause mortality for rate- versus rhythm-control strategies

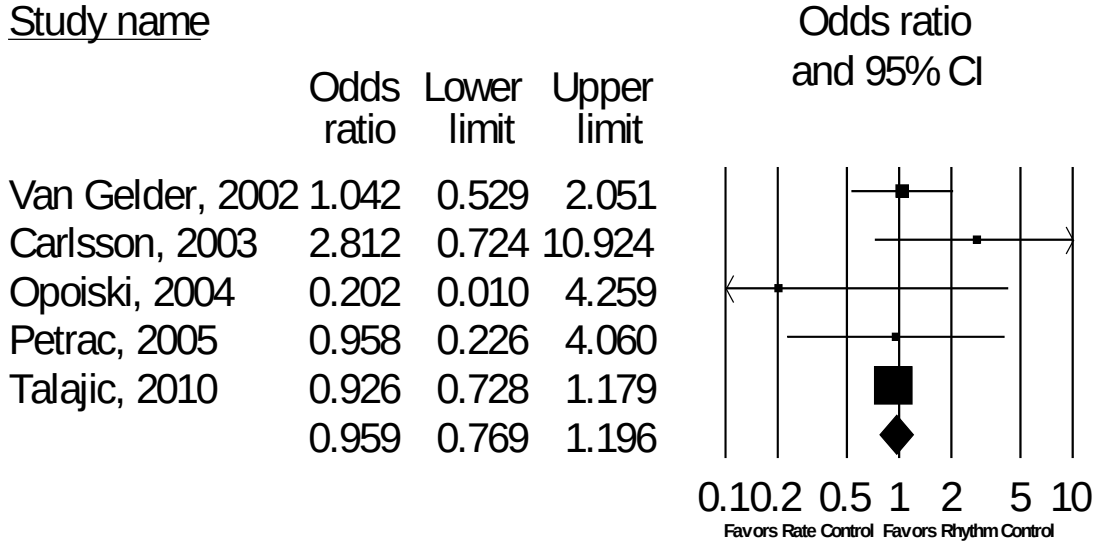


Abbreviation: CI=confidence interval

Cardiovascular Mortality

Five studies representing 2,405 patients were included in our meta-analysis of cardiovascular mortality.[156,159,296,299,301] Figure 21 shows that the OR of rate control versus rhythm control for cardiac mortality was 0.96 (95% CI, 0.77 to 1.20), showing no difference between rate- and rhythm-control strategies on cardiovascular mortality (moderate strength of evidence). Although the point estimates were inconsistent and confidence intervals wide for two of the included studies,[296,299] there was no evidence of heterogeneity, and therefore our strength of evidence rating was not lowered. The Q-value was 3.55 for 4 degrees of freedom, p=0.470.

Figure 21. Forest plot of cardiovascular mortality for rate- versus rhythm-control strategies



Abbreviation: CI=confidence interval

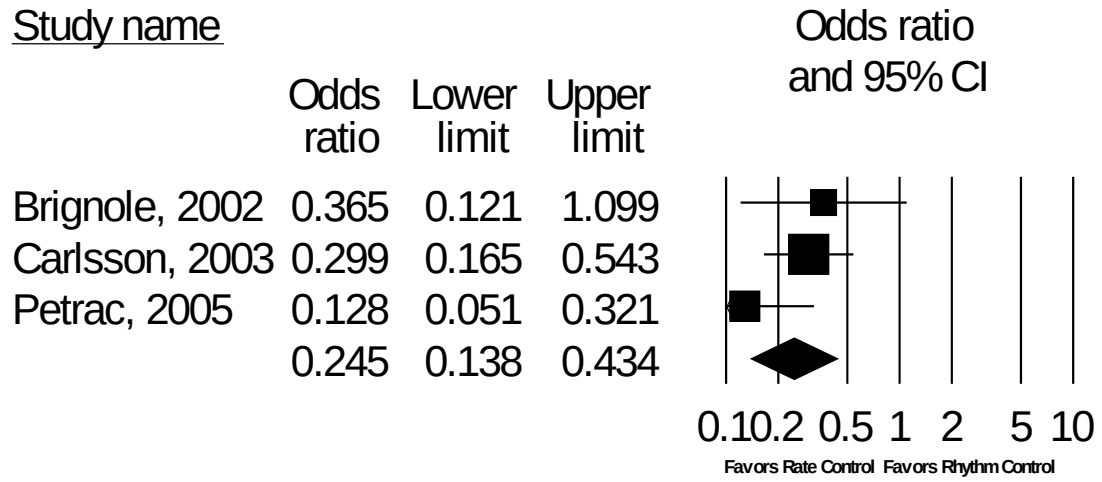
Myocardial Infarction

One study[295] compared rates of MI in patients treated with rate control (2.9%) versus patients treated with rhythm control (1.5%) and found no significant difference between the two groups, although the numbers were very small (p=0.51). This outcome was examined by only one other study,[159] which also showed no significant difference between rate control and rhythm control (5.8% vs. 10%). The small number of studies and sample size resulted in a low strength of evidence rating.

Cardiovascular Hospitalizations

A meta-analysis of three studies[159,295,296] representing 439 patients found an OR of 0.25 (95% CI, 0.14 to 0.43) for cardiovascular hospitalizations (Figure 22), demonstrating a statistically significant reduction in cardiovascular hospitalizations for patients on rate-control strategies compared with rhythm-control strategies (high strength of evidence). There was no evidence of heterogeneity (Q-value=2.83 for 2 degrees of freedom, p=0.243).

Figure 22. Forest plot of cardiovascular hospitalizations for rate- versus rhythm-control strategies



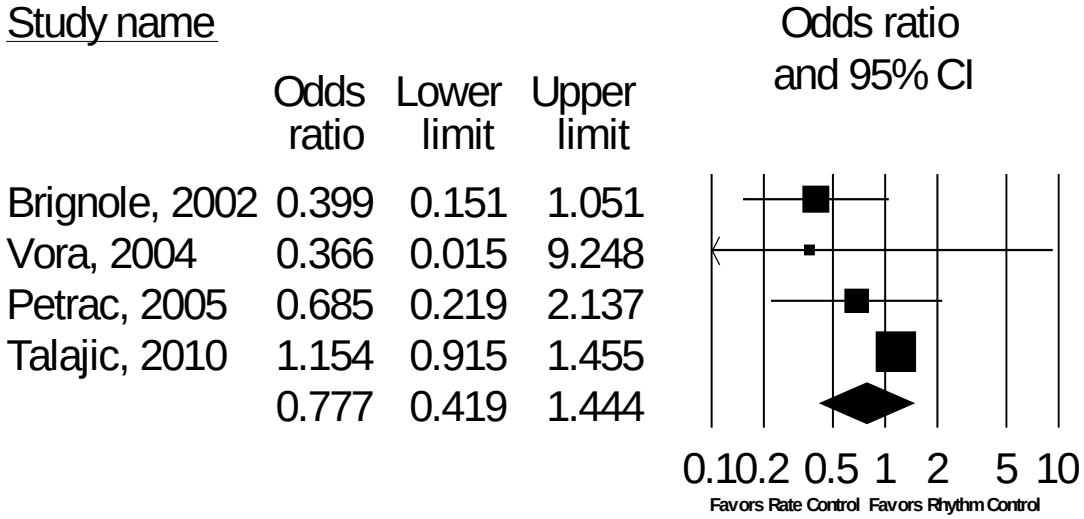
Abbreviation: CI=confidence interval

One study[301] reported specifically on AF hospitalizations. After 3 years of followup, AF hospitalizations were significantly higher in the rhythm-control group than in the rate-control group (14% vs. 9%; p=0.001) Lack of additional studies resulted in an insufficient strength of evidence rating.

Heart Failure Symptoms

Four studies representing 1,700 patients were included in our meta-analysis of the presence or worsening of heart failure symptoms.[159,295,301,302] Figure 23 shows that the OR of rate control versus rhythm control for presence or worsening of heart failure symptoms was 0.78 (95% CI, 0.42 to 1.44), showing a potential benefit of a rhythm-control strategy which did not reach statistical significance (low strength of evidence). There was no evidence of heterogeneity (Q-value=5.4 for 3 degrees of freedom, p=0.145).

Figure 23. Forest plot of heart failure symptoms for rate- versus rhythm-control strategies



Abbreviation: CI=confidence interval

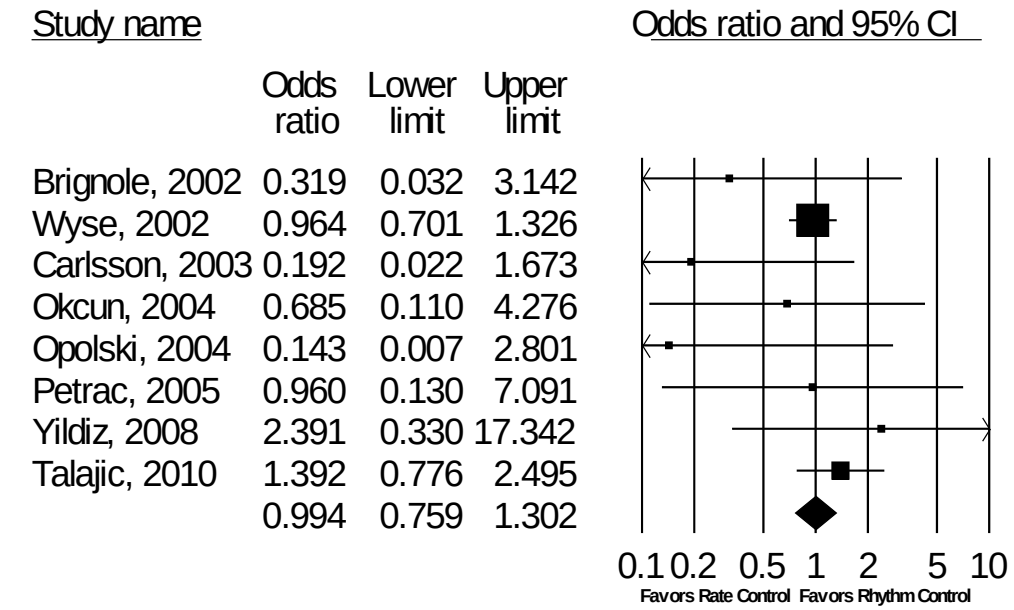
Quality of Life/Functional Status

Quality of life/functional status or control of AF symptoms was assessed in nine studies using a variety of instruments and metrics.[155,156,295-297,299,300,302,303] Two of these studies[299,302] demonstrated a statistically significant benefit of rhythm-control strategies on quality of life or functional status. None of the other studies demonstrated a significant difference between the two strategies. The variation in metrics and findings resulted in an insufficient strength of evidence rating for this outcome.

Stroke

Eight studies representing 6,424 patients were included in our meta-analysis of stroke.[155,159,295,296,298,299,301,303] Figure 24 shows that the OR of rate control versus rhythm control for stroke was 0.99 (95% CI, 0.76 to 1.30), demonstrating no difference between rate- and rhythm-control strategies in stroke outcomes (moderate strength of evidence). There was no evidence of heterogeneity, but the findings were mostly driven by one large good-quality RCT contributing 4,060 patients, which was inconsistent with several of the smaller studies, reducing our confidence in the finding and therefore the strength of evidence. The Q-value was 7.02 for 7 degrees of freedom, p=0.427.

Figure 24 . Forest plot of stroke for rate- versus rhythm-control strategies

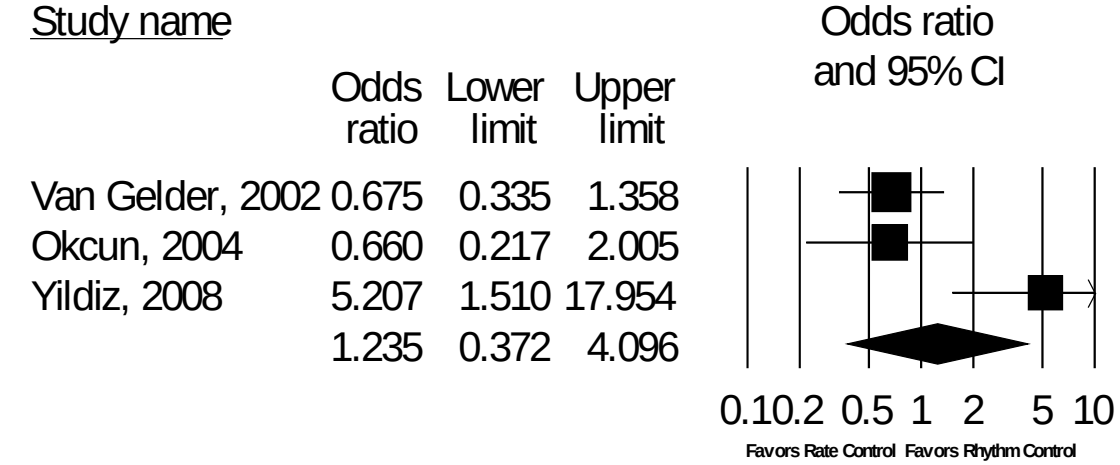


Abbreviation: CI=confidence interval

Mixed Embolic Events Including Stroke

Three studies representing 866 patients were included in our meta-analysis of mixed embolic events including stroke.[156,298,303] Figure 25 shows that the OR of rate control versus rhythm control for mixed embolic events (including stroke) was 1.24 (95% CI, 0.37 to 4.10), demonstrating a potential reduction in embolic events in the rhythm-control strategies; however, this impact did not reach statistical significance and had a wide confidence interval, and therefore the finding is to be viewed with caution (low strength of evidence). There was significant heterogeneity driven by a poor-quality study which lacked sufficient detail to evaluate the applicability of the findings to our population of interest, which therefore lowered the strength of evidence rating. The Q-value was 8.57 for 32 degrees of freedom, p=0.014.

Figure 25. Forest plot of mixed embolic events for rate- versus rhythm-control strategies

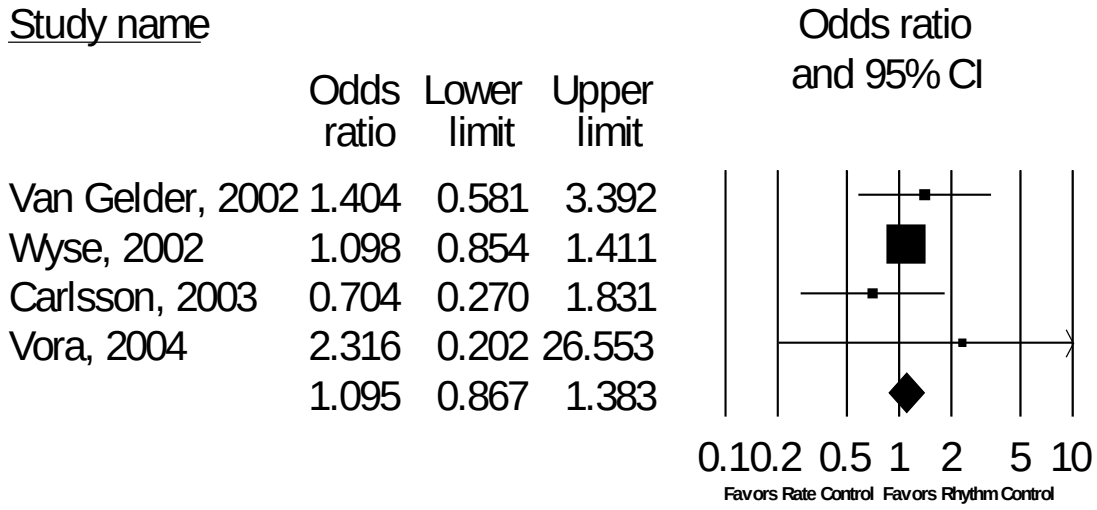


Abbreviation: CI=confidence interval

Bleeding Events

Five studies representing 5,072 patients were included in our meta-analysis of bleeding events.[155,156,296,299,302] Figure 26 shows that the OR of rate control versus rhythm control for bleeding 1.10 (95% CI, 0.87 to 1.38), demonstrating no difference between rate- and rhythm-control strategies for this outcome (moderate strength of evidence). There was no evidence of heterogeneity. The Q-value was 1.49 for 3 degrees of freedom, p=0.684.

Figure 26. Forest plot of bleeding events for rate- versus rhythm-control strategies



Abbreviation: CI=confidence interval

Composite Outcomes

Six studies examined composite outcomes.[155,156,159,296,299,301] Because the components of these outcomes differed across studies, combining them was deemed inappropriate. One study[296] examined a composite of all-cause mortality, stroke, embolic events other than stroke, and cardiopulmonary resuscitation, and found no significant difference in this outcome between patients managed with a rate-control strategy (10%) and those managed with a rhythm-control strategy (9%; p=0.99). Another study[299] examined a composite of all-cause mortality, mixed embolic events including stroke, and bleeding events including hemorrhagic stroke. During a mean followup of 1.7 years, investigators found no difference in this outcome between patients treated with a rate-control strategy and those treated with a rhythm-control strategy (OR 1.98; 95% CI, 0.28 to 22.30; p>0.71). In another study,[159] after a mean followup of 26.6±9.5 months, the primary outcome of stroke or cardiovascular death occurred in 6 out of 52 patients with VVIR pacing (5.3% per year), and in 6 out of 50 patients with DDDR pacing and antiarrhythmic drugs (5.9% per year; p=0.9). One study[301] found that time to the composite outcome of all-cause mortality, heart failure symptoms, and stroke was not significantly different between the rate-control group and the rhythm-control group (HR 0.90; 95% CI, 0.77 to 1.06; p=0.20). In another study,[156] the risk of the combined outcome of cardiovascular mortality, mixed embolic events including stroke, bleeding events (including hemorrhagic stroke), heart failure, need for a permanent pacemaker, and severe adverse events from antiarrhythmic medications was not significantly different between the rate-control group and the rhythm-control group (17.2% vs. 22.6%; 90% CI, -11.0 to 0.4%; p value NR). Finally, one study[155] compared the rate of the combined outcome of all-cause mortality, stroke, bleeding events (including hemorrhagic stroke) and adverse drug reactions in patients treated with rate-control and patients treated with rhythm

control and found no significant difference between the two groups over a mean followup of 3.5 years (20.5% for rate control vs. 21.9%; p=0.33 for rhythm control).

Adverse Events

Reporting of adverse events was inconsistent across studies. Hypotension and hypothyroidism were not reported as adverse events in any of the studies. Adverse events that were reported included: hyperthyroidism (0 in rate control vs. 2 in rhythm control[299]), bradycardia (4 studies, with results as follows: rate control 4.2% vs. rhythm control 6.0% [p=0.001];[155] rate control 3% vs. rhythm control 1.9% [p=NS];[299] rate control 3% vs. rhythm control 6% [p=NR];[301] and rate control 3% vs. rhythm control 8% [p=NR]).[156] Proarrhythmia was reported (0 in rate control 4 in rhythm control, p=NS).[299] In one study,[155] the rate of pulmonary toxicity was 4.6 percent (1.7% in the rate-control group vs. 7.3% in the rhythm-control group; p<0.001). In one study,[297] 10 patients (4%) developed ocular toxicity, all in the rhythm-control arm. In one study,[155] heart failure occurred in 2.1 percent of patients treated with rate control versus 2.7 percent of patients treated with rhythm control (p=0.58). In the same study,[155] corrected QT interval prolongation >520 ms occurred in 0.3 percent of patients in the rate-control group versus 1.9 percent in the rhythm-control group (p<0.001).

Comparison 2: Rate-Control Strategy Versus Rhythm-Control Strategy Using PVI

Maintenance of Sinus Rhythm

In one poor-quality study,[305] after 6 months of followup, PVI resulted in maintenance of sinus rhythm in only 50 percent of patients (compared with none in the medical treatment arm). In the other study,[304] which was rated as good quality, maintenance of sinus rhythm at 6 months was higher among patients who underwent PVI versus those who underwent AVN ablation and a biventricular pacemaker implantation (71% vs. 0%, p value=NR) (low strength of evidence).

Quality of Life/Functional Status

In one study,[304] functional capacity was measured by the 6-minute walk test, and investigators found that the distance increased from 269±54 m at baseline to 340±49 m at 6 months in the group that underwent PVI as compared with 281±44 m to 297±36 m in the group that underwent AVN with biventricular pacing (p<0.001). In the group that underwent PVI, the mean MLWHF score improved, with a reduction from 89±12 at baseline to 60±8 at 6 months. In the group that underwent AVN ablation with biventricular pacing, a reduction was observed from 89±11 at baseline to 82±14 at 6 months (p<0.001for the comparison between the two groups).

The second study,[305] which was rated as poor quality, also examined 6-minute walk distance and quality of life based on the Kansas City Cardiomyopathy Questionnaire, SF-36 physical component summary, and SF-36 mental component summary at 6 months. PVI did not improve quality of life as assessed by the 6-minute walk distance (mean change of 20.1 m for PVI vs. 21.4 m in the rate-control group; p=0.96), the Kansas City Cardiomyopathy Questionnaire (mean change in score of 7.1 in PVI vs. 5.6 in the rate-control group; p=0.81), or the SF-36 mental component (mean within-group change 0.4±9.5 for PVI vs. 5.9±8.5 for the rate-control group; p=0.07). The SF-36 physical component was significantly better in the PVI group than in the

rate-control group (mean within-group change 4±9.5 for PVI vs. -1±4.4 for the rate-control group; p=0.042) (insufficient strength of evidence).

Composite Outcomes

One study[304] compared the composite outcome of quality of life/functional status as defined by the 6-minute walk distance, Minnesota Living With Heart Failure (MLWHF) questionnaire, and LVEF in patients who received PVI as the rhythm-control strategy versus patients who underwent AVN ablation and pacemaker as the rate-control strategy. After 6 months of followup, this outcome was significantly better in the PVI group (p=0.017).

Reported separately, the components of the primary outcome were as follows: For PVI as compared with AVN ablation with biventricular pacing, the LVEF was significantly higher (35±9% vs. 28±6%; p<0.001), the 6-minute walking distance significantly longer (340±49 m vs. 297±36 m; p<0.001), and the MLWHF scores significantly better (60±8 vs. 82±14; p<0.001).

Adverse Events

In one poor-quality study,[305] within 6 months of followup, the rate of serious complications related to PVI was 15 percent versus 0 percent in the rate-control group. These complications included: one stroke, two cardiac tamponades, and one readmission to the hospital within 1 week after the procedure. In the other study,[304] bleeding occurred in 4 patients (9.8%) in the PVI group versus 2 (5%) in the AVN ablation and biventricular pacemaker implantation group. One patient in the PVI group developed pulmonary edema, and one patient in the AVN ablation with biventricular pacemaker implantation group developed pneumothorax.

Results in Specific Subgroups of Interest

No results were reported for outcomes of interest in specific subgroups of interest.

Strength of Evidence

Our review identified 14 studies that evaluated the comparative safety and effectiveness of rate- and rhythm-control strategies among patients with AF. We were able to quantitatively synthesize 12 of these RCTs focusing on pharmacological rate- and rhythm-control strategies and explore the comparative safety and effectiveness of the interventions. Evidence supported the comparable effectiveness of rate- and rhythm-control strategies in terms of the impact on all-cause mortality, cardiovascular mortality, and stroke. Our analysis is the largest to date addressing this issue and provides further confirmation that rate-control strategies and rhythm-control strategies have comparable effectiveness in patients who are similar to patients enrolled in the included RCTs, i.e., older patients with mild symptoms from AF. Evidence was high that rhythm-control strategies are more effective than rate-control strategies for maintaining sinus rhythm, while rate-control strategies were associated with decreased cardiovascular hospitalizations.

Our review identified only two studies comparing a rhythm-control strategy that involved PVI with a rate-control strategy that involved atrioventricular node (AVN) ablation and implantation of a pacemaker or rate-controlling medications. Findings of these two studies were inconsistent, and evidence was insufficient to determine the comparative effectiveness of the studied interventions.

Table 22 summarizes the strength of evidence for the outcomes of interest comparing rate-control and rhythm-control strategies. Most outcomes of interest were explored quantitatively

through meta-analyses using low risk of bias RCTs. We lowered our strength of evidence rating in some of the findings because of inconsistent results across RCTs and wide confidence intervals of the summary effect estimates.

Table 22. Strength of evidence domains for rhythm versus rate control

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Rate vs. Rhythm Control Using AADs						
Maintenance of Sinus Rhythm	7 (1,473)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 0.18 (95% CI, 0.11 to 0.28) favoring rhythm-control strategies
Ventricular Rate Control	2 (727)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** Significantly better in rhythm-control strategies
All-Cause Mortality	8 (6,372)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** OR 1.34 (95% CI, 0.89 to 2.02) demonstrating a potential benefit of a rhythm-control strategy which did not reach statistical significance. Since 6 of the 8 studies had ORs that crossed 1 (including 95% of the patients), and given significant heterogeneity, we assessed these studies as demonstrating no difference between rate- and rhythm-control strategies.
CV Mortality	5 (2,405)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** OR 0.96 (95% CI, 0.77 to 1.20) demonstrating no difference between rate- and rhythm-control strategies
Myocardial Infarction	2 (246)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Low** Both studies showed no significant difference between rate- and rhythm-control strategies

Table 22. Strength of evidence domains for rhythm versus rate control (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
CV hospitalizations	3 (439)	RCT/Low	Consistent	Direct	Precise	**SOE=High** OR 0.25 (95% CI, 0.14 to 0.43) favoring rate-control strategies
Heart Failure Symptoms	4 (1,700)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 0.78 (95% CI, 0.42 to 1.44) showing a potential benefit of rhythm control which did not reach statistical significance
Quality of Life	9 (5,806)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Stroke	8 (6,424)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** OR 0.99 (95% CI, 0.76 to 1.30) demonstrating no difference between rate- and rhythm-control strategies
Mixed Embolic Events Including Stroke	3 (866)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** OR 1.24 (95% CI, 0.37 to 4.09) demonstrating a potential benefit of rhythm-control strategies which did not reach statistical significance
Bleeding Events	5 (5,072)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** OR 1.10 (95% CI, 0.87 to 1.38) demonstrating no difference between rate- and rhythm-control strategies
Rate vs. Rhythm Control Using PVI						
Maintenance of Sinus Rhythm	2 (122)	RCT/Moderate	Consistent	Direct	Imprecise	**SOE=Low** Significantly better in rhythm-control strategies (OR not reported)
Quality of Life	2 (122)	RCT/Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: AAD(s)=antiarrhythmic drug(s); CI=confidence interval; CV=cardiovascular; OR=odds ratio; NA=not applicable; PVI=pulmonary vein isolation; RCT=randomized controlled trial; SOE=strength of evidence

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 148 studies represented by 182 publications and involving 25,524 patients that directly compared rate- and rhythm-control strategies in patients with atrial fibrillation (AF).

KQ 1. Rate-Control Drugs

Our review of rate-control drugs explored the comparative effectiveness of beta blockers, calcium channel blockers, digoxin, and other antiarrhythmics in controlling ventricular rate. The 14 included studies varied in terms of the drugs involved, and the lack of multiple studies exploring similar comparisons decreased our ability to quantitatively synthesize their findings. Our findings highlight the lack of definitive data on the superiority of one beta blocker over another or against calcium channel blockers. Our findings underscore the importance of conducting studies comparing the effectiveness, tolerability and safety of different beta blockers and calcium channel blockers and in different patient populations.

Table 23 summarizes the strength of evidence for the most commonly used classes of therapies and evaluated outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results chapter. For ventricular rate control, most comparisons were evaluated in one small study, resulting in insufficient evidence to support conclusions about comparative effectiveness. Exceptions were as follows: There was low strength of evidence that amiodarone was comparable to the calcium channel blocker diltiazem, and that amiodarone controlled ventricular rate better than digoxin, and there was high strength of evidence for a consistent benefit of verapamil or diltiazem compared with digoxin for rate control. There was insufficient evidence regarding the effect of rate-control therapies on quality of life.

Table 23. Summary of strength of evidence and effect estimate for KQ 1

Treatment Comparison	Ventricular Rate Control	Quality of Life
Beta Blockers vs. Digoxin	SOE=Insufficient (1 study, 47 patients)	SOE=Insufficient (No studies)
Beta Blockers vs. Calcium Channel Blockers	SOE=Insufficient (1 study, 40 patients)	SOE=Insufficient (No studies)
Beta Blockers vs. Calcium Channel Blockers in Patients Taking Digoxin	SOE=Insufficient (1 study, 29 patients)	SOE=Insufficient (1 study, 29 patients)
Sotalol vs. Metoprolol in Patients Taking Digoxin	SOE=Insufficient (1 study, 23 patients)	SOE=Insufficient (No studies)
Amiodarone vs. Calcium Channel Blockers	SOE=Low (3 studies, 271 patients) Amiodarone is comparable to the calcium channel blocker diltiazem for rate control	SOE=Insufficient (No studies)
Amiodarone vs. Digoxin	SOE=Low (3 studies, 390 patients) Amiodarone controlled ventricular rate better than digoxin across 2 studies (both p=0.02) but did not demonstrate a difference in a third study	SOE=Insufficient (No studies)

Table 23. Summary of strength of evidence and effect estimate for KQ 1 (continued)

Treatment Comparison	Ventricular Rate Control	Quality of Life
Calcium Channel Blockers Plus Digoxin vs. Digoxin Alone	SOE=Insufficient (1 study, 52 patients)	SOE=Insufficient (No studies)
Calcium Channel Blockers vs. Digoxin	SOE=High (4 studies, 422 patients) Consistent benefit of verapamil or diltiazem compared with digoxin (p<0.05 across studies)	SOE=Insufficient (No studies)

Abbreviations: KQ=Key Question; SOE=strength of evidence

KQ 2. Strict Versus Lenient Rate-Control Strategies

Our review identified only one RCT and two observational studies representing secondary analyses of RCTs exploring the comparative safety and effectiveness of strict versus lenient rate-control strategies. Table 24 summarizes the strength of evidence for strict versus lenient rate control and the outcomes of interest. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results chapter. Across outcomes, data were limited by the number of studies and the imprecision of their findings. We based our findings on the evidence from the one RCT and then evaluated whether the observational studies were consistent or not with these findings. In general, the included studies were consistent in showing no significant difference between strict and lenient rate control with respect to mortality, cardiovascular hospitalizations, heart failure symptoms, quality of life, thromboembolic events, bleeding events, and composite outcomes. However, the RCT differed from the observational studies in showing a statistically significantly lower stroke rate with lenient rate control.

Table 24. Summary of strength of evidence and effect estimate for KQ 2

Outcome	Strength of Evidence and Effect Estimate
All-Cause Mortality	SOE=Insufficient (1 study, 614 patients)
CV Mortality	SOE=Insufficient (2 studies, 828 patients)
CV Hospitalizations	SOE=Insufficient (2 studies, 1,705 patients)
Heart Failure Symptoms	SOE=Insufficient (2 studies, 828 patients)
Quality of Life	SOE=Insufficient (2 studies, 828 patients)
Thromboembolic Events	SOE=Low (2 studies, 828 patients) HR 0.35 (90% CI, 0.13 to 0.92) in RCT favoring lenient control; while also favoring lenient control, the observational study did not demonstrate a statistically significant difference (absolute difference of 1.6; 95% CI -5.3 to 8.6)
Bleeding Events	SOE=Insufficient (2 studies, 828 patients)

Abbreviations: CI=confidence interval; CV=cardiovascular; HR=hazard ratio; KQ=Key Question; RCT=randomized controlled trial; SOE=strength of evidence

KQ 3. Rate-Control Procedures Versus Drugs or Versus Other Procedures in Patients Failing Initial Pharmacotherapy

Our review identified six RCTs evaluating the comparative effectiveness of a procedural intervention versus a primarily pharmacological intervention for rate control of AF, or comparing two primarily procedural interventions. We also included data from a separately published subgroup analysis of one of the RCTs.

The included studies varied in the types of procedures and pharmacological interventions tested. In line with our a priori definition of rate-control procedures, all studies included at least one treatment arm with radiofrequency ablation of either the AVN or His bundle, most often in conjunction with pacemaker placement. The comparison arms included a pharmacological intervention whose main purpose was to control ventricular heart rate rather than converting the underlying rhythm of AF, based on the description of outcomes; this was combined with a procedure in some studies.

Tables 25 and 26 summarize the strength of evidence for rate-control procedures versus drugs and for one rate-control procedure versus another, respectively. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results chapter. Across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias and the outcomes were direct, the findings were often imprecise and based on only one or two studies.

Table 25. Summary of strength of evidence and effect estimate for KQ 3—rate-control procedures versus drugs

Outcome	Strength of Evidence and Effect Estimate
Ventricular Rate Control	SOE=Moderate (3 studies, 175 patients) Using different metrics, all 3 studies found that patients in the procedure arm had a significantly lower heart rate at 12 months than those on drugs
All-Cause Mortality	SOE=Low (2 studies, 201 patients) No significant difference
CV Mortality	SOE=Low (1 study, 102 patients) No significant difference
Exercise Capacity	SOE=Low (2 studies, 135 patients) Studies did not show significant differences between procedure and drug arms
Quality of Life	SOE=Insufficient (2 studies,135 patients)

Abbreviations: CV=cardiovascular; KQ=Key Question; SOE=strength of evidence

Table 26. Summary of strength of evidence and effect estimate for KQ 3—one rate-control procedure versus another

Outcome	Strength of Evidence and Effect Estimate
Ventricular Rate Control	SOE=Low (1 study, 40 patients) No difference between those assigned to anterior vs. posterior approach
All-Cause Mortality	SOE=Low (1 study, 184 patients) No significant difference among those in the biventricular pacing group compared with those receiving RV pacing (p=0.16)
Exercise Capacity	SOE=Low (1 study, 184 participants) Improvement in walking distance significantly greater among those in the biventricular pacing group compared with those receiving RV pacing (p=0.04)
Quality of Life	SOE=Insufficient (1 study, 184 participants)

Abbreviations: KQ=Key Question; RV=right ventricular; SOE=strength of evidence

KQ 4. Antiarrhythmic Drugs and Electrical Cardioversion for Conversion to Sinus Rhythm

Our review identified 42 studies exploring the use of antiarrhythmic drugs and electrical cardioversion for conversion to sinus rhythm. Table 27 summarizes the strength of evidence for the available comparisons and evaluated outcomes. Details about the specific components of

these ratings (risk of bias, consistency, directness, and precision) are available in the Results chapter. Across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias and the evidence was based on direct outcomes, some findings were limited in terms of precision and consistency, as well as by the available number of studies.

Table 27. Summary of strength of evidence and effect estimate for KQ 4

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF
Various Methods for External Electrical Cardioversion (Biphasic vs. Monophasic Waveforms)	SOE=High (4 studies, 411 patients) OR 4.39 (95% CI, 2.84 to 6.78) favoring biphasic waveform	SOE=Insufficient (1 study, 83 patients)	SOE=Low (1 study, 216 patients) No difference
Various Methods for External Electrical Cardioversion (Anterolateral vs. Anteroposterior Cardioversions)	SOE=Low (4 studies, 393 patients) OR 0.87 (95% CI, 0.20 to 3.72) showing potential benefit of anterolateral electrode placement which did not reach statistical significance	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)
Various Methods for External Electrical Cardioversion (Energy Protocols)	SOE=High (3 studies, 432 patients) OR 0.16 (95% CI, 0.05 to 0.53) favoring 360 J vs. 200 J monophasic shock	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)
Drug Enhancement of External Electrical Cardioversion (vs. No Drug Enhancement)	SOE=Moderate (2 studies, 218 patients) No significant benefit for patients given ibutilide or metoprolol pretreatment (p values NR)	SOE=Moderate (2 studies, 195 patients) Significant benefit for patients given verapamil or metoprolol pretreatment (p values of 0.04 and 0.027 in the 2 studies)	SOE=Low (1 study, 88 patients) Significant benefit of verapamil pretreatment (p=0.02)
Drugs for Pharmacological Cardioversion (Amiodarone vs. Sotalol)	SOE=Low (4 studies, 736 patients) OR 1.12 (95% CI, 0.81 to 1.56) demonstrating a potential benefit of amiodarone which did not reach statistical significance	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)
Drugs for Pharmacological Cardioversion (Amiodarone vs. Rate-Control Drugs)	SOE=High (7 studies, 613 patients) OR 2.99 (95% CI, 1.64 to 5.44) demonstrating a significant benefit of amiodarone	SOE=Insufficient (No studies)	SOE=Low (1 study, 152 patients) No difference between amiodarone vs. ibutilide within 24 hours

Abbreviations: AF=atrial fibrillation; CI=confidence interval; J=Joules; KQ=Key Question; NR=not reported; OR=odds ratio; SOE=strength of evidence

KQ 5. Rhythm-Control Procedures and Drugs for Maintenance of Sinus Rhythm

Our review identified 65 RCTs evaluating procedures for rhythm control and 18 studies evaluating the safety or effectiveness of pharmacological agents with or without external electrical cardioversion for maintaining sinus rhythm in patients with AF.

Tables 28 and 29 summarize the strength of evidence for the evaluated therapies and outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results chapter. Across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias and used direct evidence, the findings were often inconsistent or imprecise, limiting our findings.

Table 28 . Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events Including Stroke)	Bleeding Events
Transcatheter PVI vs. AADs	SOE= Insufficient (No studies)	SOE=High (8 studies, 921 patients) OR 6.51 (95% CI, 3.22 to 13.16) favoring transcatheter PVI	SOE= Insufficient (No studies)	All-Cause: SOE= Insufficient (1 study, 69 patients) Cardiac: SOE= Insufficient (No studies)	CV: SOE= Moderate (2 studies, 268 patients) Both studies demonstrated significant increase in CV hospitaliza-tions in the AAD arm vs. PVI AF: SOE= Insufficient (1 study, 67 patients)	SOE= Insufficient (No studies)	SOE= Insufficient (6 studies, 647 patients)	Stroke: SOE= Insufficient (No studies) Mixed: SOE= Low (2 studies, 140 patients) No embolic events in either the PVI or AAD arm	SOE= Insufficient (1 study, 67 patients)
Transcatheter PVI Using Different Types of Ablation Catheters	SOE= Insufficient (No studies)	SOE=Low (3 studies, 264 patients) No difference between different types of ablation catheters	SOE=Low (1 study, 102 patients) No difference between a multipolar circular ablation catheter and a point-by-point PVI with an irrigated tip ablation catheter (p=0.8)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	Stroke: SOE= Insufficient (1 study, 82 patients) Mixed: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)

Table 28 . Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies (continued)

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events Including Stroke)	Bleeding Events
Transcatheter Circumferential PVI vs. Transcatheter Segmental PVI	SOE= Insufficient (1 study, 80 patients)	SOE=Low (5 studies, 500 patients) OR 1.31 (95% CI, 0.59 to 2.93) demonstrating a potential benefit of circumferential PVI which did not reach statistical significance	SOE= Insufficient (No studies)	All-Cause: SOE=Low (1 study, 110 patients) No events in either arm after 48 months Cardiac: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)
Transcatheter PVI With CTI Ablation vs. Transcatheter PVI Without CTI Ablation	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (2 studies, 257 patients)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)
Transcatheter PVI With CFAE Ablation vs. Transcatheter PVI Without CFAE Ablation	SOE=Low (2 studies, 247 patients) 2 studies showing significant benefit of CFAE arm	SOE=Low (9 studies, 817 patients) OR 1.48 (95% CI, 0.74 to 2.98) showing a potential benefit of CFAE which did not reach statistical significance	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (1 study, 60 patients)	Stroke: SOE= Low (1 study, 144 patients) No events in any arm after 16 months Mixed: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)

Table 28 . Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies (continued)

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events Including Stroke)	Bleeding Events
Transcatheter PVI vs. Transcatheter PVI With Additional Ablation Sites Other Than CTI and CFAE and Transcatheter PVI Involving all Four PVs vs. Transcatheter PVI Involving Arrhythmo-genic PVs Only	SOE= Insufficient (2 studies, 384 patients)	SOE= Insufficient (15 studies, 1,926 patients)	SOE= Insufficient (6 studies, 572 patients)	All-Cause: SOE= Insufficient (2 studies, 405 patients) Cardiac: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE=Low (2 studies, 152 patients) No significant difference between arms in 2 studies	Stroke: SOE= Insufficient (2 studies, 361 patients) Mixed: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)
Transcatheter PVI Alone vs. Transcatheter PVI plus Postablation AADs	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (2 studies, 217 patients)	SOE= Insufficient (No studies)	CV: SOE= Insufficient (No studies) AF: SOE=Low (1 study, 110 patients) No difference between arms	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)

Table 28 . Summary of strength of evidence and effect estimate for KQ 5—procedural rhythm-control therapies (continued)

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	CV/AF Hospitaliza-tions	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events Including Stroke)	Bleeding Events
Surgical Maze vs. Standard of Care (Mitral Valve Surgery)	SOE= Insufficient (No studies)	SOE= Moderate (7 studies, 361 patients) OR 5.80 (95% CI, 1.79 to 18.81) demonstrating large and significant benefit of Maze	SOE= Insufficient (No studies)	All-cause: SOE=Low (6 studies, 384 patients) OR 1.97 (95% CI, 0.81 to 4.80) demonstrating potentially greater mortality with Maze which did not reach statistical significance Cardiac: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (1 study, 30 patients)	SOE= Insufficient (No studies)	Stroke: SOE= Insufficient (1 study, 30 patients) Mixed: SOE= Insufficient (1 study, 67 patients)	SOE= Insufficient (1 study, 60 patients)
PVI at the Time of Cardiac Surgery vs. Cardiac Surgery Alone or in Combination with AADs or Catheter Ablation	SOE=High (3 studies, 181 patients) OR 12.30 (95% CI, 1.31 to 115. 29) demonstrating statistically significant benefit of PVI at time of cardiac surgery	SOE=High (8 studies, 532 patients) OR 3.91 (95% CI, 1.54 to 9.91) demonstrating statistically significant benefit of PVI at time of cardiac surgery	SOE= Insufficient (No studies)	All-cause: SOE=Low (2 studies, 88 patients) 2 studies showing no difference between groups Cardiac: SOE= Insufficient (1 study, 97 patients)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (2 studies, 229 patients)	Stroke: SOE=Low (2 studies, 140 patients) 2 studies showing no difference between groups Mixed: SOE= Insufficient (No studies)	SOE= Insufficient (1 study, 43 patients)

Abbreviations: AAD(s)=antiarrhythmic drug(s); AF=atrial fibrillation; CFAE=complex fractionated atrial electrogram; CI=confidence interval; CTI=cavotricuspid isthmus; CV=cardiovascular; KQ=Key Question; NA=not applicable; OR=odds ratio; PV(s)=pulmonary vein(s); PVI=pulmonary vein isolation; SOE=strength of evidence

Table 29. Summary of strength of evidence and effect estimates for KQ 5—pharmacological rhythm-control therapies

Treatment Comparison	Restoration of Sinus Rhythm	Maintenance of Sinus Rhythm	Recurrence of AF	All-Cause and CV Mortality	AF and CV Hospitalizations	Heart Failure Symptoms/ Control of AF Symptoms	Quality of Life	Stroke (and Mixed Embolic Events Including Stroke)	Bleeding Events
Pharmacological Therapy in Which Electrical Cardioversion is a Key Component of the Treatment	SOE= Insufficient (No studies)	SOE= Insufficient (1 study, 168 patients)	SOE= Insufficient (4 studies, 414 patients)	All-cause: SOE= Insufficient (1 study, 168 patients) Cardiac: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (No studies)	SOE= Insufficient (1 study, 144 patients)	Stroke: SOE= Insufficient (1 study, 168 patients) Mixed: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)
Comparison of Pharmacological Agents	SOE= Insufficient (No studies)	SOE=Low (9 studies, 2,095 patients) Amiodarone appears better than sotalol, but no different from propafenone	SOE=Low (10 studies, 3,223 patients) Amiodarone appears better than dronedarone or sotalol, but no different from propafenone	All-Cause: SOE= Insufficient (5 studies, 2,076 patients) Cardiac: SOE= Low (4 studies, 1,664 patients) No difference between study arms in arrhythmic deaths	CV: SOE= Insufficient (No studies) AF: SOE=Low (1 study, 403 patients) Rate and mean length of stay of AF hospitalization were lower with amiodarone than with sotalol or propafenone	Heart Failure: SOE= Insufficient (No studies) AF Symptoms: SOE=Low (1 study, 403 patients) No difference between amiodarone versus sotalol or propafenone	SOE=Low (2 studies, 1,068 patients) No significant difference in either study	Stroke: SOE= Insufficient (2 studies, 1,068 patients) Mixed: SOE= Insufficient (No studies)	SOE= Insufficient (No studies)

Abbreviations: AF=atrial fibrillation; CV=cardiovascular; KQ=Key Question; SOE=strength of evidence

KQ 6. Rate- Versus Rhythm-Control Therapies

A total of 14 RCTs were included in our analysis, 12 that explored a rhythm-control strategy using pharmacological therapy versus a rate-control strategy, and 2 that compared a rhythm-control strategy with PVI versus a rate-control strategy that involved AVN ablation and implantation of a pacemaker in one case and rate-controlling medications in the other.

Table 30 summarizes the strength of evidence for the rate- and rhythm-control therapies and evaluated outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results chapter.

Table 30. Summary of strength of evidence and effect estimate for KQ 6—rate- versus rhythm-control strategies

Outcome	Strength of Evidence and Effect Estimate
Maintenance of Sinus Rhythm	Using AADs for Rhythm Control: SOE=High (7 studies, 1,473 patients) OR 0.18 (95% CI, 0.11 to 0.28) favoring rhythm-control strategies Using PVI for Rhythm Control: SOE=Low (2 studies, 122 patients) Significantly better in rhythm-control strategies (OR not reported)
Ventricular Rate Control	Using AADs for Rhythm Control: SOE=Low (2 studies, 727 patients) Significantly better in rhythm-control strategies
All-Cause Mortality	Using AADs for Rhythm Control: SOE=Moderate (8 studies, 6,372 patients) OR 1.34 (95% CI, 0.89 to 2.02) demonstrating a potential benefit of a rhythm-control strategy which did not reach statistical significance. Since 6 of the 8 studies had ORs that crossed 1 (including 95% of the patients), and given significant heterogeneity, we assessed these studies as demonstrating no difference between rate- and rhythm-control strategies.
CV Mortality	Using AADs for Rhythm Control: SOE=Moderate (5 studies, 2,405 patients) OR 0.96 (95% CI, 0.77 to 1.20) demonstrating no difference between rate- and rhythm-control strategies
Myocardial Infarction	Using AADs for Rhythm Control: SOE=Low (2 studies, 246 patients) Both studies showed no significant difference between rate- and rhythm-control strategies
CV Hospitalizations	Using AADs for Rhythm Control: SOE=High (3 studies, 439 patients) OR 0.25 (95% CI, 0.14 to 0.43) favoring rate-control strategies
Heart Failure Symptoms	Using AADs for Rhythm Control: SOE=Low (4 studies, 1,700 patients) OR 0.78 (95% CI, 0.42 to 1.44) showing a potential benefit of rhythm control which did not reach statistical significance
Quality of Life	Using AADs for Rhythm Control: SOE=Insufficient (9 studies, 5,806 patients) Using PVI for Rhythm Control: SOE=Insufficient (2 studies, 122 patients)
Stroke	Using AADs for Rhythm Control: SOE=Moderate (8 studies, 6,424 patients) OR 0.99 (95% CI, 0.76 to 1.30) demonstrating no difference between rate- and rhythm-control strategies

Table 30. Summary of strength of evidence and effect estimate for KQ 6—rate- versus rhythm-control strategies (continued)

Outcome	Strength of Evidence and Effect Estimate
Mixed Embolic Events Including Stroke	Using AADs for Rhythm Control: SOE=Low (3 studies, 866 patients) OR 1.24 (95% CI, 0.37 to 4.09) demonstrating a potential benefit of rhythm-control strategies which did not reach statistical significance
Bleeding Events	Using AADs for Rhythm Control: SOE=Moderate (5 studies, 5,072 patients) OR 1.10 (95% CI, 0.87 to 1.38) demonstrating no difference between rate- and rhythm-control strategies

Abbreviations: AADs=antiarrhythmic drugs; CI=confidence interval; CV=cardiovascular; KQ=Key Question; OR=odds ratio; PVI=pulmonary vein isolation; SOE=strength of evidence

Findings in Relationship to What Is Already Known

In general, there are two broad strategies for AF management—a rate-control strategy and a rhythm-control strategy. While some have argued that being in sinus rhythm is superior to being in AF, restoration and maintenance of sinus rhythm are not always easy, and the required therapies may pose harms, thus raising the fundamental question of whether a strategy focused only on controlling the ventricular rate as opposed to being focused on restoring and maintaining sinus rhythm may be safer and more effective. To further complicate treatment decisions, there are many pharmacological and nonpharmacological methods for controlling ventricular rate and for restoring and maintaining sinus rhythm; therefore, a complete understanding of the comparative safety and effectiveness of treatments within each strategy is needed for optimal treatment.

Because our review was restricted to evidence published in 2000 or later, it is important to summarize what was known based on the evidence prior to 2000 to allow our findings to be viewed in context. As summarized in the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation,[25-27] several medications were found to be efficacious in conversion of AF and subsequent maintenance of sinus rhythm. Unfortunately, as described below, these findings were largely based on comparisons with placebo or control therapy rather than with other active agents, and therefore the scope of this previous review is not directly applicable to that of this current comparative effectiveness review. Specifically, flecainide (OR 24.7; 95% CI, 9.0 to 68) and ibutilide/dofetilide (OR 29.1; 95% CI, 9.8 to 86) demonstrated the strongest evidence of successful conversion when compared with control. Strong evidence of efficacy with a fairly large treatment effect size also existed for propafenone (OR 4.6; 95% CI, 2.6 to 8.2). Quinidine had moderate evidence of efficacy and a modest treatment effect size compared with control treatment (OR 2.9; 95% CI, 1.2 to 7.0). Disopyramide (OR 7.0; 95% CI, 0.3 to 152) and amiodarone (OR 5.7; 95% CI, 1.0 to 33.4) had suggestive evidence of efficacy, while sotalol (OR 0.4; 95% CI 0.0 to 3.0) had suggestive evidence of negative efficacy for conversion. For maintenance of sinus rhythm, strong evidence of efficacy when compared with control treatment existed for quinidine (OR 4.1; 95% CI, 2.5 to 6.7), disopyramide (OR 3.4; 95% CI, 1.6 to 7.1), flecainide (OR 3.1; 95% CI, 1.5 to 6.2), propafenone (OR 3.7; 95% CI, 2.4 to 5.7), and sotalol (OR 7.1; 95% CI, 3.8 to 13.4). For rate control, the design and outcome measures of included trials were too disparate for meta-analysis. In general, however, the evidence suggested that calcium channel blockers and some beta blockers were effective for controlling heart rate during exercise. Although the evidence for several individual therapies compared with control or placebo was strong, the lack of evidence supporting the comparative effectiveness of these therapies highlights the need for the current report.

In the United States, the 2006 Guidelines for the Management of Patients with Atrial Fibrillation—prepared jointly by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC)[14] —along with a focused update in 2011 by the ACC, AHA, and Heart Rhythm Society,[16] now serves as the primary resource for synthesized evidence and treatment recommendations. Published randomized controlled trials (RCTs), prior meta-analyses, and the above-mentioned Guidelines indicated that there did not appear to be a significant difference in outcomes of a rate- versus rhythm-control strategy; however, the results were driven primarily by one study (the Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM] trial.[155] Unlike AFFIRM and prior meta-analyses, in the current systematic review we included more patients and gathered data on multiple outcome measures from all studies comparing a rate-control strategy with a pharmacological rhythm-control strategy and also looked for studies using nonpharmacological rate- and rhythm-control treatments. We found no statistically significant difference in all-cause mortality or cardiovascular mortality between a rate-control strategy and a rhythm-control strategy using antiarrhythmic drugs, which is consistent with prior reviews. Our review extends beyond the findings of prior reviews, as it shows no significant difference in stroke or bleeding events between the strategies and shows a potential benefit of rhythm control for reduction in heart failure symptoms which, however, did not reach statistical significance. Our review confirms the findings of AFFIRM regarding all these outcomes. Confirming the findings related to heart failure symptoms and bleeding events is of particular interest due to the relatively small number of these events in AFFIRM. As expected, the rhythm-control strategy was associated with better maintenance of sinus rhythm than the rate-control strategy.

Our review also looked specifically at comparisons of pharmacological and nonpharmacological rate-control therapies, including comparisons of lenient versus strict rate control. We found that digoxin was generally less effective than other rate-control therapies, which was consistent with prior evidence and guidelines. Also consistent with prior knowledge was the lack of definitive evidence for better rate control with beta blockers as compared with verapamil or diltiazem, and a general lack of information on comparative safety of the agents overall and within specific patient subgroups. Our review highlights the lack of data on the superiority of one beta blocker over another, which we hope will challenge current assumptions regarding the superiority of one beta-blocker over another and highlight the need for well-designed RCTs addressing this issue. Amiodarone has previously been considered an alternative to other rate-control drugs when those other drugs fail. In this review, amiodarone appeared comparable to diltiazem and better than digoxin for rate control, but due to the small number of patients and relative lack of comparable safety data, these results do not substantially modify prior clinical assumptions. Sotalol was also evaluated as a rate-control treatment, but due to a small number of studies and lack of comparable safety data, the results are inconclusive. Nonpharmacological therapies for rate control were compared with pharmacological therapy in only five RCTs, and none of these evaluated final clinical outcomes such as mortality. Differences in methods for assessing outcomes such as quality of life made comparisons across studies challenging. Patients receiving nonpharmacological rate-control therapies generally had lower heart rates, but as stated above, other important outcomes were not well addressed or comparable. This vast lack of data on final outcomes underscores the importance of doing well-designed studies evaluating these outcomes in patients receiving rate-controlling medications versus those receiving rate-controlling procedures. This lack of data should be highlighted in counseling patients about the alternative therapies available to control their heart rate.

Although we found limited data on the question of use of a lenient rate control versus strict rate control, by emphasizing the limitations in the available data and the paucity of data on lenient versus strict rate control, our findings highlight the need for more research in this area. In addition to one RCT (Rate Control Efficacy in Permanent Atrial Fibrillation-II [RACE-II] trial[17]), two observational studies that were secondary analyses of RCTs were included to address this question.[152,153] Consistent with the results of the single RCT, no differences in all-cause mortality, cardiovascular mortality, heart failure symptoms, cardiovascular hospitalizations, quality of life, or control of AF symptoms were found between lenient versus strict rate control.

With regard to rhythm-control therapies, external electrical cardioversion is known to be more effective than antiarrhythmic drugs in acute conversion of AF to sinus rhythm and thus not addressed in our review. We focused instead on the comparative safety and effectiveness of drugs and procedures for the acute restoration of sinus rhythm and for longer term maintenance of sinus rhythm. By showing that biphasic cardioversion is superior to monophasic cardioversion we confirmed the findings of prior reviews. Despite strongly held beliefs about the superiority of one positioning of cardioversion electrodes over another, we found no significant difference in restoration of sinus rhythm with use of an anterolateral versus anteroposterior positioning of cardioversion electrodes, although with a low strength of evidence for this finding. While data suggest that drug pretreatment enhances electrical cardioversion in terms of restoration and maintenance of sinus rhythm, our review does not support the current assumption that one antiarrhythmic medication is clearly superior to others in such pretreatment. Given the widespread use of these drugs, more studies are needed comparing the effectiveness and safety of different antiarrhythmic medications in enhancing restoration of sinus rhythm.

PVI is currently recommended as a second- or third-line therapy for patients with AF and is used only after antiarrhythmic drug therapy has failed. Although data continue to be needed on final clinical outcomes such as all-cause mortality, stroke, and heart failure, there was substantial evidence supporting the use of PVI versus antiarrhythmic drugs for reducing recurrences of AF in patients with paroxysmal AF who were younger, and who had only mild structural heart disease and mild left atrium enlargement. These studies mostly examined PVI as second-line therapy. One recent study compared PVI with antiarrhythmic medications as first-line therapy in patients with paroxysmal AF. It found no significant difference in the burden of AF over a period of 2 years.[306] More studies are needed on PVI as first-line therapy. The effect of PVI on final outcomes including mortality is being assessed by the ongoing NHLBI-funded Catheter Ablation versus Antiarrhythmic Drug Therapy for AF (CABANA) trial. There was less evidence supporting use of PVI versus antiarrhythmic drugs in similar types of patients with persistent AF. By combining data from nine RCTs, our review is the largest to date to address the clinical question of whether CFAE ablation in addition to PVI is better than PVI only at maintaining sinus rhythm. Unlike prior studies, our review showed that CFAE ablation in addition to PVI did not significantly increase maintenance of sinus rhythm compared with PVI alone.[88,97] This difference is largely driven by the inclusion of two recent studies[216,223] not included in prior reviews which did not demonstrate a benefit of CFAE. One of these studies was limited to patients with persistent AF, which raises questions about the influence of type and duration of AF on the outcomes of CFAE ablation. This underscores the importance of conducting well-powered and well-designed RCTs to address this issue definitively, especially as it relates to appropriate patient selection for CFAE ablation.

In addition, a surgical Maze procedure at time of other cardiac surgery (specifically mitral valve surgery) was superior to mitral valve surgery alone in reducing AF recurrences in patients

with persistent AF. Data on final clinical outcomes such as all-cause mortality associated with surgical Maze were largely absent. Likewise, rhythm control using PVI at the time of cardiac surgery is superior to cardiac surgery alone or in combination with AAD or with catheter ablation in reducing AF recurrence over 12 months of followup in patients with persistent AF. This supports exploring these interventions further with regard to their effect on final outcomes and in different patient populations.

In examining the comparative effectiveness of different antiarrhythmic medications for reducing mortality, we found only one study, a substudy of the AFFIRM study, that systematically assessed differences in mortality between antiarrhythmic drugs and found no statistically significant difference between amiodarone and sotalol. We found no data on the comparative effectiveness of different antiarrhythmic medications in relation to other final outcomes. Most studies examined the effect of different antiarrhythmic medications on the maintenance of sinus rhythm; amiodarone, sotalol, and propafenone were the most frequently studied antiarrhythmic drugs in RCTs. With regard to maintaining sinus rhythm or decreasing recurrences of AF, amiodarone did not appear to be different from propafenone in the two studies of fair quality that reported results on this comparison. Comparisons of other antiarrhythmic drugs were infrequent and often led to conflicting results. Indeed, the superiority of one antiarrhythmic medication over another has been debated for years, and there has been a long-standing need to better understand the comparative effectiveness of different antiarrhythmic medications at maintaining sinus rhythm. Our findings further highlight the importance of future research to compare different antiarrhythmic medications.

Applicability

Table 31 illustrates the specific issues with the applicability of our included evidence base by KQ. Although the included studies were conducted in a broad range of geographic locations, we note that the 2006 AF guidelines that have guided our management of AF for the past 6 years was put together by ACC, AHA and the ESC. We believe that clinical practices across the geographic locations are more similar than different and not a major detriment to the evidence base applicability. One question is why more studies are conducted outside of the United States. Although the reason for this is unknown, it is most likely partially driven both by fewer regulations and greater ease of patient enrollment.

Table 31. Potential issues with applicability of included studies

Issues	Key Question						
	KQ 1 N=14	KQ 2 N=3	KQ 3 N=6	KQ 4 N=42	KQ 5 N=83	KQ 6 N=14	Total N=148
Population (P)							
Narrow eligibility criteria and exclusion of those with comorbidities	2	0	1	1	6	3	12
Large differences between demographics of study population and community patients	1	0	0	6	16	2	22
Narrow or unrepresentative severity, stage of illness, or comorbidities	0	1	0	2	2	1	5
Run-in period with high exclusion rate for nonadherence or side effects	0	0	0	2	0	0	2
Event rates much higher or lower than observed in population-based studies	0	0	0	1	0	0	1
Intervention (I)							
Doses or schedules not reflected in current practice	1	0	0	2	2	0	5
Monitoring practices or visit frequency not used in typical practice	0	0	0	0	0	0	0
Older versions of an intervention no longer in common use	0	0	0	7	3	0	10
Cointerventions that are likely to modify effectiveness of therapy	2	0	0	4	7	0	9
Highly selected intervention team or level of training/proficiency not widely available	0	0	4	0	40	2	45
Comparator (C)							
Inadequate comparison therapy	0	0	0	5	2	1	7
Use of substandard alternative therapy	0	0	0	4	3	1	8
Outcomes (O)							
Composite outcomes that mix outcomes of different significance	0	1	1	0	4	2	8
Short-term or surrogate outcomes	13	0	2	31	12	4	55
Setting (S)							
Standards of care differ markedly from setting of interest	0	0	0	0	1	0	1
Specialty population or level of care differs from that seen in community	0	0	0	0	0	0	0

Abbreviation: KQ=Key Question

As demonstrated in Table 31, the main issues related to applicability of the evidence base included concerns about short-term or surrogate outcomes (37% of studies), whether the intervention team or level of training represented in the study would be widely available (30% of studies), and large potential differences between the study population and community patients (15% of studies).

Implications for Clinical and Policy Decisionmaking

Management of AF in contemporary clinical practice is complex and challenging. Being in sinus rhythm as compared with AF may benefit patients; however, benefits associated with being in sinus rhythm may not always outweigh the risks associated with available methods to restore sinus rhythm. Therefore, clinicians and patients are faced with difficult decisions not only in determining an appropriate general strategy (rate or rhythm control) but also in determining the optimal treatment within the selected strategy. At the time the current U.S. guidelines for management of AF were developed (developed in 2006 and then the topic of a focused update in 2011) there were few direct comparisons between specific drugs/procedures or even between the general rate- versus rhythm-control strategies. Since that time, relatively few comparative studies have been conducted, and those that have been done have been primarily focused on intermediary outcomes rather than final outcome measures such as mortality. Given the risks associated with AF, the growing number of patients with AF, and the costs and risks associated with treatments for AF, a better understanding of comparative safety and effectiveness of therapies is of paramount importance.

As new drugs and new procedures are introduced, determining their relative risks and benefits in the overall AF management scheme minimizes the use of potentially less effective, more costly, and less safe therapies. Although the current CER is consistent with existing guidelines, it strengthens the findings in these guidelines and helps to identify gaps in the evidence base and areas of needed future research.

Limitations of the Evidence Base and the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature across the KQs include: (1) few studies in specific patient subgroups of interest; (2) few studies that assess long term clinical outcomes, including mortality, cardiac events, and stroke, as well as adverse effects; (3) few studies that compare specific rate- or rhythm-control strategies across similar outcomes allowing quantitative synthesis; (4) narrow eligibility criteria of included studies and exclusion of those with comorbidities; (5) trials of procedures which use highly selected intervention teams; and (6) inadequate comparison therapies in terms of representing either standard of care of novel alternative therapy. Specific to the clinical outcomes evaluated in this literature, one of the main outcomes assessed is AF recurrence. We note, however, that there are several limitations to this outcome; findings should therefore be viewed with caution. Specifically, recurrences of AF may be asymptomatic in many patients, and in the absence of continual ECG monitoring these episodes could be missed. Continual ECG monitoring is not routinely done due to the cumbersomeness of the monitoring devices and the long period of time that these devices would need to be worn. In addition, symptoms alone have recently been shown to underestimate postablation AF burden.[307] Furthermore, recurrent episodes of AF may be of varying lengths of time from seconds to months. This wide variation in duration may have very different effects on the development of other clinically important outcomes such as exacerbation of heart failure or development of stroke.

Our review methods also had limitations. Our study was limited to English-language publications. It was the opinion of the investigators and the Technical Expert Panel (TEP) that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources. We do note,

however, that many of our included studies were conducted in Europe and there is the possibility that negative studies from such geographic locations might not have been translated into English, resulting in publication bias. Our review of ClinicalTrials.gov did not, however, provide evidence of this concern. We also limited our analysis to RCTs except for specific key questions (KQ 2 and KQ 5, focusing on cardiac resynchronization therapy). Although the inclusion of observational studies would have expanded the evidence base for our review, it was the opinion of the investigators and the TEP that the resources needed to include the potential observational studies would not be justified given the number of RCTs available and the potential risk for bias intrinsic in the observational evidence. These studies, however, may have provided additional useful information on safety and effectiveness data in patients with comorbidities and adverse events. Our review is also limited in that the evidence included in our synthesis is based on the published literature rather than through direct access to the included studies' datasets or collaboration with the primary authors. This restriction means that the methods described within an included article for a specific study, or the description of a particular outcome of interest, may not be sufficiently detailed for us to determine the relevance of a study's population, interventions, or outcomes for our review. Finally, as a comparative effectiveness study, we restricted our analysis to studies that compared two active therapies for AF and did not include placebo-controlled trials. Inclusion of such placebo-controlled trials may have allowed additional quantitative analyses to be performed used mixed treatment meta-analyses.

Research Gaps

AF is one of the most common arrhythmias and is associated with increased morbidity, increased mortality, and high health-related costs. There are several established treatments for both rate control and rhythm control, as well as newer pharmacological and procedural treatments for both. In our analyses, we found research gaps related to patient-centered outcomes for both established as well as newer therapies. We used the framework recommended by Robinson et al. to identify gaps in evidence and describe why these gaps exist.[308] This approach considers PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) to identify gaps and classifies gaps as due to (a) insufficient or imprecise information; (b) biased information; (c) inconsistency or unknown consistency; and (d) not the right information. Results are as follows:

KQ 1. Research Gaps: Rate-Control Drugs

Evidence gaps in the comparative effectiveness of rate-control drugs specifically included:

- What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with AF in terms of their impact on long-term outcomes of all-cause mortality, cardiovascular mortality, or other cardiovascular-related outcomes?
- Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest including patients stratified by age, with different types of AF, for whom a prior rate- or rhythm-control strategy was ineffective, with specific comorbidities, by sex, with an enlarged left atrium, or those at high risk for stroke and bleeding events?
- What are the comparative safety and effectiveness of specific beta-blockers used for ventricular rate control in patients with AF?

Fourteen RCTs compared the different pharmacological agents and their impact on outcomes of interest. No comparator studies included evaluated long-term outcomes of all-cause mortality, cardiovascular mortality, or other cardiovascular-related outcomes. Based on our analyses, more RCTs are needed comparing different rate-control agents among general patients with AF, as well as in patients with AF and heart failure. We identified only one study comparing the effectiveness of different beta blockers. Given that beta blockers are some of the most commonly used drugs for rate control, additional comparative studies are needed. Of particular interest would likely be the comparison between the beta blockers metoprolol and carvedilol, both of which are commonly used but which have different properties that could make them more suitable for certain subgroups of patients (e.g., patients with heart failure). An additional area of future research would be the exploration of beta blockers and calcium channel blockers used together. Patients in these studies should be followed long term to determine long-term outcomes.

KQ 2. Research Gaps: Strict Versus Lenient Rate-Control Strategies

Evidence gaps in the comparative effectiveness of strict versus lenient rate-control strategies include:

- What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with AF?
- Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest including patients stratified by age, with different types of AF, for whom a prior rate- or rhythm-control strategy was ineffective, with specific comorbidities, by sex, with an enlarged left atrium, or those at high risk for stroke and bleeding events?

Unfortunately very few studies, and only one RCT, examined the comparative effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with AF. In addition, no clear subgroups of interest were examined in the single RCT included in this analysis. This RCT was, however, of good quality and found no significant difference in outcomes among patients treated with strict or lenient rate control except for stroke risk, which favored lenient rate control. However, further studies are needed that are adequately powered to evaluate clinically meaningful outcomes, including stroke risk, and these studies should also be carried out among general patients with AF but also among subgroups of patients, such as those with heart failure. In order to better compare future studies, achieving consensus on standardized definitions of strict and lenient rate control is needed. There also remains a need to define how best to assess the adequacy of rate control. Some investigators have relied on periodic Holter monitoring, but it remains unclear whether this is the best way to assess this important outcome.

KQ 3. Research Gaps: Rate-Control Procedures Versus Drugs in Patients for Whom Initial Pharmacotherapy Was Ineffective

Evidence gaps in the comparative effectiveness of rate-control procedures versus drugs in patients for whom initial pharmacotherapy was ineffective include:

- What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients with AF for whom initial pharmacotherapy was ineffective?
- Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest including patients stratified by age, with different types of AF, for whom a prior rate- or rhythm-control strategy was ineffective, with specific comorbidities, by sex, with an enlarged left atrium, or those at high risk for stroke and bleeding events?

Six RCTs examined this question but compared fairly different treatments for rate control, thus limiting our ability to combine studies to strengthen the power of these results. In terms of assessing subgroups of interest, only one study compared the comparative effectiveness of treatments among patients with a left ventricular ejection fraction (LVEF) ≤45 percent.

Given the renewed interest in treatment of AF with rate-control therapies, it is somewhat surprising how few studies compared the effectiveness of different rate-control strategies. Further study is needed to evaluate AVN (or His bundle) ablation with pacemaker as well as specific rate-control agents for rate control and symptom management for patients who cannot tolerate pharmacological therapies. AVN ablation with pacemaker placement needs to be studied further regarding its effects on patients with different AF duration, type of AF, or underlying conditions such as heart failure. Further study is also needed to evaluate additional pacing strategies and the use of concomitant biventricular pacing. The timing of AVN ablation and pacemaker implantation needs to be better defined given that this procedure is one of last resort in patients with AF. All of the above treatment strategies should be evaluated in subgroups of interest such as sex, age, left ventricular function, and other comorbidities. In addition, further studies are needed to determine if treatment outcomes vary in patients with different types of AF.

KQ 4. Research Gaps: Antiarrhythmic Drugs and Electrical Cardioversion for Conversion to Sinus Rhythm

Evidence gaps in the comparative effectiveness of antiarrhythmic drugs and electrical cardioversion for conversion to sinus rhythm include:

- What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion procedures for conversion of AF to sinus rhythm?
- Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest including patients stratified by age, with different types of AF, for whom a prior rate- or rhythm-control strategy was ineffective, with specific comorbidities, by sex, with an enlarged left atrium, or those at high risk for stroke and bleeding events?

Although 42 studies evaluated different approaches to cardioversion, the treatment arms were highly divergent and outcomes of interest were not reported for specific subgroups. Therefore, future research in this area needs to focus on subgroups of interest, in particular patients with underlying heart disease or heart failure. Differences in the comparative effectiveness of such treatments may also exist by sex, race, or age of patients. In addition, further research is needed to determine the most appropriate subsequent treatment step following a failed electrical

cardioversion. A specific area for future research would be to explore the risk for proarrhythmias especially in women (and particularly with certain medications like dofetilide).

KQ 5. Research Gaps: Rhythm-Control Procedures and Drugs for Maintenance of Sinus Rhythm

Evidence gaps in the comparative effectiveness of rhythm-control drugs and procedures for the maintenance of sinus rhythm include:

- What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents (either separately or in combination with each other) for maintenance of sinus rhythm in patients with AF?
- Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest including patients stratified by age, with different types of AF, for whom a prior rate- or rhythm-control strategy was ineffective, with specific comorbidities, by sex, with an enlarged left atrium, or those at high risk for stroke and bleeding events?

Sixty-two studies evaluated the comparative effectiveness of the relatively newer procedural rhythm-control therapies. However, these studies were not conducted in subgroups of interest and in general did not evaluate longer term outcomes. Despite the large number of trials, there is a need for further study to determine the comparative effectiveness of these procedures on longer term outcomes, including mortality, the occurrence of stroke, and heart failure. It is not clear if certain procedures achieve better outcomes in subgroups of patients, based either on underlying cardiac characteristics or duration or type of AF. It is also not clear if anticoagulation can be stopped safely after rhythm control has been achieved or the timing of this. Further study is needed on issues related to quality of life and cost.

Although there are numerous drug therapies available for rhythm control of AF, the included RCTs all compare different combinations of drugs, limiting our ability to synthesize these results to increase their power. In addition, most studies of drug therapies reported outcomes related to rhythm control, while fewer reported long-term outcomes or complications related to therapy. Six studies did evaluate outcomes by subgroups of interest; however, these studies generally evaluated outcomes of rhythm control. Five studies reported longer-term outcomes, but these outcomes were not reported for subgroups of interest. Only one study evaluated quality of life, and the agents compared—digoxin and verapamil—are generally not used for rhythm control. Future studies are needed to compare the effectiveness of the most commonly used agents for rhythm control, and future studies are needed to evaluate longer-term outcomes, including mortality and cardiac outcomes such as heart failure, as well as outcomes related to adverse effects and quality of life, particularly for agents such as amiodarone which are known to have the potential for significant adverse effects. Unfortunately, long-term studies involving procedures are often difficult to design and execute. In addition to the need for significant resources, there are issues of cross over between arms, lack of compliance with the therapy, and loss of patients back to their referring physician making long-term followup difficult.

KQ 6. Research Gaps: Rate- Versus Rhythm-Control Therapies

Evidence gaps in the comparative effectiveness of rate- and rhythm-control strategies include:

- What are the comparative safety and effectiveness of rate-control therapies versus rhythm-control therapies in patients with AF?
- Does the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest including patients stratified by age, with different types of AF, for whom a prior rate- or rhythm-control strategy was ineffective, with specific comorbidities, by sex, with an enlarged left atrium, or those at high risk for stroke and bleeding events?

Fourteen RCTs evaluated the comparative effectiveness of rate-control therapies versus rhythm-control therapies in patients with AF; however, few of these studies examined this issue in subgroups of interest. While studies have shown that a rate-control strategy is at least as good as a rhythm-control strategy, this may be only true in patients similar to the patients enrolled in the clinical trials; i.e., older patients with no debilitating symptoms due to AF. Studies that focus on younger patients or patients with more symptomatic AF would be of interest to the clinical and policymaking community. Also, trials evaluating longer term outcomes tended to be trials that included pharmacological agents, particularly for rhythm control. Few studies compared rate-control therapies to procedural-based rhythm-control therapies, which could be associated with fewer adverse effects than antiarrhythmic drug therapy. These newer procedural-based rhythm-control therapies should be compared with rate-control therapies for longer term outcomes including mortality, cardiac events, and stroke, as well as for adverse effects.

Conclusions

In assessing clinical outcomes associated with rate- versus rhythm-control strategies, our review of recent evidence agrees with prior reviews demonstrating little overall difference in outcomes between these two strategic approaches. However, it is important to acknowledge that these studies have focused primarily on a subset of patients with AF (typically older patients with fewer symptoms), and differences between the strategic approaches in other patients are largely unknown. In addition, there is a wide range of options within each strategic approach. Very few studies evaluated the comparative safety and effectiveness of specific rate-control drugs or procedures especially within specific subgroups of patients who are likely to be encountered in clinical practice (such as those with heart failure). In addition, very few studies were done to assess outcomes associated with strict versus more lenient rate-control targets. The wide variety of rhythm-control drugs and procedures also posed a challenge to quantitative assessments of the comparative safety and effectiveness of these different drugs and procedures. Importantly, the review highlights the need for more data on the effect of these procedures on final outcomes such as mortality, stroke, and cardiovascular hospitalizations.

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Abbreviations

AAD	antiarrhythmic drug
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-Up Investigation of Rhythm Management
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AIRCRAFT	Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial
AVN	atrioventricular node
bpm	beats per minute
CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial
CAD	coronary artery disease
CARE-HF	Cardiac REsynchronization in Heart Failure
CDSR	Cochrane Database of Systematic Reviews
CER	comparative effectiveness review
CFAE	complex fractionated atrial electrogram
CRT	cardiac resynchronization therapy
CTI	cavotricuspid isthmus
CV	cardiovascular
DDDR	dual chamber demand rate-responsive
ECG	electrocardiogram
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
HR	hazard ratio
HRS	Heart Rhythm Society
ICD	implantable cardioverter defibrillator;
ICTRP	International Clinical Trials Registry Platform
IOM	Institute of Medicine
IQR	interquartile range
J	Joules
KQ(s)	Key Question(s)
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MI	myocardial infarction
NR	not reported
NS	not statistically significant
NYHA	New York Heart Association
PICOTS	Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PV	pulmonary vein
PVI	pulmonary vein isolation
RACE(-II)	Rate Control Efficacy in Permanent Atrial Fibrillation(-II)
RCT(s)	randomized controlled trial(s)

RFA	radiofrequency ablation
RV	right ventricular
SD	standard deviation
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
TEP	Technical Expert Panel
VVIR	ventricular demand rate-responsive
WHO	World Health Organization

Appendix A. Exact Search Strings

PubMed® Search Strategy (Final Search Date August 1, 2012)

KQ 1—What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	"Anti-Arrhythmia Agents"[Mesh] OR "Anti-Arrhythmia Agents"[Pharmacological Action] OR ((antiarrhythmic[tiab] OR antiarrhythmia[tiab]) AND (agent[tiab] OR agents[tiab] OR drug[tiab] OR drugs[tiab])) OR "metoprolol"[MeSH Terms] OR "metoprolol"[tiab] OR "atenolol"[MeSH Terms] OR "atenolol"[tiab] OR "carvedilol"[Supplementary Concept] OR "carvedilol"[tiab] OR "bisoprolol"[MeSH Terms] OR "bisoprolol"[tiab] OR "timolol"[MeSH Terms] OR "timolol"[tiab] OR "esmolol"[Supplementary Concept] OR "esmolol"[tiab] OR "nebivolol"[Supplementary Concept] OR "nebivolol"[tiab] OR verapamil[tiab] OR "verapamil"[MeSH Terms] OR "diltiazem"[MeSH Terms] OR "diltiazem"[tiab] OR "digoxin"[MeSH Terms] OR "digoxin"[tiab] OR "Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic beta-Antagonists"[Pharmacological Action] OR beta-blocker[tiab] OR beta-blockers[tiab] OR "Calcium Channel Blockers"[Mesh] OR "Calcium Channel Blockers" [Pharmacological Action] OR "Acebutolol"[Mesh] OR acebutolol[tiab] OR "Nadolol"[Mesh] OR Nadolol[tiab] OR "Amiodarone"[Mesh] OR Amiodarone[tiab] OR "dronedarone" [Supplementary Concept] OR dronedarone[tiab]
#3	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[sb] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#4	#1 AND #2 AND #3
#5	#4 NOT (animals[mh] NOT humans[mh])
#6	#5 limits: English, Publication Date from 2000-present

KQ 2—What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	((rate[tiab] OR "heart rate"[MeSH Terms]) AND control[tiab]) AND (strategy[tiab] OR lenient[tiab] OR strict[tiab])
#3	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[sb] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR

Set #	Terms
	"meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#4	#1 AND #2 AND #3
#5	#4 NOT (animals[mh] NOT humans[mh])
#6	#5 limits: English, Publication Date from 2000-present

KQ 3—What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients with atrial fibrillation who have failed initial pharmacotherapy? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	nonpharmacological[tiab] OR non-pharmacological[tiab] OR "Pacemaker, Artificial"[Mesh] OR pacemaker[tiab] OR (cardiac[tiab] AND (pace[tiab] OR pacing[tiab]) AND artificial[tiab]) OR "Cardiac Pacing, Artificial"[Mesh] OR "Atrioventricular Node"[Mesh] OR AVN[tiab] OR ((atrioventricular[tiab] OR atrio-ventricular[tiab]) AND (nodal[tiab] OR node[tiab])) OR "catheter ablation"[MeSH Terms] OR "catheter ablation"[tiab]
#3	rate[tiab] OR heart rate[Mesh]
#4	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#5	#1 AND #2 AND #3 AND #4
#6	#5 NOT (animals[mh] NOT humans[mh])
#7	#6 limits: English, Publication Date from 2000-present

KQ 4—What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]

Set #	Terms
#2	"Anti-Arrhythmia Agents"[Mesh] OR "Anti-Arrhythmia Agents"[Pharmacological Action] OR ((antiarrhythmic[tiab] OR antiarrhythmia[tiab]) AND (agent[tiab] OR agents[tiab] OR drug[tiab] OR drugs[tiab])) OR "flecainide"[MeSH Terms] OR "flecainide"[tiab] OR "propafenone"[MeSH Terms] OR "propafenone"[tiab] OR "amiodarone"[MeSH Terms] OR "amiodarone"[tiab] OR "sotalol"[MeSH Terms] OR "sotalol"[tiab] OR "ibutilide"[Supplementary Concept] OR "ibutilide"[tiab] OR "dofetilide"[Supplementary Concept] OR "dofetilide"[tiab] OR "dronedarone"[Supplementary Concept] OR "dronedarone"[tiab] OR "Disopyramide"[Mesh] OR Disopyramide[tiab]
#3	"electric countershock"[MeSH Terms] OR electrical[tiab] OR cardioversion[tiab]
#4	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#5	#1 AND (#2 OR #3) AND #4
#6	#5 NOT (animals[mh] NOT humans[mh])
#7	#6 limits: English, Publication Date from 2000-present

KQ 5—What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	"Catheter Ablation"[Mesh] OR "Cardiac Resynchronization Therapy"[Mesh] OR non-pharmacological[tiab] OR nonpharmacological[tiab] OR ablation[tiab] OR "surgical maze"[tiab] OR (surgical[tiab] AND maze[tiab]) OR resynchroni*[tiab] OR (ganglionic[tiab] AND ablation[tiab]) OR (ganglionated[tiab] AND ablation[tiab]) OR denervation[tiab] OR "pulmonary vein isolation"[tiab] OR (pulmonary[tiab] AND isolation[tiab]) OR "electric countershock"[MeSH Terms] OR electrical[tiab] OR cardioversion[tiab]
#3	"Anti-Arrhythmia Agents"[Mesh] OR "Anti-Arrhythmia Agents"[Pharmacological Action] OR ((antiarrhythmic[tiab] OR antiarrhythmia[tiab]) AND (agent[tiab] OR agents[tiab] OR drug[tiab] OR drugs[tiab])) OR "flecainide"[MeSH Terms] OR "flecainide"[tiab] OR "propafenone"[MeSH Terms] OR "propafenone"[tiab] OR "amiodarone"[MeSH Terms] OR "amiodarone"[tiab] OR "sotalol"[MeSH Terms] OR "sotalol"[tiab] OR "ibutilide"[Supplementary Concept] OR "ibutilide"[tiab] OR "dofetilide"[Supplementary Concept] OR "dofetilide"[tiab] OR "dronedarone"[Supplementary Concept] OR "dronedarone"[tiab] OR "Disopyramide"[Mesh] OR Disopyramide[tiab]
#4	rhythm[tiab]
#5	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#6	#1 AND (#2 OR #3) AND #4 AND #5

Set #	Terms
#7	#6 NOT (animals[mh] NOT humans[mh])
#8	#7 Limits English, Publication Date from 2000-present

KQ 6—What are the comparative safety and effectiveness of rate-control therapies versus rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	((nonpharmacological[tiab] OR non-pharmacological[tiab] OR "Pacemaker, Artificial"[Mesh] OR pacemaker[tiab] OR (cardiac[tiab] AND (pace[tiab] OR pacing[tiab]) AND artificial[tiab]) OR "Cardiac Pacing, Artificial"[Mesh] OR "Atrioventricular Node"[Mesh] OR AVN[tiab] OR ((atrioventricular[tiab] OR atrio-ventricular[tiab]) AND (nodal[tiab] OR node[tiab])) OR "catheter ablation"[MeSH Terms] OR "catheter ablation"[tiab] OR "Anti-Arrhythmia Agents"[Mesh] OR "Anti-Arrhythmia Agents"[Pharmacological Action] OR ((antiarrhythmic[tiab] OR antiarrhythmia[tiab]) AND (agent[tiab] OR agents[tiab] OR drug[tiab] OR drugs[tiab]))) AND ("heart rate"[mesh] OR rate[tiab])) OR "metoprolol"[MeSH Terms] OR "metoprolol"[tiab] OR "atenolol"[MeSH Terms] OR "atenolol"[tiab] OR "carvedilol"[Supplementary Concept] OR "carvedilol"[tiab] OR "bisoprolol"[MeSH Terms] OR "bisoprolol"[tiab] OR "timolol"[MeSH Terms] OR "timolol"[tiab] OR "esmolol"[Supplementary Concept] OR "esmolol"[tiab] OR "nebivolol"[Supplementary Concept] OR "nebivolol"[tiab] OR verapamil[tiab] OR "verapamil"[MeSH Terms] OR "diltiazem"[MeSH Terms] OR "diltiazem"[tiab] OR "digoxin"[MeSH Terms] OR "digoxin"[tiab] OR "Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic beta-Antagonists"[Pharmacological Action] OR beta-blocker[tiab] OR beta-blockers[tiab] OR "Calcium Channel Blockers"[Mesh] OR "Calcium Channel Blockers" [Pharmacological Action] OR "Acebutolol"[Mesh] OR acebutolol[tiab] OR "Nadolol"[Mesh] OR Nadolol[tiab]
#3	("Catheter Ablation"[Mesh] OR "Cardiac Resynchronization Therapy"[Mesh] OR non-pharmacological[tiab] OR nonpharmacological[tiab] OR ablation[tiab] OR "surgical maze"[tiab] OR (surgical[tiab] AND maze[tiab]) OR resynchroni*[tiab] OR (ganglionic[tiab] AND ablation[tiab]) OR (ganglionated[tiab] AND ablation[tiab]) OR denervation[tiab] OR "pulmonary vein isolation"[tiab] OR (pulmonary[tiab] AND isolation[tiab]) OR "electric countershock"[MeSH Terms] OR electrical[tiab] OR cardioversion[tiab] OR "Anti-Arrhythmia Agents"[Mesh] OR "Anti-Arrhythmia Agents"[Pharmacological Action] OR ((antiarrhythmic[tiab] OR antiarrhythmia[tiab]) AND (agent[tiab] OR agents[tiab] OR drug[tiab] OR drugs[tiab])) AND rhythm[tiab]) OR "flecainide"[MeSH Terms] OR "flecainide"[tiab] OR "propafenone"[MeSH Terms] OR "propafenone"[tiab] OR "amiodarone"[MeSH Terms] OR "amiodarone"[tiab] OR "sotalol"[MeSH Terms] OR "sotalol"[tiab] OR "ibutilide"[Supplementary Concept] OR "ibutilide"[tiab] OR "dofetilide"[Supplementary Concept] OR "dofetilide"[tiab] OR "dronedarone"[Supplementary Concept] OR "dronedarone"[tiab] OR "Disopyramide"[Mesh] OR Disopyramide[tiab]
#4	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#5	#1 AND #2 AND #3 AND #4
#6	#5 NOT (animals[mh] NOT humans[mh])
#7	#6 limits: English, Publication Date from 2000-present

Eliminated KQ*—What are the comparative diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy of echocardiographic studies and other clinical

parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with atrial fibrillation?

*Note: This KQ was eliminated from the CER for scoping reasons following discussions with AHRQ and the TEP members. Since the KQ was removed after the original PubMed® searches were performed on December 9, 2011, we have included documentation of the search strategy below. This portion of the search was not included in the final search update on August 1, 2012. The results from this search are reflected in the totals depicted in the literature flow diagram.

Set #	Terms
#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	predictors[tiab] OR predict[tiab] OR predicting[tiab] OR predicts[tiab] OR predicted[tiab] OR prognosis[tiab] OR prognostic[tiab] OR prognosis[MeSH] OR accurately[tiab] OR accuracy[tiab] OR accurate[tiab] OR reliability[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "Sensitivity and Specificity"[Mesh] OR "Treatment Outcome"[MeSH] OR Diagnosis[MeSH] OR diagnostic[tiab]
#3	maintain[tiab] OR maintenance[tiab] OR maintained[tiab] OR success[tiab] OR successful[tiab] OR conversion[tiab] OR restoration[tiab] OR restored[tiab]
#4	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#5	#1 AND #2 AND #3 AND #4
#6	#5 NOT (animals[mh] NOT humans[mh])
#7	#6 English, Publication Date from 2000-present

Embase® Search Strategy (Final Search Date August 1, 2012)

Platform: Embase.com

KQ 1—What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti

Set #	Terms
#2	'antiarrhythmic agent'/exp OR 'metoprolol'/exp OR 'atenolol'/exp OR 'carvedilol'/exp OR 'bisoprolol'/exp OR 'timolol'/exp OR 'esmolol'/exp OR 'nebivolol'/exp OR 'verapamil'/exp OR 'diltiazem'/exp OR 'digoxin'/exp OR 'acetyldigoxin'/exp OR 'alpha acetyldigoxin'/exp OR 'metildigoxin'/exp OR 'digoxigenin'/exp OR 'beta adrenergic receptor blocking agent'/exp OR 'calcium channel blocking agent'/exp OR 'acebutolol'/exp OR 'nadolol'/exp OR 'amiodarone'/exp OR 'dronedarone'/exp OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) OR metoprolol:ab,ti OR atenolol:ab,ti OR carvedilol:ab,ti OR bisoprolol:ab,ti OR timolol:ab,ti OR esmolol:ab,ti OR nebivolol:ab,ti OR verapamil:ab,ti OR diltiazem:ab,ti OR digoxin:ab,ti OR beta-blocker:ab,ti OR beta-blockers:ab,ti OR acebutolol:ab,ti OR Nadolol:ab,ti OR Amiodarone:ab,ti OR dronedarone:ab,ti
#3	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#4	#1 AND #2 AND #3
#5	#4, Limits: Humans, English, 2000-present
#6	#5 AND [embase]/lim NOT [medline]/lim

KQ 2—What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR 'atrial flutter':ab,ti
#2	((rate:ab,ti OR 'heart rate'/exp) AND control:ab,ti) AND (strategy:ab,ti OR lenient:ab,ti OR strict:ab,ti)
#3	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#4	#1 AND #2 AND #3
#5	#4, Limits: Humans, English, 2000-present
#6	#5 AND [embase]/lim NOT [medline]/lim

KQ 3—What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients with atrial fibrillation who have failed initial pharmacotherapy? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR 'atrial flutter':ab,ti
#2	nonpharmacological:ab,ti OR non-pharmacological:ab,ti OR 'artificial heart pacemaker'/exp OR pacemaker:ab,ti OR (cardiac:ab,ti AND (pace:ab,ti OR pacing:ab,ti) AND artificial:ab,ti) OR 'heart pacing'/exp OR 'heart atrioventricular node'/exp OR AVN:ab,ti OR ((atrioventricular:ab,ti OR atrio-ventricular:ab,ti) AND (nodal:ab,ti OR node:ab,ti)) OR 'catheter ablation'/exp OR "catheter ablation":ab,ti
#3	rate:ab,ti OR 'heart rate'/exp
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND #2 AND #3 AND #4
#6	#5, Limits: Humans, English, 2000-present
#7	#6 AND [embase]/lim NOT [medline]/lim

KQ 4 —What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR 'atrial flutter':ab,ti
#2	'antiarrhythmic agent'/exp OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) OR 'flecainide'/exp OR flecainide:ab,ti OR 'propafenone'/exp OR propafenone:ab,ti OR 'amiodarone'/exp OR amiodarone:ab,ti OR 'sotalol'/exp OR sotalol:ab,ti OR 'ibutilide'/exp OR ibutilide:ab,ti OR 'dofetilide'/exp OR dofetilide:ab,ti OR 'dronedarone'/exp OR dronedarone:ab,ti OR 'disopyramide'/exp OR Disopyramide:ab,ti
#3	'cardioversion'/exp OR 'defibrillation'/exp OR electrical:ab,ti OR cardioversion:ab,ti
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND (#2 OR #3) AND #4
#6	#5, Limits: Humans, English, 2000-present
#7	#6 AND [embase]/lim NOT [medline]/lim

KQ 5— What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological

agents for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR 'atrial flutter':ab,ti
#2	'catheter ablation'/exp OR 'cardiac resynchronization therapy'/exp OR non-pharmacological:ab,ti OR nonpharmacological:ab,ti OR ablation:ab,ti OR "surgical maze":ab,ti OR (surgical:ab,ti AND maze:ab,ti) OR resynchroni*:ab,ti OR (ganglionic:ab,ti AND ablation:ab,ti) OR (ganglionated:ab,ti AND ablation:ab,ti) OR denervation:ab,ti OR "pulmonary vein isolation":ab,ti OR (pulmonary:ab,ti AND isolation:ab,ti) OR 'heart stimulation'/exp OR electrical:ab,ti OR cardioversion:ab,ti
#3	'antiarrhythmic agent'/exp OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) OR 'flecainide'/exp OR flecainide:ab,ti OR 'propafenone'/exp OR propafenone:ab,ti OR 'amiodarone'/exp OR amiodarone:ab,ti OR 'sotalol'/exp OR sotalol:ab,ti OR 'ibutilide'/exp OR ibutilide:ab,ti OR 'dofetilide'/exp OR dofetilide:ab,ti OR 'dronedarone'/exp OR dronedarone:ab,ti OR 'disopyramide'/exp OR Disopyramide:ab,ti
#4	rhythm:ab,ti
#5	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#6	#1 AND (#2 OR #3) AND #4 AND #5
#7	#6, Limits: Humans, English, 2000-present
#8	#7 AND [embase]/lim NOT [medline]/lim

KQ 6—What are the comparative safety and effectiveness of rate-control therapies versus rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR 'atrial flutter':ab,ti
#2	((nonpharmacological:ab,ti OR non-pharmacological:ab,ti OR 'artificial heart pacemaker'/exp OR pacemaker:ab,ti OR (cardiac:ab,ti AND (pace:ab,ti OR pacing:ab,ti) AND artificial:ab,ti) OR 'heart pacing'/exp OR 'heart atrioventricular node'/exp OR AVN:ab,ti OR ((atrioventricular:ab,ti OR atrio-ventricular:ab,ti) AND (nodal:ab,ti OR node:ab,ti)) OR 'catheter ablation'/exp OR "catheter ablation":ab,ti OR 'antiarrhythmic agent'/exp OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti))) AND ('heart rate'/exp OR rate:ab,ti)) OR 'metoprolol'/exp OR metoprolol:ab,ti OR 'atenolol'/exp OR atenolol:ab,ti OR 'carvedilol'/exp OR carvedilol:ab,ti OR 'bisoprolol'/exp OR bisoprolol:ab,ti OR 'timolol'/exp OR timolol:ab,ti OR 'esmolol'/exp OR esmolol:ab,ti OR 'nebivolol'/exp OR nebivolol:ab,ti OR verapamil:ab,ti OR 'verapamil'/exp OR 'diltiazem'/exp OR diltiazem:ab,ti OR 'digoxin'/exp OR 'acetyldigoxin'/exp OR 'alpha acetyldigoxin'/exp OR 'metildigoxin'/exp OR digoxin:ab,ti OR 'beta adrenergic receptor blocking agent'/exp OR beta-blocker:ab,ti OR beta-blockers:ab,ti OR 'calcium channel blocking agent'/exp OR 'acebutolol'/exp OR acebutolol:ab,ti OR 'nadolol'/exp OR Nadolol:ab,ti

Set #	Terms
#3	('catheter ablation'/exp OR 'cardiac resynchronization therapy'/exp OR non-pharmacological:ab,ti OR nonpharmacological:ab,ti OR ablation:ab,ti OR "surgical maze":ab,ti OR (surgical:ab,ti AND maze:ab,ti) OR resynchroni*:ab,ti OR (ganglionic:ab,ti AND ablation:ab,ti) OR (ganglionated:ab,ti AND ablation:ab,ti) OR denervation:ab,ti OR "pulmonary vein isolation":ab,ti OR (pulmonary:ab,ti AND isolation:ab,ti) OR 'cardioversion'/exp OR 'defibrillation'/exp OR electrical:ab,ti OR cardioversion:ab,ti OR 'antiarrhythmic agent'/exp OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) AND rhythm:ab,ti) OR 'flecainide'/exp OR flecainide:ab,ti OR 'propafenone'/exp OR propafenone:ab,ti OR 'amiodarone'/exp OR amiodarone:ab,ti OR 'sotalol'/exp OR sotalol:ab,ti OR 'ibutilide'/exp OR ibutilide:ab,ti OR 'dofetilide'/exp OR dofetilide:ab,ti OR 'dronedarone'/exp OR dronedarone:ab,ti OR 'disopyramide'/exp OR Disopyramide:ab,ti
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND #2 AND #3 AND #4
#6	#5, Limits: English, Humans, 2000-present
#7	#6 AND [embase]/lim NOT [medline]/lim

Eliminated KQ*—What are the comparative diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy of echocardiographic studies and other clinical parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with atrial fibrillation?

*Note: This KQ was eliminated from the CER for scoping reasons following discussions with AHRQ and the TEP members. Since the KQ was removed after the original Embase searches were performed on December 16, 2011, we have included documentation of the search strategy below. This portion of the search was not included in the final search update on August 1, 2012. The results from this search are reflected in the totals depicted in the literature flow diagram.

Set #	Terms
#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR 'atrial flutter':ab,ti
#2	predictors:ab,ti OR predict:ab,ti OR predicting:ab,ti OR predicts:ab,ti OR predicted:ab,ti OR prognosis:ab,ti OR prognostic:ab,ti OR 'prognosis'/exp OR accurately:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR reliability:ab,ti OR sensitivity:ab,ti OR specificity:ab,ti OR 'sensitivity and specificity'/exp OR 'treatment outcome'/exp OR 'diagnosis'/exp OR diagnostic:ab,ti
#3	maintain:ab,ti OR maintenance:ab,ti OR maintained:ab,ti OR success:ab,ti OR successful:ab,ti OR conversion:ab,ti OR restoration:ab,ti OR restored:ab,ti

#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND #2 AND #3 AND #4
#6	#5, Limits: English, Humans, 2000-present
#7	#6 AND [embase]/lim NOT [medline]/lim

Cochrane Search Strategy (Final Search Date August 1, 2012)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ 1—What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	MeSH descriptor Anti-Arrhythmia Agents explode all trees OR MeSH descriptor Adrenergic beta-Antagonists explode all trees OR MeSH descriptor Calcium Channel Blockers explode all trees OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) OR metoprolol:ab,ti,kw OR atenolol:ab,ti,kw OR carvedilol:ab,ti,kw OR bisoprolol:ab,ti,kw OR timolol:ab,ti,kw OR esmolol:ab,ti,kw OR nebivolol:ab,ti,kw OR verapamil:ab,ti,kw OR diltiazem:ab,ti,kw OR digoxin:ab,ti,kw OR beta-blocker:ab,ti OR beta-blockers:ab,ti OR Acebutolol:ab,ti,kw OR Nadolol:ab,ti,kw OR Amiodarone:ab,ti,kw OR dronedarone:ab,ti,kw
#3	#1 AND #2
#4	#3, Limits: Cochrane Reviews, 2000-2012

KQ 2—What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	((rate:ab,ti OR heart rate:ab,ti,kw) AND control:ab,ti) AND (strategy:ab,ti OR lenient:ab,ti OR strict:ab,ti)
#3	#1 AND #2
#4	#3, Limits: Cochrane Reviews, 2000-2012

KQ 3—What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients

with atrial fibrillation who have failed initial pharmacotherapy? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	MeSH descriptor Pacemaker, Artificial explode all trees OR MeSH descriptor Cardiac Pacing, Artificial explode all trees OR MeSH descriptor Atrioventricular Node explode all trees OR MeSH descriptor Catheter Ablation explode all trees OR nonpharmacological:ab,ti OR non-pharmacological:ab,ti OR pacemaker:ab,ti OR (cardiac:ab,ti AND (pace:ab,ti OR pacing:ab,ti) AND artificial:ab,ti) OR AVN:ab,ti OR ((atrioventricular:ab,ti OR atrio-ventricular:ab,ti) AND (nodal:ab,ti OR node:ab,ti)) OR "catheter ablation":ab,ti
#3	rate:ab,ti OR heart rate:ab,ti,kw
#4	#1 AND #2 AND #3
#5	#4, Limits: Cochrane Reviews, 2000-2012

KQ 4—What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	MeSH descriptor Anti-Arrhythmia Agents explode all trees OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) OR flecainide:ab,ti,kw OR propafenone:ab,ti,kw OR amiodarone:ab,ti,kw OR sotalol:ab,ti,kw OR ibutilide:ab,ti,kw OR dofetilide:ab,ti,kw OR dronedarone:ab,ti,kw OR Disopyramide:ab,ti,kw
#3	MeSH descriptor Electric Countershock explode all trees OR electrical:ab,ti OR cardioversion:ab,ti
#4	#1 AND (#2 OR #3)
#5	#4, Limits: Cochrane Reviews, 2000-2012

KQ 5—What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	MeSH descriptor Catheter Ablation explode all trees OR MeSH descriptor Cardiac Resynchronization Therapy explode all trees OR MeSH descriptor Electric Countershock explode all trees OR non-pharmacological:ab,ti OR nonpharmacological:ab,ti OR ablation:ab,ti OR "surgical maze":ab,ti OR (surgical:ab,ti AND maze:ab,ti) OR resynchroni*:ab,ti OR (ganglionic:ab,ti AND ablation:ab,ti) OR (ganglionated:ab,ti AND ablation:ab,ti) OR denervation:ab,ti OR "pulmonary vein isolation":ab,ti OR (pulmonary:ab,ti AND isolation:ab,ti) OR electrical:ab,ti OR cardioversion:ab,ti
#3	MeSH descriptor Anti-Arrhythmia Agents explode all trees OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) OR flecainide:ab,ti,kw OR propafenone:ab,ti,kw OR amiodarone:ab,ti,kw OR sotalol:ab,ti,kw OR ibutilide:ab,ti,kw OR dofetilide:ab,ti,kw OR dronedarone:ab,ti,kw OR Disopyramide:ab,ti,kw
#4	rhythm:ab,ti
#5	#1 AND (#2 OR #3) AND #4
#6	#5, Limits: Cochrane Reviews, 2000-2012

KQ 6—What are the comparative safety and effectiveness of rate-control therapies versus rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	MeSH descriptor Pacemaker, Artificial explode all trees OR MeSH descriptor Cardiac Pacing, Artificial explode all trees OR MeSH descriptor Atrioventricular Node explode all trees OR MeSH descriptor Catheter Ablation explode all trees OR MeSH descriptor Anti-Arrhythmia Agents explode all trees OR MeSH descriptor Adrenergic beta-Antagonists explode all trees OR MeSH descriptor Calcium Channel Blockers explode all trees OR ((nonpharmacological:ab,ti OR non-pharmacological:ab,ti OR pacemaker:ab,ti OR (cardiac:ab,ti AND (pace:ab,ti OR pacing:ab,ti) AND artificial:ab,ti)) OR AVN:ab,ti OR ((atrioventricular:ab,ti OR atrio-ventricular:ab,ti) AND (nodal:ab,ti OR node:ab,ti)) OR "catheter ablation":ab,ti OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti) AND (heart rate:ab,ti,kw OR rate:ab,ti)) OR metoprolol:ab,ti,kw OR atenolol:ab,ti,kw OR carvedilol:ab,ti,kw OR bisoprolol:ab,ti,kw OR timolol:ab,ti,kw OR esmolol:ab,ti,kw OR nebivolol:ab,ti,kw OR verapamil:ab,ti,kw OR diltiazem:ab,ti,kw OR digoxin:ab,ti,kw OR OR beta-blocker:ab,ti OR beta-blockers:ab,ti OR Acebutolol:ab,ti,kw OR Nadolol:ab,ti,kw
#3	MeSH descriptor Catheter Ablation explode all trees OR MeSH descriptor Cardiac Resynchronization Therapy explode all trees OR MeSH descriptor Electric Countershock explode all trees OR MeSH descriptor Anti-Arrhythmia Agents explode all trees OR non-pharmacological:ab,ti OR nonpharmacological:ab,ti OR ablation:ab,ti OR "surgical maze":ab,ti OR (surgical:ab,ti AND maze:ab,ti) OR resynchroni*:ab,ti OR (ganglionic:ab,ti AND ablation:ab,ti) OR (ganglionated:ab,ti AND ablation:ab,ti) OR denervation:ab,ti OR "pulmonary vein isolation":ab,ti OR (pulmonary:ab,ti AND isolation:ab,ti) OR electrical:ab,ti OR cardioversion:ab,ti OR ((antiarrhythmic:ab,ti OR antiarrhythmia:ab,ti) AND (agent:ab,ti OR agents:ab,ti OR drug:ab,ti OR drugs:ab,ti)) AND rhythm:ab,ti) OR flecainide:ab,ti,kw OR propafenone:ab,ti,kw OR amiodarone:ab,ti,kw OR sotalol:ab,ti,kw OR ibutilide:ab,ti,kw OR dofetilide:ab,ti,kw OR dronedarone:ab,ti,kw OR Disopyramide:ab,ti,kw
#4	#1 AND #2 AND #3
#5	#4, Limits: Cochrane Reviews, 2000-2012

Eliminated KQ*—What are the comparative diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy of echocardiographic studies and other clinical parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with atrial fibrillation?

*Note: This KQ was eliminated from the CER for scoping reasons following discussions with AHRQ and the TEP members. Since the KQ was removed after the original Cochrane searches were performed on December 9, 2011, we have included documentation of the search strategy below. This portion of the search was not included in the final search update on August 1, 2012. The results from this search are reflected in the totals depicted in the literature flow diagram.

Set #	Terms
#1	MeSH descriptor Atrial Fibrillation explode all trees OR MeSH descriptor Atrial Flutter explode all trees OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	MeSH descriptor Prognosis explode all trees OR MeSH descriptor Sensitivity and Specificity explode all trees OR MeSH descriptor Treatment Outcome explode all trees OR MeSH descriptor Diagnosis explode all trees OR predictors:ab,ti OR predict:ab,ti OR predicting:ab,ti OR predicts:ab,ti OR predicted:ab,ti OR prognosis:ab,ti OR prognostic:ab,ti OR accurately:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR reliability:ab,ti OR sensitivity:ab,ti OR specificity:ab,ti OR diagnostic:ab,ti
#3	maintain:ab,ti OR maintenance:ab,ti OR maintained:ab,ti OR success:ab,ti OR successful:ab,ti OR conversion:ab,ti OR restoration:ab,ti OR restored:ab,ti

#4	#1 AND #2 and #3
#5	#4, Limits: Cochrane Reviews, 2000-2011

Grey Literature Searches

ClinicalTrials.gov (Final Search Date August 17, 2012)

Condition	atrial fibrillation OR afib OR atrial flutter
Intervention	Drug OR device OR procedure

Total number of results: 610

WHO: International Clinical Trials Registry Platform Search Portal (Final Search Date August 17, 2012)

Terms: atrial fibrillation OR afib OR atrial flutter

Total number of results: 858

ProQuest COS Conference Papers Index (Final Search Date August 1, 2012)

S1	All (atrial fibrillation OR afib OR atrial flutter)
S2	nonpharmacological OR non-pharmacological OR pacemaker OR (cardiac AND (pace OR pacing) AND artificial) OR AVN OR ((atrioventricular OR atrio-ventricular) AND (nodal OR node)) OR "catheter ablation" OR ((antiarrhythmic OR antiarrhythmia) AND (agent OR agents OR drug OR drugs)) OR metoprolol OR atenolol OR carvedilol OR bisoprolol OR timolol OR esmolol OR nebivolol OR verapamil OR diltiazem OR digoxin OR "Adrenergic beta-Antagonists" OR beta-blocker OR beta-blockers OR "Calcium Channel Blockers" OR Acebutolol OR Nadolol OR "Catheter Ablation" OR "Cardiac Resynchronization Therapy" OR non-pharmacological OR nonpharmacological OR ablation OR (surgical AND maze) OR resynchroni* OR (ganglionic AND ablation) OR (ganglionated AND ablation) OR denervation OR (pulmonary AND isolation) OR "electric countershock" OR electrical OR cardioversion OR flecainide OR propafenone OR propafenone OR amiodarone OR sotalol OR ibutilide OR dofetilide OR dronedarone OR Disopyramide OR (rate AND control AND (strict OR lenient OR strategy))
S3	S1 AND S2

Total number of results: 1747

Appendix B. Data Abstraction Elements

Study Characteristics

- Study Identifiers
    - Study Name or Acronym
    - Last name of first author
    - Publication Year
- Additional Articles Used in This Abstraction
- Study Objectives
- Study Dates
    - Enrollment Start (Mon and YYYY)
    - Enrollment End (Mon and YYYY)
    - Follow-up End (Mon and YYYY)
- Study Sites
    - Single Center, Multicenter, Unclear/Not reported, Other (specify)
    - Number of sites
- Geographic Location (Select all that apply)
    - US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ, Unclear/Not reported, Other (specify)
- Study Design
    - Prospective RCT
    - Prospective cohort
    - Retrospective cohort
    - Case-control
    - Cross-sectional
    - Other (specify)
- Funding Source (Select all that apply)
    - Government, Industry, Non-govt/Non-industry, Unclear/Not reported, Other (specify)
- Setting (Select all that apply)
    - In-patient, Out-patient, Emergency Room, Unclear/Not reported, Other (specify)
- Enrollment Approach (Select all that apply)
    - Consecutive patients, Convenience sample, Unclear/Not reported, Other (specify)
- Study Inclusion and Exclusion Criteria
    - Copy/paste inclusion and exclusion criteria as reported
    - Is the study entirely composed of patients with any of the following characteristics/ conditions?
        - Paroxysmal AF
        - Persistent AF
        - Permanent AF
        - Heart failure
        - Coronary artery disease
        - Kidney disease
        - Hypertrophic cardiomyopathy
        - Thyroid disease

        - Pulmonary disease
        - Previously failed a rate- or rhythm-control pharmacological therapy strategy
        - Enlarged left atrium
        - High risk for stroke and bleeding events (e.g., patients with diabetes, heart failure, and hypertension)
        - Women
        - None of the above
- Study Enrollment/Study Completion
    - N Assessed for eligibility
    - N eligible
    - N enrolled/included
    - N completed follow-up (most distal timepoint of the primary outcome)
    - N analyzed
- Key Question Applicability (select all that apply)
    - KQ1, KQ2, KQ3, KQ4, KQ5, KQ6
- Comments

Baseline Characteristics. Record the following elements for Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Number of Patients, Age, Ethnicity, and Race
    - Number of Patients
        - Total
        - Female
        - Male
    - Percentage
        - Female
        - Male
    - Age
        - Mean
        - Standard Deviation
        - Standard Error
        - Median
        - IQR
        - Min
        - Max
        - NR
    - Ethnicity
        - Hispanic or Latino
        - Not Hispanic or Latino
        - NR
    - Race
        - Black/African American
        - American Indian or Alaska Native
        - Asian
        - Native Hawaiian or other Pacific Islander

        - White
        - Multiracial
        - Other (specify)
        - NR
- Co-morbidities and Previous Treatment Failures
    - Diabetes
        - N
        - %
    - Heart failure, All types (define)
        - N
        - %
    - Heart failure, Systolic (define)
        - N
        - %
    - Heart failure, Diastolic (define)
        - N
        - %
    - Hypertension
        - N
        - %
    - Kidney disease (define)
        - N
        - %
    - Hypertrophic cardiomyopathy (define)
        - N
        - %
    - Thyroid disease (define)
        - N
        - %
    - Pulmonary disease (define)
        - N
        - %
    - Coronary artery disease
        - N
        - %
    - Enlarged left atrium (define)
        - N
        - %
    - LVEF, Mean or median
        - Mean
        - Median
        - SD
        - SE
        - IQR
    - LVEF, Number of patients (<35% or other [define])
        - N

        - %
    - Previously failed rate-control pharmacological therapy (define)
        - N
        - %
    - Previously failed rhythm-control pharmacological therapy (define)
        - N
        - %
    - Duration of AF (include units)
        - mean
        - Median
        - SD
        - SE
        - IQR
    - Permanent AF
        - N
        - %
    - Paroxysmal AF
        - N
        - %
    - Persistent AF
        - N
        - %
- Comments

Intervention Characteristics. Record the following elements for Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Intervention Characteristics
    - Intervention Components (check all that apply)
        - Placebo or control
        - Pharmacological agents for rate control
        - Procedures for rate control
        - Pharmacological agents for rhythm control
        - Procedures for rhythm control
    - Placebo/Control Details
        - Placebo
        - Usual care control/optimal medical therapy
        - Other (specify)
    - Rate-control Pharmacological Agent Details
        - Beta-blockers
            - Acebutolol
            - Atenolol
            - Bisoprolol
            - Carvedilol
            - Esmolol
            - Metoprolol
            - Nadalol

                - Nebivolol
                - Timolol
                - Specific medication not reported
            - Calcium channel blockers
                - Diltiazem
                - Verapamil
                - Specific medication not reported
                - Other
                    - Amiodarone
                    - Digoxin
                    - Dronedarone
                    - Specific medication not reported
    - Rate-control Procedure Details
        - AVN ablation and permanent pacemaker implantation
    - Rate-control Target
        - Strict (define)
        - Lenient (define)
        - Other (define)
        - NA
    - Rhythm-control Pharmacological Agent Details
        - Amiodarone
        - Beta-blockers
            - Acebutolol
            - Atenolol
            - Carvedilol
            - Esmolol
            - Metoprolol
            - Nadalol
            - Nebivolol
            - Timolol
            - Specific medication not reported
        - Calcium channel blockers
            - Diltiazem
            - Verapamil
            - Specific medication not reported
        - Disopyramide
        - Dofetilide
        - Dronedarone
        - Flecainide
        - Ibutilide
        - Propafenone
        - Sotalol
    - Rhythm-control Procedure Details
        - Electrical cardioversion
        - Pulmonary vein ablation – open surgical

        - Pulmonary vein ablation – minimally invasive
        - Pulmonary vein ablation – transcatheter
        - Surgical Maze
        - Cardiac resynchronization
- Intervention Descriptors
    - Describe the intervention received by patients in Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)
- Duration of Follow-up - Record the following elements for Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)
    - Mean follow-up
    - Mean Variability (SD, SE, IQR)
    - Median follow-up
    - Median Variability (SD, SE, IQR)
- Comments

Outcomes

- Select the outcome reported on this form
    - Restoration of sinus rhythm (conversion)
    - Maintenance of sinus rhythm
    - Recurrence of AF (specify time period)
    - Development of cardiomyopathy
    - All-cause mortality
    - Cardiac mortality
    - Myocardial infarction
    - CV hospitalizations
    - AF Hospitalizations
    - Heart failure symptoms
    - Control of AF symptoms (e.g., palpitations, exercise capacity)
    - Quality of life/ Functional status
    - Stroke
    - Other embolic events, excluding stroke (specify)
    - Mixed embolic events including stroke
    - Bleeding events (including hemorrhagic stroke)
    - Control of ventricular rate
    - Composite outcome
- Define/specify the following for the outcome, if applicable
    - Quality of life or functional status measure/scale
    - Stroke
    - Other embolic event
    - Control of ventricular rate
    - Components of composite outcomes
- Record additional details to describe outcome measure, as needed
- Timepoints to be abstracted (check all that apply)
    - Close to 1 month
    - Close to 3 months
    - Close to 6 months

    - Close to 1 yr
    - Most distal timepoint after one year
    - Untimed measure (e.g. time to event)
- For each timepoint, record the following elements as applicable
    - Group – Arm 1, Arm 2, Arm 3, Arm 4
    - N Analyzed (enter UNK if unknown)
    - Unadjusted Result
        - Mean
        - Median
        - Mean within group change
        - Mean between group change
        - Number of patients with outcome
        - % of patients with outcome
        - Events/denominator
        - Odds ratio (OR)
        - Hazard ratio (HR)
        - Relative risk (RR)
        - Other (specify)
    - Unadjusted Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - IQR
        - 95% CI
        - Other % CI (specify)
        - Other (specify)
    - Unadjusted p-value between groups
    - Unadjusted Reference group (for comparison between groups)
    - Adjusted Result
        - Mean
        - Median
        - Mean within group change
        - Mean between group change
        - Number of patients with outcome
        - % of patients with outcome
        - Events/denominator
        - Odds ratio
        - Hazard ratio
        - Relative risk
        - Other (specify)
    - Adjusted Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - IQR
        - 95% CI
        - Other % CI (specify)
        - Other (specify)

    - Adjusted p-value between groups
    - Adjusted Reference group (for comparison between groups)
    - Indicate the adjustments applied
- Subgroup analyses reported for this outcome?
    - Yes/No
        - If Yes, describe the subgroup analyses and summarize results
- Comments

Adverse Events

- Are adverse events reported? (Yes/No)
- Record the Number of patients, % of patients, and exact p-value the Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable) for the following:
    - Hypotension
    - Hypothyroidism
    - Hyperthyroidism
    - Bradyarrhythmias
    - Tachyarrhythmias
    - Proarrhythmias
    - Allergic Reactions
    - Hepatotoxicity
    - Neurotoxicity
    - Pulmonary Toxicity
    - Ophthalmologic Toxicity
    - Dermatologic Toxicity
    - Pulmonary Vein Stenosis
    - Left Atrial Esophageal Fistula
    - Phrenic Nerve Palsy
    - Other Adverse Drug Reaction (specify)
    - Other Procedural Complication (specify)
- Subgroup analyses reported for adverse events?
    - Yes/No
        - If yes, describe the subgroup analyses and summarize results
- Comments

Quality Assessment

- Study Type
    - RCT
    - Cohort
    - Case-Control
    - Cross-sectional
- If RCT:
    - Selection Bias
        - Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)? (Yes/No/Unclear)

        - Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)? (Yes/No/Unclear)
        - Were participants analyzed within the groups they were originally assigned to? (Yes/No/Unclear)
        - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (Yes/No/Unclear)
    - Performance Bias
        - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (Yes/No/Unclear)
        - Did the study maintain fidelity to the intervention protocol? (Yes/No/Unclear)
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)? (Yes/No/Unclear)
    - Detection Bias
        - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls? (Yes/No/Unclear)
        - Were the outcome assessors blinded to the intervention or exposure status of participants? (Yes/No/Unclear)
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (Yes/No/Unclear)
- If Cohort:
    - Selection Bias
        - Were participants analyzed within the groups they were originally assigned to? (Yes/No/Unclear)
        - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/No/Unclear)
        - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Unclear)
        - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (Yes/No/Unclear)
    - Performance Bias

        - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (Yes/No/Unclear)
        - Did the study maintain fidelity to the intervention protocol? (Yes/No/Unclear)
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)? (Yes/No/Unclear)
    - Detection Bias
        - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls? (Yes/No/Unclear)
        - Were the outcome assessors blinded to the intervention or exposure status of participants? (Yes/No/Unclear)
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (Yes/No/Unclear)
- If Case-Control:
    - Selection Bias
        - Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status) (Yes/No/Unclear)
        - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (Yes/No/Unclear)
    - Performance Bias
        - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (Yes/No/Unclear)
        - Did the study maintain fidelity to the intervention protocol? (Yes/No/Unclear)
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)? (Yes/No/Unclear)
    - Detection Bias

        - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls? (Yes/No/Unclear)
        - Were the outcome assessors blinded to the intervention or exposure status of participants? (Yes/No/Unclear)
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (Yes/No/Unclear)
- If Cross-sectional:
    - Selection Bias
        - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/No/Unclear)
        - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (Yes/No/Unclear)
    - Performance Bias
        - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (Yes/No/Unclear)
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)? (Yes/No/Unclear)
    - Detection Bias
        - Were the outcome assessors blinded to the intervention or exposure status of participants? (Yes/No/Unclear)
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
        - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (Yes/No/Unclear)
- Other Bias
    - If applicable, describe any other concerns that may impact risk of bias.

- Overall Study Rating (Good/Fair/Poor)
    - **Good** (low risk of bias). These studies have the least bias, and the results are considered valid. These studies adhere to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
    - **Fair**. These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
    - **Poor** (high risk of bias). These studies have significant flaws that may have invalidated the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.
    - If the study is rated as "Fair" or "Poor," provide rationale.

Applicability. Use the PICOS format to identify specific issues, if any, that may limit the applicability of the study to this review.

- Population (P)
    - Narrow eligibility criteria and exclusion of those with comorbidities
    - Large differences between demographics of study population and community patients
    - Narrow or unrepresentative severity, stage of illness, or comorbidities
    - Run-in period with high exclusion rate for nonadherence or side effects
    - Event rates much higher or lower than observed in population-based studies
- Intervention (I)
    - Doses or schedules not reflected in current practice
    - Monitoring practices or visit frequency not used in typical practice
    - Older versions of an intervention no longer in common use
    - Cointerventions that are likely to modify effectiveness of therapy
    - Highly selected intervention team or level of training/proficiency not widely available
- Comparator (C)
    - Inadequate comparison therapy
    - Use of substandard alternative therapy
- Outcomes (O)
    - Composite outcomes that mix outcomes of different significance
    - Short-term or surrogate outcomes
- Setting (S)
    - Standard of care differ markedly from setting of interest
    - Specialty population nor level of care differs from that seen in community
- Comments

Appendix C. List of Included Studies

Abreu Filho CA, Lisboa LA, Dallan LA, et al. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. Circulation. 2005;112(9 Suppl):I20-5. PMID: 16159816.

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Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Not Available in English

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No Outcomes of Interest

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Not an RCT for KQs 1, 3, 4, 5, or 6 (Observational Studies Also Allowed for KQ 5 if Addressing CRT)

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Appendix E. Key to Included Primary and Companion Articles

Appendix Table E-1. Included primary and companion articles

Study Designation	Primary Abstracted Article	Companion Articles*
5A Study (Antiarrhythmics After Ablation of Atrial Fibrillation)	Roux, 2009[1]	Leong-Sit, 2011[2]
A4 Study (Catheter ablation versus antiarrhythmic drugs for atrial fibrillation)	Jais, 2008[3]	None
AF-CHF (Atrial Fibrillation and Congestive Heart Failure)	Talajic, 2010[4]	Roy, 2008[5]
AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management)	Anonymous, 2003[6]	None
	Wyse, 2002[7]	Guglin, 2010[8] Jenkins, 2005[9] Sherman, 2005[10] Steinberg, 2004[11] Bush, 2006[12] Chung, 2005[13] Curtis, 2005[14] Anonymous, 2002[15]*
AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) RACE (RAte Control vs. Electrical cardioversion)	Van Gelder, 2006[16]	Wyse, 2002[7] Van Gelder, 2002[17]
AIRCRAFT (Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial)	Weerasooriya, 2003[18]	Lim, 2007[19]
APAF (Ablation for Paroxysmal Atrial Fibrillation)	Pappone, 2006[20]	Pappone, 2011[21]
BEST AF (Biphasic energy selection for transthoracic cardioversion of atrial fibrillation)	Glover, 2008[22]	None
CACAF (Catheter Ablation For The Cure Of Atrial Fibrillation Study)	Stabile, 2006[23]	None
CAFE-II (chronic atrial fibrillation and heart failure)	Shelton, 2009[24]	None

Study Designation	Primary Abstracted Article	Companion Articles*
CTAF (Canadian Trial of Atrial Fibrillation)	Roy, 2000[25]	Dorian, 2002[26] Dorian, 2003[27] Lumer, 2002[28]
CRRAFT (Control of Rate versus Rhythm in rheumatic Atrial Fibrillation Trial)	Vora, 2004[29]	Vora, 2004 [30]
DIONYSOS (Randomized, Double-Blind TrIal to Evaluate the Efficacy and Safety of DrOnedarone [400 mg bid] Versus AmiodaroNe [600 mg qd for 28 daYS, then 200 mg qd Thereafter] for at Least 6 mOnths for the Maintenance of Sinus Rhythm in Patients with AF)	Le Heuzey, 2010[31]	None
FAST (Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment)	Boersma, 2011[32]	None
HOT CAFÉ (How to Treat Chronic Atrial Fibrillation)	Opolski, 2004[33]	Opolski, 2003[34] Pietrasik, 2007[35] Szulc, 2006[36]
MOBIPAPA	Kirchhof, 2005[37]	None
PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure)	Khan, 2008[38]	None
PAF 2 (paroxysmal atrial Fibrillation)	Brignole, 2002[39]	None
PAVE (Post AV Nodal Ablation Evaluation)	Doshi, 2005[40]	None
PIAF (Pharmacological Intervention in Atrial Fibrillation)	Hohnloser, 2000[41]	Gronefeld, 2003[42]
QOLAF (Quality of Life and Atrial Fibrillation)	Tsuneda, 2006[43]	None

Study Designation	Primary Abstracted Article	Companion Articles*
RACE (RAte Control vs.Electrical cardioversion)	Groenveld, 2009[44]	Van Gelder, 2002[17]
	Van Gelder, 2002[17]	Hagens, 2004[45] Hagens, 2006[46] Rienstra, 2007[47] Rienstra, 2005[48] Hagens, 2005[49]
RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II)	Van Gelder, 2010[50]	Groenveld, 2011[51] Smit, 2011[52] Van Gelder, 2006[53]*
RASTA (Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation)	Dixit, 2012[54]	None
SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial)	Singh, 2005[55]	Atwood, 2007[56] Batcher, 2007[57] Singh, 2009[58] Singh, 2003[59]*
SAFIR (Surgery for atrial fibrillation)	Chevalier, 2009[60]	None
STAF (Strategies of Treatment of Atrial Fibrillation)	Carlsson, 2003[61]	Carlsson, 2003[62]
STAR AF (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation)	Verma, 2010[63]	None
SWEDMAF (SWEDish Multicentre Atrial Fibrillation study)	Blomstrom-Lundqvist, 2007[64]	None
ThermoCool AF (ThermoCool Atrial Fibrillation)	Wilber, 2010[65]	Reynolds, 2010[66]
VEPARAF (VErapamil Plus Antiarrhythmic drugs Reduce Atrial Fibrillation recurrences after an electrical Cardioversion)	De Simone, 2003[67]	None
VERDICT (The Verapamil versus Digoxin Cardioversion Trial)	Van Noord, 2001[68]	None
VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial)	Hemels, 2006[69]	None
None	Abreu Filho, 2005[70]	None

Study Designation	Primary Abstracted Article	Companion Articles*
None	Akpinar, 2003[71]	None
None	Alatawi, 2005[72]	None
None	Albrecht, 2009[73]	None
None	Alp, 2000[74]	None
None	Ambler, 2006[75]	None
None	Arentz, 2007[76]	None
None	Balla, 2011[77]	None
None	Bellandi, 2001[78]	None
None	Bertaglia, 2002[79]	None
None	Bittner, 2011[80]	None
None	Boodhoo, 2007[81]	None
None	Boos, 2003[82]	None
None	Brazdzionyte, 2006[83]	None
None	Bulava, 2010[84]	None
None	Calo, 2006[85]	None
None	Capucci, 2000[86]	None
None	Chen, 2011[87]	None
None	Corrado, 2010[88]	None
None	de Lima, 2004[89]	None
None	De Simone, 2002[90]	None
None	Deisenhofer, 2009[91]	None
None	Delle Karth, 2001[92]	None
None	Demircan, 2005[93]	None
None	Deneke, 2002[94]	Khargi, 2001[95]
None	Di Biase, 2009[96]	None
None	Dixit, 2006[97]	None
None	Dixit, 2008[98]	None
None	Doukas, 2005[99]	None
None	Elayi, 2008[100]	None
None	Fassini, 2005[101]	None
None	Fiala, 2008[102]	None
None	Forleo, 2009[103]	None

Study Designation	Primary Abstracted Article	Companion Articles*
None	Fragakis, 2009[104]	None
None	Gaita, 2008[105]	None
None	Gavin, 2011[106]	None
None	Hassan, 2007[107]	None
None	Haissaguerre, 2004[108]	None
None	Hocini, 2005[109]	None
None	Hofmann, 2006[110]	None
None	Holming, 2001[111]	None
None	Jessurun, 2003[112]	None
None	Joglar, 2000[113]	None
None	Joseph, 2000[114]	None
None	Kafkas, 2007[115]	None
None	Kanoupakis, 2004[116]	None
None	Katritsis, 2004[117]	None
None	Katritsis, 2003[118]	None
None	Kawabata, 2007[119]	None
None	Khand, 2003[120]	None
None	Khaykin, 2003[121]	None
None	Khaykin, 2009[122]	None
None	Kim, 2010[123]	None
None	Kirchhof, 2002[124]	None
None	Kirkutis, 2004[125]	None
None	Kochiadakis, 2004[126]	None
None	Kochiadakis, 2004[127]	None
None	Kochiadakis, 2000[128]	None
None	Kochiadakis, 2001[129]	None
None	Kochiadakis, 2000[130]	None
None	Korantzopoulos, 2006[131]	None
None	Krittayaphong, 2003[132]	None
None	Lee, 2000[133]	None
None	Levy, 2001[134]	None
None	Lindholm, 2004[135]	None

Study Designation	Primary Abstracted Article	Companion Articles*
None	Liu, 2010[136]	None
None	Liu, 2006[137]	None
None	MacDonald, 2011[138]	None
None	Manios, 2003[139]	None
None	Marinsek, 2003[140]	None
None	Mazzocca, 2006[141]	None
None	Mortensen, 2008[142]	None
None	Mun, 2012[143]	None
None	Nergardh, 2007[144]	None
None	Nilsson, 2006[145]	None
None	Okcun, 2004[146]	None
None	Oral, 2004[147]	None
None	Oral, 2005[148]	None
None	Oral, 2006[149]	None
None	Oral, 2008[150]	None
None	Oral, 2009[151]	None
None	Page, 2002[152]	None
None	Petrac, 2005[153]	None
None	Pires, 2010[154]	None
None	Plewan, 2001[155]	None
None	Pontoppidan, 2009[156]	None
None	Rashba, 2002[157]	None
None	Rashba, 2004[158]	None
None	Redfearn, 2006[159]	None
None	Ricard, 2001[160]	None
None	Sawhney, 2010[161]	None
None	Scholten, 2003[162]	None
None	Schuetz, 2003[163]	None
None	Sheikh, 2006[164]	None
None	Siaplaouras, 2005[165]	None
None	Siaplaouras, 2004[166]	None
None	Simpson, 2001[167]	None

Study Designation	Primary Abstracted Article	Companion Articles*
None	Siu, 2009[168]	None
None	Srivastava, 2008[169]	None
None	Tamborero, 2009[170]	None
None	Thomas, 2004[171]	None
None	Turco, 2007[172]	None
None	Van Breugel, 2010[173]	None
None	Vijayalakshmi, 2006[174]	None
None	Villani, 2000[175]	None
None	von Oppell, 2009[176]	None
None	Wang, 2008[177]	None
None	Wang, 2009[178]	None
None	Wattanasuwan, 2001[179]	None
None	Wazni, 2003[180]	None
None	Wazni, 2005[181]	None
None	Willems, 2006[182]	None
None	Yildiz, 2008[183]	None
None	Knaut, 2010[184]	None
None	Karch, 2005[185]	None

*The three companion articles marked with an asterisk did not individually meet criteria for inclusion but were considered for supplemental information (e.g., methods data pertinent to an included study).

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Appendix F. Study Characteristics Tables

The tables in this appendix summarize basic study characteristics for each Key Question (KQ). A comprehensive list of references is provided at the end of the appendix.

Appendix Table F-1. Study characteristics—KQ 1

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Capucci, 2000[1]	RCT; Inpatient; Europe; Fair	Total N: 61 Arm 1: Amiodarone (31) Arm 2: Diltiazem (30)	Arm 1: 59 (SD 15) Arm 2: 58 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 16.3 wk (SD 6) Arm 2: 18 wk (SD 5)	Persistent AF	NR	Arm 1: 49 (SD 8) Arm 2: 50 (SD 5)	Arm 1: 4N Arm 2: 5N	Restoration of sinus rhythm, Recurrence of AF, Control of ventricular rate
Holming, 2001[2]	RCT; Outpatient; Europe; Fair	Total N: 31 Arm 1: Sotalol (NR) Arm 2: Digoxin (NR) Arm 3: Sotalol + Digoxin (NR)	Total: 68	NR	NR	None	NR	NR	NR	Control of ventricular rate, Quality of life/functional status
Delle Karth, 2001[3]	RCT; Inpatient; Europe; Good	Total N: 60 Arm 1: Diltiazem, 24 hours (20) Arm 2: Amiodarone, 15 minutes (20) Arm 3: Amiodarone, 24 hours (20)	Total: 67 (SD 10) Arm 1: 64.8 (SD 10) Arm 2: 67.8 (SD 9) Arm 3: 71.2 (SD 9)	NR	NR	None	Total: 22% Arm 1: 25% Arm 2: 20% Arm 3: 20%	NR	Total: 6.6% Arm 1: 10% Arm 2: 10% Arm 3: 0	Control of ventricular rate

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Kochiadakis, 2001[4]	RCT; Outpatient; Europe; Good	Total N: 23 Arm 1: Placebo (NR) Arm 2: Metoprolol (NR) Arm 3: Sotalol (NR)	Total: 63 (SD 8)	NR	NR	None	Total: 0%	NR	Total: 0%	Control of ventricular rate, Control of AF symptoms
Simpson, 2001[5]	RCT; ER; Canada; Fair	Total N: 40 Arm 1: Clonidine (12) Arm 2: Digoxin (15) Arm 3: Verapamil (13)	Arm 1: 69 (SD 19) Arm 2: 61 (SD 14) Arm 3: 61 (SD 12)	Total: 0, 20%, 0 Arm 1: 0, 16.7%, 0 Arm 2: 0, 20%, 0 Arm 3: 0, 23.07%, 0	NR	None	NR	NR	NR	Control of ventricular rate, Restoration of sinus rhythm
Wattanasu-wan, 2001[6]	RCT; Inpatient, ER; US; Fair	Total N: 52 Arm 1: Diltiazem + digoxin (26) Arm 2: Digoxin (26)	Arm 1: 61 (SD 21) Arm 2: 64 (SD 18)	Total: 0, 83%, 0 Arm 1: 0, 81%, 0 Arm 2: 0, 85%, 0	NR	None	Total: 25% Arm 1: 23% Arm 2: 27%	Arm 1: 54 (SD 14) Arm 2: 47 (SD 16)	Total: 10% Arm 1: 8% Arm 2: 11%	Control of ventricular rate
Khand, 2003[7]	RCT; Outpatient; UK; Good	Total N: 47 Arm 1: Carvedilol (24) Arm 2: Digoxin (23)	Arm 1: 68.6 (SD 9.4) Arm 2: 68.4 (SD 9.8)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 152.8 wk (SD 204) Arm 2: 109.2 wk (SD 123.4)	Persistent AF	NR	Arm 1: 23.7 (SD 10.4) Arm 2: 24.7 (SD 9.5)	NR	Control of AF symptoms, Heart failure symptoms

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Lindholm, 2004[8]	RCT; Outpatient; Europe; Fair	Total N: 100 Arm 1: Digoxin (50) Arm 2: Verapamil (50)	Arm 1: 72 (SD 7) Arm 2: 66 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: 8.4 mo Arm 1: 7.5 mo (SD 6) Arm 2: 10.7 mo (SD 8.5)	Persistent AF	NR	Patients with LVEF > 55% Arm 1: 42 Arm 2: 44	NR	Control of ventricular rate, Maintenance of sinus rhythm, Restoration of sinus rhythm
Thomas, 2004[9]	RCT; ER; Australia/NZ; Fair	Total N: 140 Arm 1: Amiodarone (52) Arm 2: Sotalol (45) Arm 3: Digoxin (43)	Arm 1: 54.3 (SD 15.9) Arm 2: 57.7 (SD 15.9) Arm 3: 55.5 (SD 16.5)	NR	NR	None	NR	NR	Total: 15% Arm 1: 7% Arm 2: 4% Arm 3: 4%	Restoration of sinus rhythm, Control of ventricular rate
Demircan, 2005[10]	RCT; ER; Europe; Good	Total N: 40 Arm 1: Diltiazem (20) Arm 2: Metoprolol (20)	Total: 62.1 (SD 12.9) Arm 1: 60.2 Arm 2: 64	NR	NR	None	NR	NR	NR	Control of ventricular rate
Hemels, 2006[11] (VERDICT)	RCT; NR; Europe; Fair	Total N: 144 Arm 1: Electrical cardioversion (early or routine), Digoxin (70) Arm 2: Electrical cardioversion (early or routine), Verapamil (74)	Arm 1: 65 (SD 11) Arm 2: 65 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 140 days Arm 2: 117 days	Persistent AF	Arm 1: 7% Arm 2: 5%	NR	Arm 1: 19% Arm 2: 12%	Restoration of sinus rhythm, Control of ventricular rate, Recurrence of AF, Maintenance of sinus rhythm, Quality of life/ Functional status

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Hofmann, 2006[12]	RCT; Inpatient; Europe; Good	Total N: 100 Arm 1: Amiodarone (50) Arm 2: Digoxin (50)	Arm 1: 68.3 (SD 13) Arm 2: 69.3 (SD 13)	Total: 0, 11%, 12% Arm 1: 0, 12%, 10% Arm 2: 0, 10%, 14%	NR	None	Total: 12% Arm 1: 16% Arm 2: 8%	Arm 1: 55.2 (SD 19) Arm 2: 54.3 (SD 14)	NR	Control of ventricular rate, Restoration of sinus rhythm
Tsuneda, 2006[13] (QOLAF)	RCT; Outpatient; Asia; Fair	Total N: 29 (12 patients received the other monotherapy in crossover fashion) Arm 1: Beta blockers (19) Arm 2: Verapamil (22)	Total: 67 (SD 8) Arm 1: 68.6 (SD 8.4) Arm 2: 65.5 (SD 7.7)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 91.8 mo (SD 34.5) Arm 2: 103.5 mo (SD 116.5)	Permanent AF	Arm 1: 10.53 % Arm 2: 13.64 %	NR	NR	Quality of life/functional status
Siu, 2009[14]	RCT; ER; Asia; Good	Total N: 150 Arm 1: Diltiazem (50) Arm 2: Digoxin (50) Arm 3: Amiodarone (50)	Total: 71.5 (SD 11.8) Arm 1: 70.6 (SD 12.4) Arm 2: 71 (SD 13.1) Arm 3: 73 (SD 9.7)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0 Arm 3: 0, 100%, 0	NR	Paroxysmal AF	NR	Arm 1: 63.8 (SD 12.2) Arm 2: 66 (SD 11) Arm 3: 63.2 (SD 11.9)	NR	Control of AF symptoms, Control of ventricular rate, Restoration of sinus rhythm, AF hospitalizations

Abbreviations: AF=atrial fibrillation; CAD=coronary artery disease; CV=cardiovascular; ER=emergency room; HF=heart failure; KQ=Key Question; LVEF=left ventricular ejection fraction; mo=month(s); N=number of participants; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; wk=week(s); yr=year(s)

Appendix Table F-2. Study characteristics—KQ 2

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Van Gelder, 2006[15] (AFFIRM, RACE)	Retrospective cohort; Outpatient; NR; Fair	Total N: 1091 [a] Arm 1: Strict (874) Arm 2: Lenient (217)	Arm 1: 69.3 (SD 9.1) Arm 2: 68.1 (SD 9.2)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	Arm 1: 8% Arm 2: 52%	NR	Arm 1: 37% Arm 2: 28%	Composite outcome (all-cause mortality, MI, CV hospitalizations);CV hospitalizations; MI; all-cause mortality
Groenveld, 2009[16] (RACE)	Retrospective cohort; Outpatient; Europe; Good	Total N: 214 Arm 1: Strict (75) Arm 2: Lenient (139)	Arm 1: 70 (SD 8) Arm 2: 68 (SD 10)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 662 days (IQR, 66 to 14,909) Arm 2: 408 days (IQR, 14 to 4219)	Permanent AF	Arm 1: 45% Arm 2: 50%	NR	Arm 1: 27% Arm 2: 27%	Composite outcome (cardiac mortality; heart failure symptoms; mixed embolic events, including stroke; bleeding events, including hemorrhagic stroke; bradyarrythmia; other adverse drug reaction); cardiac mortality; heart failure symptoms; mixed embolic events, including stroke; bleeding events; quality of life
Van Gelder, 2010[17] (RACE II) Groenveld 2011[18] (RACE II substudy) Smit, 2011[19]	RCT; Outpatient; Europe; Good	Total N: 614 Arm 1: Strict (303) Arm 2: Lenient (311)	Total: 68 (SD 8) Arm 1: 67 (SD 9) Arm 2: 69 (SD 8)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: Median 16 mo (IQR, 6 to 54) Arm 2: Median 20 mo (IQR, 6 to 64)	Permanent AF	Total: 34.9% Arm 1: 36% Arm 2: 33.8%	Total: 52 (SD 12) Arm 1: 52 (SD 12) Arm 2: 52 (SD 11)	Total: 18.1% Arm 1: 14.5% Arm 2: 21.5%	Composite outcome (cardiac mortality; CV hospitalizations; stroke; other embolic events, excluding stroke; bleeding events, including hemorrhagic stroke; bradyarrythmia; proarrhythmias; other adverse drug reactions); cardiac mortality; heart failure symptoms; stroke; other embolic events, including stroke; bleeding events; all-cause mortality; control of AF symptoms; quality of life

[a]Includes patients from Groenveld, 2009.[16]

Abbreviations: AF=atrial fibrillation; AFFIRM=Atrial Fibrillation Follow-Up Investigation of Rhythm Management; CAD=coronary artery disease; CV=cardiovascular; IQR=interquartile range; KQ=Key Question; LVEF=left ventricular ejection fraction; MI=myocardial infarction; mo=month(s); N=number of patients; NR=not reported; RACE(-II)=Rate Control Efficacy in Permanent Atrial Fibrillation(-II); RCT=randomized controlled trial; SD=standard deviation

Appendix Table F-3. Study characteristics—KQ 3

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Levy, 2001[20]	RCT; Outpatient; UK; Good	Total N: 36 Arm 1: VVIR pacing + rate-control medications (18) Arm 2: VVIR pacing + His-bundle ablation (18)	Total: 69 (SD 7) Arm 1: 69 (SD 7) Arm 2: 68 (SD 8)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 3.5 yr (SD 3.8) Arm 2: 3.8 yr (SD 4.0)	Permanent AF	NR	Arm 1: 67 (SD 9) Arm 2: 61 (SD 9)	NR	Control of ventricular heart rate (24-hour Holter monitor), Exercise duration by treadmill testing, Quality of life/functional status
Weera-sooriya, 2003[21] (AIRCRAFT= Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial) Lim, 2007[22]	RCT; NR; Australia/ NZ; Fair	Total N: 99 Arm 1: Rate-control medications (50) Arm 2: AVN ablation + VVIR pacemaker (49)	Total: 68 (SD 8.7) Arm 1: 67.9 (SD 9) Arm 2: 68 (SD 8.5)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Total: 68 mo (SD 104) Arm 1: 78 mo (SD 131) Arm 2: 58 mo (SD 66)	Permanent AF	NR	NR	Total: 40% Arm 1: 38% Arm 2: 43%	All-cause mortality, Myocardial infarction, Control of AF symptoms, Control of ventricular rate, Quality of life/functional status, Exercise duration (by treadmill test)
Kirkutis, 2004[23]	RCT; NR; NR; Poor	Total N: 76 Arm 1: Amiodarone (38) Arm 2: AVN ablation + His bundle pacemaker (38)	Total: 62 Min age: 45 Max age: 82	100% "resistant chronic AF"	NR	None	NR	NR	NR	Control of ventricular rate

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Doshi, 2005[24]	RCT; NR; US, Canada; Fair	Total N: 184 Arm 1: RV pacing (81) Arm 2: BiV pacing (103)	Arm 1: 67 (SD 10) Arm 2: 70 (SD 10)	Total: 100%, 0, 0	NR	Permanent AF	NR	Arm 1: 45 (SD 15) Arm 2: 47 (SD 16)	Arm 1: 30% Arm 2: 38%	All-cause mortality Quality of life/ Functional status
Petrac, 2005[25]	RCT; Outpatient; Europe; Good	Total N: 102 Arm 1: AVN ablation + VVIR pacemaker (52) Arm 2: AVN ablation + DDDR pacemaker + antiarrhythmic medication (50)	Arm 1: 62 (SD 10) Arm 2: 60 (SD 11)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	Arm 1: 23.1% Arm 2: 12%	NR	Arm 1: 23.1% Arm 2: 16%	Cardiac mortality, Stroke, All-cause mortality, CV hospitalizations, Recurrence of AF, Heart failure symptoms, Myocardial ischemia, Composite outcome (cardiac mortality, stroke)
Lee, 2000[26]	RCT; NR; Asia; Fair	Total N: 40 Arm 1: AF ablation by PVI (transcatheter, anterior) (18) Arm 2: AF ablation by PVI (transcatheter, posterior) (22)	Arm 1: 67 (SD 8) Arm 2: 66 (SD 11)	Arm 1: 50%, 50%, 0 Arm 2: 55%, 45%, 0	Arm 1: 4.9 yr (SD 1.6) Arm 2: 5.2 yr (SD 1.8)	None	NR	Arm 1: 48 (SD 7) Arm 2: 46 (SD 9)	Arm 1: 6% Arm 2: 14%	Restoration of sinus rhythm, Control of ventricular rate

Abbreviations: AF=atrial fibrillation; CAD=coronary artery disease; CV=cardiovascular; HF=heart failure; IQR=interquartiles range; KQ=Key Question; LVEF=left ventricular ejection fraction; mo=month(s); N=number of participants; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; wk=week(s); yr=year(s)

Appendix Table F-4. Study characteristics—KQ 4

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Alp, 2000[27]	RCT; NR; UK; Fair	Total N: 59 Arm 1: AL/AP (30) Arm 2: AP/AL (29)	Arm 1: 67.8 (SD 8.1) Arm 2: 66.8 (SD 7.9)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 23 wk Arm 2: 31 wk	Persistent AF	NR	Arm 1: 52 (SD 17) Arm 2: 50 (SD 12)	Arm 1: 6N Arm 2: 3N	Restoration of sinus rhythm (conversion)
Capucci, 2000[1]	RCT; Inpatient; Europe; Fair	Total N: 61 Arm 1: Amiodarone (31) Arm 2: Digoxin (30)	Arm 1: 59 (SD 15) Arm 2: 58 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 16.3 wk (SD 6) Arm 2: 18 wk (SD 5)	Persistent AF	NR	Arm 1: 49 (SD 8) Arm 2: 50 (SD 5)	Arm 1: 4N Arm 2: 5N	Restoration of sinus rhythm (conversion), Recurrence of AF, Control of ventricular rate
Joglar, 2000[28]	RCT; Outpatient; US; Good	Total N: 64 Arm 1: DCC 100 (NR) Arm 2: DCC 200 (NR) Arm 3: DCC 360 (NR)	Total: 62 (SD 11)	Total: 0, 0, 100%	NR	Persistent AF	Total: 14N	NR	NR	Restoration of sinus rhythm (conversion)
Joseph, 2000[29]	RCT; ER; Australia/NZ; Fair	Total N: 115 Arm 1: Digoxin (36) Arm 2: Amiodarone (39) Arm 3: Sotalol (40)	Arm 1: 64.9 (SE 2) Arm 2: 61.3 (SE 2.6) Arm 3: 62.8 (SE 2.4)	NR	NR	None	NR	NR	Arm 1: 3N Arm 2: 8N Arm 3: 7N	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Villani, 2000[30]	RCT; Outpatient; Europe; Fair	Total N: 120 Arm 1: Diltiazem (46) Arm 2: Amiodarone (44) Arm 3: Digoxin (30)	Arm 1: 59 (SD 3) Arm 2: 58 (SD 7) Arm 3: 56 (SD 5)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100%	Arm 1: 18.0 wk (SD 5) Arm 2: 16.3 wk (SD 6) Arm 3: 16 wk (SD 3)	Persistent AF	NR	Arm 1: 50 (SD 5) Arm 2: 49 (SD 8) Arm 3: 52 (SD 5)	Arm 1: 5N Arm 2: 4N Arm 3: 2N	Restoration of sinus rhythm (conversion), Recurrence of AF
Ricard, 2001[31]	RCT; NR; Europe; Fair	Total N: 57 Arm 1: Monophasic (30) Arm 2: Biphasic (27)	Arm 1: 69 (SD 10) Arm 2: 66 (SD 12)	Arm 1: 0, 2N, 0 Arm 2: 0, 2N, 0	NR	None	NR	Arm 1: 58 (SD 10) Arm 2: 56 (SD 11)	Arm 1: 6N Arm 2: 2N	Restoration of sinus rhythm (conversion)
Van Noord, 2001[32] (VERDICT)	RCT; NR; Europe; Poor	Total N: 97 Arm 1: Verapamil (48) Arm 2: Digoxin (49)	Arm 1: 66 (SD 13) Arm 2: 66 (SD 11)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: Median 18 days Arm 2: Median 21 days	Persistent AF	NR	NR	Arm 1: 12N Arm 2: 8N	Restoration of sinus rhythm (conversion), Recurrence of AF
De Simone, 2002[33]	RCT; Inpatient; Europe; Poor	Total N: 88 Arm 1: Verapamil + DCC (43) Arm 2: DCC (45)	Arm 1: 60 (SD 11) Arm 2: 60 (SD 12)	NR	Arm 1: 94 days (SD 79) Arm 2: 87 days (SD 65)	None	NR	Arm 1: 50 (SD 8.1) Arm 2: 50 (SD 7)	Arm 1: 6N Arm 2: 7N	Recurrence of AF
Kirchhof, 2002[34]	RCT; Outpatient; Europe; Good	Total N: 108 Arm 1: AP (52) Arm 2: AL (56)	Arm 1: 62 (SD 2) Arm 2: 58 (SD 2)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: Median 5 mo (IQR, 0.1 to 120) Arm 2: Median 4 mo (IQR, 0.1 to 120	Persistent AF	Arm 1: 7N Arm 2: 13N	NR	Arm 1: 13N Arm 2: 14N	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Page, 2002[35]	RCT; NR; US, Europe; Good	Total N: 203 Arm 1: Monophasic (107) Arm 2: Biphasic (96)	Arm 1: 65 (SD 13) Arm 2: 65 (SD 14)	NR	NR	None	Arm 1: 31% Arm 2: 31%	NR	Arm 1: 19% Arm 2: 24%	Restoration of sinus rhythm (conversion)
Rashba, 2002[36]	RCT; NR; US; Fair	Total N: 110 Arm 1: Standard (55) Arm 2: Reverse (55)	NR	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	NR	NR	NR	Restoration of sinus rhythm (conversion)
Boos, 2003[37]	RCT; NR; UK; Fair	Total N: 107 Arm 1: Initial 360 DCC (50) Arm 2: Initial 200 DCC (57)	Arm 1: 64.4 (SD 10.5) Arm 2: 67.7 (SD 9.6)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	NR	NR	Arm 1: 24% Arm 2: 25%	Restoration of sinus rhythm (conversion)
Khaykin, 2003[38]	RCT; Inpatient; Canada; Good	Total N: 56 Arm 1: Monophasic (28) Arm 2: Biphasic (28)	Arm 1: 59.7 (SD 10.8) Arm 2: 58.3 (SD 14.6)	NR	Arm 1: 26 wk (SD 19) Arm 2: 24 wk (SD 18)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	NR	NR	Restoration of sinus rhythm (conversion)
Manios, 2003[39]	RCT; NR; Europe; Fair	Total N: 106 Arm 1: Diltiazem (35) Arm 2: Amiodarone (34) Arm 3: Placebo (37)	Arm 1: 64 (SD 8) Arm 2: 66 (SD 7) Arm 3: 62 (SD 11)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100%	Arm 1: 37 mo (SD 35) Arm 2: 35 mo (SD 29) Arm 3: 32 mo (SD 34)	Persistent AF	NR	Arm 1: 61 (SD 8.6) Arm 2: 59 (SD 6.3) Arm 3: 62 (SD 6.6)	Arm 1: 4N Arm 2: 4N Arm 3: 2N	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Marinsek, 2003[40]	RCT; Outpatient; Europe; Fair	Total N: 83 Arm 1: Monophasic (40) Arm 2: Biphasic (43)	Arm 1: 67 (SD 8) Arm 2: 69 (SD 6)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	NR	Arm 1: 57 (SD 11) Arm 2: 56 (SD 11)	Arm 1: 8% Arm 2: 14%	Maintenance of sinus rhythm
Scholten, 2003[41]	RCT; NR; Europe; Fair	Total N: 227 Arm 1: Monophasic (109) Arm 2: Biphasic (118)	Arm 1: 59.9 (SD 14) Arm 2: 59.6 (SD 12.4)	NR	Arm 1: Median 41 days Arm 2: Median 20.5 days	None	Arm 1: 12N Arm 2: 11N	NR	Arm 1: 6N Arm 2: 5N	Restoration of sinus rhythm (conversion)
Kanoupakis, 2004[42]	RCT; Outpatient; Europe; Fair	Total N: 142 Arm 1: Carvedilol (48) Arm 2: Amiodarone (48) Arm 3: Control (46)	Arm 1: 66 (SD 9) Arm 2: 64 (SD 8) Arm 3: 61 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100%	Arm 1: 10 mo (SD 8) Arm 2: 10 mo (SD 12) Arm 3: 13 mo (SD 17)	Persistent AF	NR	Arm 1: 60 (SD 7.3) Arm 2: 58 (SD 5.6) Arm 3: 57 (SD 9)	Arm 1: 6N Arm 2: 5N Arm 3: 4N	Restoration of sinus rhythm (conversion), Recurrence of AF
Lindholm, 2004[8]	RCT; Outpatient; Europe; Fair	Total N: 100 Arm 1: Digoxin (50) Arm 2: Verapamil (50)	Arm 1: 72 (SD 7) Arm 2: 66 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: 8.4 mo Arm 1: 7.5 mo (SD 6) Arm 2: 10.7 mo (SD 8.5)	Persistent AF	NR	NR	NR	Control of ventricular rate, Maintenance of sinus rhythm, Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Rashba, 2004[43]	RCT; NR; US; Fair	Total N: 120 Arm 1: 20 DCC (30) Arm 2: 50 DCC (30) Arm 3: 100 DCC (30) Arm 4: 200 DCC (30)	Arm 1: 65 (SD 12) Arm 2: 69 (SD 13) Arm 3: 65 (SD 12) Arm 4: 63 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100% Arm 4: 0, 0, 100%	Arm 1: 71 days (SD 80) Arm 2: 86 days (SD 100) Arm 3: 136 days (SD 177) Arm 4: 176 days (SD 371)	Persistent AF	NR	Arm 1: 50 (SD 16) Arm 2: 41 (SD 16) Arm 3: 50 (SD 13) Arm 4: 50 (SD 15)	Arm 1: 33% Arm 2: 30% Arm 3: 33% Arm 4: 27%	Restoration of sinus rhythm (conversion)
Siaplaouras, 2004[44]	RCT; NR; Europe; Fair	Total N: 216 Arm 1: Biphasic (NR) Arm 2: Monophasic (NR)	Arm 1: 65 (SD 10) Arm 2: 66 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 3.2 mo (SD 4) Arm 2: 4.1 mo (SD 10)	Persistent AF	NR	Arm 1: 62 (SD 15) Arm 2: 59 (SD 13)	Arm 1: 17% Arm 2: 20%	Recurrence of AF, Restoration of sinus rhythm (conversion)
Thomas, 2004[9]	RCT; ER; Australia/NZ; Fair	Total N: 140 Arm 1: Amiodarone (52) Arm 2: Sotalol (45) Arm 3: Digoxin (43)	Arm 1: 54.3 (SD 15.9) Arm 2: 57.7 (SD 15.9) Arm 3: 55.5 (SD 16.5)	NR	NR	None	NR	NR	Total: 15% Arm 1: 7% Arm 2: 4% Arm 3: 4%	Restoration of sinus rhythm (conversion), Control of ventricular rate
Alatawi, 2005[45]	RCT; Inpatient; US; Fair	Total N: 141 Arm 1: Truncated (70) Arm 2: Rectilinear (71)	Arm 1: 65.3 (SD 14.5) Arm 2: 67.6 (SD 12.9)	NR	NR	None	NR	Arm 1: 53.9 (SD 12.7) Arm 2: 54 (SD 13)	Arm 1: 20% Arm 2: 32%	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Kirchhof, 2005[46]	RCT; Outpatient; Europe; Good	Total N: 201 Arm 1: Steel (104) Arm 2: Adhesive (97)	Arm 1: 63 (SD 1) Arm 2: 63 (SD 1)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 8.1 mo (SD 2) Arm 2: 4.5 mo (SD 0.2)	Persistent AF	NR	NR	Arm 1: 36N Arm 2: 25N	Restoration of sinus rhythm (conversion)
Korantzo-poulos, 2005[47]	RCT; Inpatient; Europe; Good	Total N: 100 Arm 1: Ibutilide (51) Arm 2: Propafenone + ibutilide (49)	Total: 65 (SD 10) Arm 1: 66 (SD 9) Arm 2: 65 (SD 11)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: 99 days (SD 92) Arm 1: 98 days (SD 83) Arm 2: 99 days (SD 100)	Persistent AF	NR	Arm 1: 58 (SD 6) Arm 2: 59 (SD 10)	Arm 1: 19% Arm 2: 16%	Restoration of sinus rhythm (conversion)
Siaplaouras, 2005[48]	RCT; NR; Europe; Fair	Total N: 123 Arm 1: AP (60) Arm 2: AL (63)	Arm 1: 67 (SD 10) Arm 2: 66 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 3.0 mo (SD 5) Arm 2: 3.8 mo (SD 9)	Persistent AF	NR	Arm 1: 60 (SD 13) Arm 2: 59 (SD 13)	Arm 1: 10N Arm 2: 16N	Restoration of sinus rhythm (conversion), Recurrence of AF
Singh, 2005[49] (SAFE-T) Atwood, 2007[50] Batcher, 2007[51] Singh, 2009[52]	RCT; Outpatient; US; Good	Total N: 665 Arm 1: Amiodarone (267) Arm 2: Sotalol (261) Arm 3: Placebo (137)	Arm 1: 67.1 (SD 9.4) Arm 2: 66.8 (SD 8.9) Arm 3: 67.7 (SD 9.8)	NR	NR	None	Arm 1: 67N Arm 2: 72N Arm 3: 33N	Arm 1: 50.5 (SD 12.4) Arm 2: 51.5 (SD 11.9) Arm 3: 49.4 (SD 12.7)	Arm 1: 71N Arm 2: 66N Arm 3: 31N	Restoration of sinus rhythm (conversion) Stroke All-cause mortality Recurrence of AF
Ambler, 2006[53]	RCT; NR; UK; Fair	Total N: 128 Arm 1: Monophasic (NR) Arm 2: Biphasic (NR)	Total: Median 70 Min Age: 22 Max Age: 87	NR	NR	None	NR	NR	NR	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Brazdzionyte, 2006[54]	RCT; NR; Europe; Fair	Total N: 103 Arm 1: AL (55) Arm 2: AP (48)	Arm 1: 63.84 (SD 11.67) Arm 2: 62.31 (SD 10.37)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	NR	Arm 1: 48.6 (SD 9.45) Arm 2: 48.8 (SD 6.08)	Arm 1: 47.3% Arm 2: 33.3%	Restoration of sinus rhythm (conversion)
Hemels, 2006[11] (VERDICT)	RCT; NR; Europe; Fair	Total N: 144 Arm 1: Digoxin (70) Arm 2: Verapamil (74)	Arm 1: 65 (SD 11) Arm 2: 65 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 140 days Arm 2: 117 days	Persistent AF	Arm 1: 7% Arm 2: 5%	NR	Arm 1: 19% Arm 2: 12%	Control of ventricular rate, Restoration of sinus rhythm (conversion) Recurrence of AF, Maintenance of sinus rhythm, Quality of life/ Functional status
Hofmann, 2006[12]	RCT; Inpatient; Europe; Good	Total N: 100 Arm 1: Amiodarone (50) Arm 2: Digoxin (50)	Arm 1: 68.3 (SD 13) Arm 2: 69.3 (SD 13)	Total: 0, 11%, 12% Arm 1: 0, 12%, 10% Arm 2: 0, 10%, 14%	NR	None	Total: 12% Arm 1: 16% Arm 2: 8%	Arm 1: 55.2 (SD 19) Arm 2: 54.3 (SD 14)	NR	Control of ventricular rate, Restoration of sinus rhythm (conversion)
Mazzocca, 2006[55]	RCT; NR; Europe; Fair	Total N: 50 Arm 1: DCC (25) Arm 2: Ibutilide + DCC (25)	Arm 1: 64 (SD 14) Arm 2: 69 (SD 9)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 86 days (SD 79) Arm 2: 84 days (SD 73)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Persistent AF	NR	Arm 1: 53 (SD 9) Arm 2: 53 (SD 10)	NR	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Redfearn, 2006[56]	RCT; NR; UK; Fair	Total N: 23 Arm 1: Verapamil+DCC (9) Arm 2: DCC (14)	Arm 1: 63.9 (SD 13.7) Arm 2: 69.9 (SD 8.1)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 9.13 mo (SD 3.94) Arm 2: 11.2 mo (SD 12.9)	Persistent AF	NR	NR	NR	Maintenance of sinus rhythm
Vijayalakshmi, 2006[57]	RCT; NR; UK; Good	Total N: 94 Arm 1: Control (31) Arm 2: Amiodarone (27) Arm 3: Sotalol (36)	Arm 1: 64.8 (SD 9.1) Arm 2: 65.5 (SD 10.5) Arm 3: 62.8 (SD 9.3)	NR	Arm 1: 7 mo (SD 4) Arm 2: 6.6 mo (SD 3.9) Arm 3: 7.3 mo (SD 4.4)	None	Arm 1: 1N Arm 2: 1N Arm 3: 1N	Arm 1: 40 Arm 2: 51 Arm 3: 40	NR	All-cause mortality, Maintenance of sinus rhythm, Restoration of sinus rhythm (conversion)
Boodhoo, 2007[58]	RCT; NR; UK; Fair	Total N: 261 Arm 1: Initial 200J (125) Arm 2: 360 DCC (136)	Arm 1: 70 (SD 10) Arm 2: 72 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	Arm 1: 6% Arm 2: 1%	Arm 1: 65 Arm 2: 65	Arm 1: 11% Arm 2: 9%	Restoration of sinus rhythm (conversion), Maintenance of sinus rhythm, All-cause mortality, Mixed embolic events including stroke
Hassan, 2007[59]	RCT; ER; US; Fair	Total N: 50 Arm 1: Diltiazem (24) Arm 2: Esmolol (26)	Arm 1: 62 (SD 15) Arm 2: 65 (SD 15)	Arm 1: 0, 8N, 0 Arm 2: 0, 11N, 0	NR	None	NR	Arm 1: 54.5 (SD 14) Arm 2: 50.5 (SD 14)	Arm 1: 4N Arm 2: 2N	Restoration of sinus rhythm (conversion), Control of ventricular rate
Kafkas, 2007[60]	RCT; Inpatient; Europe; Fair	Total N: 152 Arm 1: Ibutilide (79) Arm 2: Amiodarone (73)	Arm 1: 62 (SD 16) Arm 2: 64 (SD 18)	NR	NR	None	NR	Arm 1: 53 (SD 6) Arm 2: 52 (SD 8)	Arm 1: 36N Arm 2 : 38N	Restoration of sinus rhythm (conversion), Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Kawabata, 2007[61]	RCT; ER; S. America; Good	Total N: 154 Arm 1: Biphasic (77) Arm 2: Monophasic (77)	Arm 1: 55 (SD 13.5) Arm 2: 60 (SD 13.3)	NR	NR	None	NR	NR	Arm 1: 3N Arm 2: 10N	Restoration of sinus rhythm (conversion)
Nergardh, 2007[62]	RCT; Outpatient; Europe; Good	Total N: 168 Arm 1: Metoprolol + DCC (83) Arm 2: Placebo + DCC (85)	Arm 1: 68.2 (SD 10.1) Arm 2: 66.5 (SD 12.2)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 5.3 mo (SD 2.9) Arm 2: 5.1 mo (SD 2.8)	Persistent AF	NR	Arm 1: 48.6 (SD 7.9) Arm 2: 49.7 (SD 6.7)	Arm 1: 4N Arm 2: 3N	Control of ventricular rate, Maintenance of sinus rhythm, Restoration of sinus rhythm (conversion), All-cause mortality, Stroke
Glover, 2008[63] (BEST AF)	RCT; Outpatient; UK; Good	Total N: 380 Arm 1: Electrical cardioversion (low energy) (193) Arm 2: Electrical cardioversion (high energy) (187)	Total: 67 (SD 10) Arm 1: 66.8 (SD 9.7) Arm 2: 67.1 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: Median 6.0 mo (IQR, 3 to 11) Arm 1: Median 6.0 mo (IQR, 4.0 to 12.0) Arm 2: Median 6.0 mo (IQR, 3.0 to 9.0)	Persistent AF	NR	Arm 1: 52 (SD 27) Arm 2: 49 (SD 29)	Arm 1: 34% Arm 2: 27%	Restoration of sinus rhythm
Mortensen, 2008[64]	RCT; Inpatient, Outpatient, ER; Europe; Fair	Total N: 95 Arm 1: Biphasic (48) Arm 2: Monophasic (47)	Total: 62 (SD 13) Arm 1: 62 (SD 12) Arm 2: 62 (SD 13)	NR	NR	None	NR	NR	Total: 23.1% Arm 1: 27% Arm 2: 19.1%	Restoration of sinus rhythm (conversion)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Fragakis, 2009[65]	RCT; Outpatient, ER; Europe; Fair	Total N: 90 Arm 1: Esmolol + ibutilide (44) Arm 2: Ibutilide (46)	Total: 63 (SD 13.5) Arm 1: 63 (SD 11.5) Arm 2: 63 (SD 15)	Arm 1: 0, 80%, 0 Arm 2: 0, 75%, 0	Arm 1: 16 days (SD 42) Arm 2: 19 days (SD 30)	None	NR	Arm 1: 63 (SD 6) Arm 2: 61 (SD 7)	Arm 1: 11% Arm 2: 9%	Restoration of sinus rhythm (conversion)
Balla, 2011[66]	RCT; ER; Europe; Good	Total N: 160 Arm 1: Flecainide (40) Arm 2: Amiodarone (40) Arm 3: Propafenone (40) Arm 4: Placebo (40)	Arm 1: 57.9 (SD 9.5) Arm 2: 58.9 (SD 10.4) Arm 3: 57.4 (SD 9.8) Arm 4: 58.6 (SD 10.7)	NR	Arm 1: 16.2 hr (SD 9.1) Arm 2: 19.1 hr (SD 12.4) Arm 3: 18.6 hr (SD 4.2) Arm 4: 17.8 hr (SD 13.9)	None	NR	NR	NR	Restoration of sinus rhythm (conversion)

Abbreviations: Abbreviations: AF=atrial fibrillation; CAD=coronary artery disease; CV=cardiovascular; IQR=interquartile range; KQ=Key Question; LVEF=left ventricular ejection fraction; MI=myocardial infarction; mo=month(s); N=number of patients; NR=not reported; RCT=randomized controlled trial; SD=standard deviation

Appendix Table F-5. Study characteristics—KQ 5

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Capucci, 2000[1]	RCT; Inpatient; Europe; Fair	Total N: 61 Arm 1: Amiodarone (31) Arm 2: Diltiazem (30)	Arm 1: 59 (SD 15) Arm 2: 58 (SD 10)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 16.3 wk (SD 6) Arm 2: 18 wk (SD 5)	Persistent AF	NR	Arm 1: 49 (SD 8) Arm 2: 50 (SD 5)	Arm 1: 4N Arm 2: 5N	Restoration of sinus rhythm (conversion), Recurrence of AF, Control of ventricular rate
Kochiadakis, 2000[67]	RCT; Outpatient, ER; Europe; Fair	Total N: 186 Arm 1: Amiodarone (65) Arm 2: Sotalol (61) Arm 3: Placebo (60)	Arm 1: 63.2 (SD 9) Arm 2: 62.8 (SD 8) Arm 3: 62.8 (SD 9.6)	Arm 1: 0, 65%, 35% Arm 2: 0, 64%, 36% Arm 3: 0, 67%, 33%	Arm 1: 9 mo (SD 6) Arm 2: 10 mo (SD 8) Arm 3: 8 mo (SD 7)	None	NR	Arm 1: 54 (SD 12) Arm 2: 52 (SD 13) Arm 3: 55 (SD 12)	NR	Composite outcome (Recurrence of AF, Other adverse drug reaction) Composite outcome (Maintenance of sinus rhythm free of side effects); Death due to arrhythmia;
Kochiadakis, 2000[68]	RCT; ER; Europe; Fair	Total N: 214 Arm 1: Amiodarone (75) Arm 2: Sotalol (75) Arm 3: Propafenone (64)	Total: 64 (SD 8) Arm 1: 63 (SD 9) Arm 2: 64 (SD 8) Arm 3: 65 (SD 7)	Arm 1: 0, 60%, 40% Arm 2: 0, 59%, 41% Arm 3: 0, 70%, 30%	Arm 1: 10 mo (SD 5) Arm 2: 9 mo (SD 7) Arm 3: 9 mo (SD 8)	None	NR	Arm 1: 53 (SD 11) Arm 2: 54 (SD 13) Arm 3: 53 (SD 12)	NR	Recurrence of AF, Composite outcome (Recurrence of AF, Other adverse drug reaction); Composite outcome (Maintenance of sinus rhythm, free from adverse drug reaction)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Roy, 2000[69] (Canadian Trial of Atrial Fibrillation) Dorian, 2003[70] Dorian, 2002[71] Lumer, 2002[72]	RCT; NR; Canada; Good	Total N: 403 Arm 1: Amiodarone (201) Arm 2: Sotalol or propafenone (202)	Arm 1: 65 (SD 11) Arm 2: 65 (SD 11)	Arm 1: 0, 49%, 51% Arm 2: 0, 43%, 57%	NR	None	NR	NR	Arm 1: 19% Arm 2: 18%	All-cause mortality, Death due to arrhythmia, Stroke, AF hospital-izations, Control of AF symptoms, Recurrence of AF, Quality of Life
Bellandi, 2001[73]	RCT; NR; Europe; Fair	Total N: 300 Arm 1: Propafenone (102) Arm 2: Sotalol (106) Arm 3: Placebo (92)	Total: 52 (SD 18) Arm 1: 50 (SD 17) Arm 2: 53 (SD 18) Arm 3: 54 (SD 18)	NR	Arm 1: 27 hrs (SD 9) Arm 2: 28 hrs (SD 11) Arm 3: 29 hrs (SD 11)	None	NR	Arm 1: 55 (SD 4) Arm 2: 56 (SD 3) Arm 3: 55 (SD 3)	Arm 1: 20N Arm 2: 21N Arm 3: 18N	Maintenance of sinus rhythm Recurrence of AF
Plewan, 2001[74]	RCT; NR; Europe; Fair	Total N: 128 Arm 1: Bisoprolol (64) Arm 2: Sotalol (64)	Total: 59 (SD 12) Arm 1: 59 (SD 6) Arm 2: 59 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: 8.7 mo (SD 17.5) Arm 1: 7.4 mo (SD 8.3) Arm 2: 10.0 mo (SD 23.1)	Persistent AF	NR	Total: 41 (SD 5) Arm 1: 41 (SD 7) Arm 2: 42 (SD 5)	Total: 45N Arm 1: 23N Arm 2: 22N	Maintenance of sinus rhythm Recurrence of AF
Bertaglia, 2002[75]	RCT; Inpatient, Outpatient; Europe; Poor	Total N: 90 Arm 1: Electrical cardioversion + AAD (45) Arm 2: AAD (45)	Arm 1: 68 (SD 7.6) Arm 2: 69 (SD 9.5)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 31.6 mo (SD 34.4) Arm 2: 39.9 mo (SD 36.7)	Persistent AF	NR	Arm 1: 56.8 (SD 9) Arm 2: 56.1 (SD 9.1)	Arm 1: 9% Arm 2: 18%	Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
De Simone, 2002[33]	RCT; Inpatient; Europe; Poor	Total N: 88 Arm 1: Verapamil (43) Arm 2: Control (45)	Arm 1: 60 (SD 11) Arm 2: 60 (SD 12)	NR	Arm 1: 94 days (SD 79) Arm 2: 87 days (SD 65)	None	NR	Arm 1: 50 (SD 8.1) Arm 2: 50 (SD 7)	Arm 1: 6N Arm 2: 7N	Recurrence of AF
Deneke, 2002[76] Khargi, 2001[77]	RCT; NR; Europe; Good	Total N: 30 Arm 1: Concomitant surgical Maze procedure (15) Arm 2: MV surgery alone (15)	Total: 68 Arm 1: 64.7 Arm 2: 69.7	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 3.6 yr Arm 2: 3.7 yr	Permanent AF	NR	Arm 1: 64 (SD 11) Arm 2: 61 (SD 9)	NR	Restoration of sinus rhythm (conversion) Maintenance of sinus rhythm Heart failure symptoms Control of AF symptoms All-cause mortality
Akpinar, 2003[78]	RCT; Inpatient; Europe; Fair	Total N: 67 Arm 1: AF ablation by PVI + surgical Maze procedure (33) Arm 2: MV surgery alone (34)	Arm 1: 53 (SD 10) Arm 2: 50 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 19.87 mo (SD 10.59) Arm 2: 21.97 mo (SD 13.9)	Persistent AF	NR	Arm 1: 55.19 (SD 6.34) Arm 2: 55.03 (SD 8.12)	NR	Maintenance of sinus rhythm All-cause mortality Mixed embolic events including stroke Quality of life/ Functional status
Anonymous, 2003[79] (AFFIRM)	RCT; NR; NR; Fair	Total N: 256 Arm 1: Amiodarone (131) Arm 2: Sotalol (125)	Arm 1: 67.9 (SD 8.5) Arm 2: 70.4 (SD 8.9)	NR	NR	None	Arm 1: 15.3% Arm 2: 25.6%	NR	Arm 1: 27.5% Arm 2: 20%	Recurrence of AF All-cause mortality Cardiac mortality Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
De Simone, 2003[80] (VEPARAF)	RCT; Inpatient; Europe; Fair	Total N: 324 Arm 1: Amiodarone (82) Arm 2: Flecainide (80) Arm 3: Amiodarone + verapamil (81) Arm 4: Flecainide + verapamil (81)	Arm 1: 62 (SD 10.5) Arm 2: 61.2 (SD 10.7) Arm 3: 63.4 (SD 11.9) Arm 4: 62.5 (SD 11.4)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100% Arm 4: 0, 0, 100%	Arm 1: 65.7 days (SD 47.7) Arm 2: 67.8 days (SD 54.6) Arm 3: 63.9 days (SD 48.6) Arm 4: 73.3 days (SD 75.6)	Persistnet AF	NR	Arm 1: 49.1 (SD 6.4) Arm 2: 50.8 (SD 7.2) Arm 3: 50.7 (SD 6.7) Arm 4: 51.3 (SD 7.6)	Arm 1: 11% Arm 2: 14% Arm 3: 10% Arm 4: 6%	Recurrence of AF Maintenance of sinus rhythm
Jessurun, 2003[81]	RCT; Inpatient; UK; Fair	Total N: 35 Arm 1: Concomitant surgical Maze procedure (25) Arm 2: MV surgery alone (10)	Arm 1: 64 (SD 12) Arm 2: 64 (SD 9)	Arm 1: 12N, 13N, 0 Arm 2: 8N, 2N, 0	NR	None	NR	NR	NR	Control of AF symptoms Quality of life/ Functional status Maintenance of sinus rhythm
Katritsis, 2003[82]	RCT; Outpatient; Europe, US; Good	Total N: 90 Arm 1: Bisoprolol (47) Arm 2: Carvedilol (43)	Arm 1: 66 (SD 9) Arm 2: 65 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	NR	NR	Arm 1: 19% Arm 2: 19%	Recurrence of AF
Krittaya-phong, 2003[83]	RCT; Inpatient, Outpatient; Asia; Fair	Total N: 30 Arm 1: Amiodarone (15) Arm 2: AF ablation by PVI (transcatheter), Amiodarone (15)	Arm 1: 48.6 (SD 15.4) Arm 2: 53.3 (SD 10.5)	Arm 1: 0, 60%, 40% Arm 2: 0, 73.3%, 26.7%	Arm 1: 48.2 mo (SD 63.7) Arm 2: 62.9 mo (SD 58.3)	None	NR	Arm 1: 61.8 (SD 8.8) Arm 2: 63.7 (SD 9.5)	Arm 1: 6.7% Arm 2: 6.7%	Recurrence of AF Control of AF symptoms Quality of life/ Functional status

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Schuetz, 2003[84]	RCT; NR; Europe; Fair	Total N: 43 Arm 1: Concomitant AF ablation (open surgical) (24) Arm 2: MV surgery or CABG alone (19)	Total: 67 (SD 9.4) Arm 1: 64.57 (SD 10.03) Arm 2: 70.21 (SD 7.9)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Total: 6.2 yr (SD 6.9) Arm 1: 3.8 yr (SD 2.84) Arm 2: 9.21 yr (SD 9.24)	Permanent AF	NR	Arm 1: 62.8 (SD 13.2) Arm 2: 54.37 (SD 17.08)	NR	Recurrence of AF
Wazni, 2003[85]	RCT; NR; NR; Fair	Total N: 108 Arm 1: CTI ablation after successful PV-LAJ disconnection (49) Arm 2: PV-LAJ disconnection only without CTI ablation (59)	Arm 1: 54 (SD 11) Arm 2: 55 (SD 11)	Arm 1: 13N, 30N, 6N Arm 2: 20N, 34N, 5N	Arm 1: 6 yr (SD 4) Arm 2: 5 yr (SD 3)	None	NR	Arm 1: 52 (SD 4) Arm 2: 53 (SD 4)	NR	Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
de Lima, 2004[86]	RCT; NR; S. America; Fair	Total N: 30 Arm 1: Comcomitant AF ablation (10) Arm 2: Concomitant surgical Maze procedure (10) Arm 3: MV surgery alone (10)	Total: 51.4 (SD 13.3) Arm 1: 54.1 (SD 9.4) Arm 2: 50.1 (SD 15.3) Arm 3: 50.1 (SD 15.4)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0 Arm 3: 100%, 0, 0	Total: Median 18 mo (IQR, 11.8 to 42.8) Arm 1: Median 23 mo (IQR, 15 to 24) Arm 2: Median 14 mo (IQR, 9 to 63) Arm 3: Median 16.5 mo (IQR, 13 to 24)	Permanent AF	NR	Total: 64 (SD 10) Arm 1: 64 (SD 12) Arm 2: 64.3 (SD 7.5) Arm 3: 64 (SD 9.5)	NR	Recurrence of AF All-cause mortality Stroke
Haïssaguerre, 2004[87]	RCT; NR; Europe; Poor	Total N: 70 Arm 1: AF ablation by PVI (transcatheter, CTI) (35) Arm 2: AF ablation by PVI (transcatheter, CTI + mitral isthmus) (35)	Arm 1: 53 (SD 8) Arm 2: 53 (SD 9)	NR	Total: 61 mo (SD 51)	None	NR	Arm 1: 65 (SD 11) Arm 2: 68 (SD 13)	NR	Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Katritsis, 2004[88]	RCT; Outpatient; Europe; Fair	Total N: 52 Arm 1: AF ablation by PVI (transcatheter, single vein) (27) Arm 2: AF ablation by PVI (transcatheter, all veins) (25)	Arm 1: 54 (SD 9) Arm 2: 50 (SD 10)	Arm 1: 0, 100 %, 0 Arm 2: 0, 100%, 0	NR	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Paroxysmal AF	NR	NR	Arm 1: 3N Arm 2: 4N	Maintenance of sinus rhythm Control of AF symptoms
Kochiadakis, 2004[89]	RCT; Outpatient, ER; Europe; Fair	Total N: 254 Arm 1: Sotalol (85) Arm 2: Propafenone (86) Arm 3: Placebo (83)	Arm 1: 63 (SD 7) Arm 2: 63 (SD 10) Arm 3: 62 (SD 10)	Arm 1: 0, 50N, 35N Arm 2: 0, 52N, 34N Arm 3: 0, 49N, 34N	Arm 1: 8 mo (SD 6) Arm 2: 9 mo (SD 7) Arm 3: 8 mo (SD 7)	None	NR	Arm 1: 52 (SD 12) Arm 2: 54 (SD 14) Arm 3: 53 (SD 11)	NR	Composite outcome (Recurrence of AF, Other adverse drug reaction); Composite outcome (Maintenance of sinus rhythm with no adverse effects from medication)
Kochiadakis, 2004[90]	RCT; Outpatient, ER; Europe; Fair	Total N: 146 Arm 1: Amiodarone (72) Arm 2: Propafenone (74)	Arm 1: 62 (SD 9) Arm 2: 64 (SD 8)	Arm 1: 0, 43N, 29N Arm 2: 0, 49N, 25N	Arm 1: 7 mo (SD 6) Arm 2: 9 mo (SD 8)	None	NR	Arm 1: 52 (SD 12) Arm 2: 54 (SD 14)	NR	Composite outcome (Recurrence of AF, Other adverse drug reaction); Recurrence of afib, Composite outcome (Maintenance of sinus rhythm, free from adverse drug reaction)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Oral, 2004[91]	RCT; Inpatient; US; Fair	Total N: 60 Arm 1: No further ablation following initial LACA (30) Arm 2: Use of electrogram guided additional LA ablation lines until AF terminated and became noninducible (30)	Arm 1: 55 (SD 11) Arm 2: 56 (SD 9)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 7 yr (SD 5) Arm 2: 6 yr (SD 4)	Previously failed a rate-or rhythm-control pharmaco-logical therapy strategy, Paroxysmal AF	NR	Arm1: 59 (SD 4) Arm 2: 58 (SD 7)	NR	Maintenance of sinus rhythm
Abreu Filho, 2005[92]	RCT; Inpatient; S. America; Fair	Total N: 70 Arm 1: Concomitant surgical Maze procedure (42) Arm 2: MV surgery alone (28)	Arm 1: 55.4 (SD 12.8) Arm 2: 50.7 (SD 9.7)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 66.1 mo (SD 57.4) Arm 2: 43.8 mo (SD 28.5)	Persistent AF	Arm 1: 100% Arm 2: 100%	Arm 1: 62.8 (SD 9.2) Arm 2: 66.1 (SD 10.5)	NR	Maintenance of sinus rhythm All-cause mortality
Doukas, 2005[93]	RCT; NR; UK; Good	Total N: 97 Arm 1: Concomitant AF ablation (open surgical) (49) Arm 2: MV surgery alone (48)	Arm 1 67.2 (SD 9) Arm 2: 67 (SD 8)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 57 mo (SD 55.1) Arm 2: 46.7 mo (SD 64.3)	Permanent AF	NR	NR	NR	Restoration of sinus rhythm (conversion) Maintenance of sinus rhythm Quality of life/ Functional status Stroke Cardiac mortality

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Fassini, 2005[94]	RCT; NR; Europe; Fair	Total N: 187 Arm 1: PVD (92) Arm 2: PVD + MIL (95)	Total: 55 (SE 11) Arm 1: 57 (SE 8) Arm 2: 54 (SE 10)	Arm 1: 0, 63N, 29N Arm 2: 0, 63N, 32N	NR	Previously failed a rate-or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 56.80 Arm 2: 55.30	NR	Maintenance of sinus rhythm
Hocini, 2005[95]	RCT; NR; Europe; Fair	Total N: 90 Arm 1: PVI (45) Arm 2: PVI + roofline (45)	Arm 1: 55 (SD 8) Arm 2: 54 (SD 10)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 56 mo (SD 44) Arm 2: 70 mo (SD 61)	Previously failed a rate-or rhythm-control pharmaco-logical therapy strategy, Paroxysmal AF	NR	Arm 1: 67 (SD 11) Arm 2: 67 (SD 8)	NR	Maintenance of sinus rhythm
Karch, 2005[96]	RCT; Inpatient; Europe; Fair	Total N: 100 Arm 1: Circumferential (50) Arm 2: AF ablation by PVI (transcatheter, segmental) (50)	Arm 1: Median 59 (IQR, 52 to 64) Arm 2: Median 61 (IQR, 54 to 65)	Arm 1: 0, 43N, 7N Arm 2: 0, 46N, 4N	Arm 1: Median 5 yr (IQR, 3 to 7) Arm 2: Mean 4 yr (IQR, 2 to 7)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: Median 64 (IQR, 61 to 72) Arm 2: Median 62 (IQR, 57 to 68)	NR	Maintenance of sinus rhythm Control of AF symptoms Mixed embolic events including stroke

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Oral, 2005[97]	RCT; NR; US; Fair	Total N: 80 Arm 1: AF ablation by PVI (transcatheter, circumferential) (40) Arm 2: AF ablation by PVI (transcatheter, nonencircling) (40)	Arm 1: 52 (SD 8) Arm 2: 55 (SD 10)	NR	Arm 1: 4 yr (SD 2) Arm 2: 5 yr (SD 4)	None	NR	Arm 1: 53 (SD 11) Arm 2: 53 (SD 6)	NR	Restoration of sinus rhythm (conversion) Recurrence of AF
Singh, 2005[49] (SAFE-T) Atwood, 2007[50] Batcher, 2007[51] Singh, 2009[52]	RCT; Outpatient; US; Good	Total N: 665 Arm 1: Amiodarone (267) Arm 2: Sotalol (261) Arm 3: Placebo (137)	Arm 1: 67.1 (SD 9.4) Arm 2: 66.8 (SD 8.9) Arm 3: 67.7 (SD 9.8)	NR	NR	None	Arm 1: 67N Arm 2: 72N Arm 3: 33N	Arm 1: 50.5 (SD 12.4) Arm 2: 51.5 (SD 11.9) Arm 3: 49.4 (SD 12.7)	Arm 1: 71N Arm 2: 66N Arm 3: 31N	Restoration of sinus rhythm (conversion) Stroke All-cause mortality; Death due to arrhythmia; Recurrence of AF Quality of Life
Wazni, 2005[98]	RCT; NR; Europe; Fair	Total N: 70 Arm 1: AF ablation by PVI (transcatheter) (33) Arm 2: Flecainide, propafenone, sotalol, amiodarone (37)	Arm 1: 53 (SD 8) Arm 2: 54 (SD 8)	Arm 1: 0, 97%, 3% Arm 2: 0, 95%, 5%	Arm 1: 5 mo (SD 2.0) Arm 2: 5 mo (SD 2.5)	None	NR	Arm 1: 53 (SD 5) Arm 2: 54 (SD 6)	NR	AF Hospitalizations Mixed embolic events including stroke Bleeding events (including hemorrhagic stroke) Quality of life/ Functional status Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Calo, 2006[99]	RCT; NR; Europe; Good	Total N: 80 Arm 1: AF ablation by PVI (transcatheter, left atrial) (41) Arm 2: AF ablation by PVI (transcatheter, biatrial) (39)	Total: 58.6 (SD 8.9) Arm 1: 59.2 (SD 9.1) Arm 2: 57.9 (SD 8.9)	Arm 1: 17N, 0, 24N Arm 2: 20N, 0, 19N	Arm 1: 7 yr (SD 4) Arm 2: 8 yr (SD 3)	None	NR	Arm 1: 51.2 (SD 7.4) Arm 2: 50.2 (SD 7.8)	Arm 1: 9N Arm 2: 8N	Recurrence of AF
Dixit, 2006[100]	RCT; NR; US; Good	Total N: 82 Arm 1: AF ablation by PVI (transcatheter, 8mm tip) (42) Arm 2: AF ablation by PVI (transcatheter, cooled tip) (40)	Arm 1: 57 (SD 8) Arm 2: 57 (SD 8)	Arm 1: 0, 72%, 0 Arm 2: 0, 73%, 0	Arm 1: 68 mo (SD 42) Arm 2: 56 mo (SD 54)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	NR	NR	Maintenance of sinus rhythm Stroke
Hemels, 2006[11] (VERDICT)	RCT; NR; Europe; Fair	Total N: 144 Arm 1: Electrical cardioversion (early or routine), Digoxin (70) Arm 2: Electrical cardioversion (early or routine), Verapamil (74)	Arm 1: 65 (SD 11) Arm 2: 66 (SD 8) Arm 3: 65 (SD 11) Arm 4: 65 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100% Arm 4: 0, 0, 100%	Arm 1: 138 days Arm 2: 113 days Arm 3: 140 days Arm 4: 117 days	Persistent AF	Arm 1: 7% Arm 2: 6% Arm 3: 7% Arm 4: 5%	NR	Arm 1: 15% Arm 2: 16% Arm 3: 19% Arm 4: 12%	Control of ventricular rate, Restoration of sinus rhythm (conversion) Recurrence of AF, Maintenance of sinus rhythm, Quality of life/ Functional status

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Liu, 2006[101]	RCT; NR; Asia; Fair	Total N: 110 Arm 1: Circumferential PVI (55) Arm 2: Segmental PVI (55)	Arm 1: 57.3 (SD 9.6) Arm 2: 58 (SD 8.1)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 5.4 yr (SD 3.6) Arm 2: 4.5 yr (SD 3.1)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Paroxysmal AF	NR	Arm 1: 64.1 (SD 6.7) Arm 2: 63.1 (SD 5.7)	NR	Maintenance of sinus rhythm Recurrence of AF
Nilsson, 2006[102]	RCT; Inpatient; Europe; Fair	Total N: 100 Arm 1: AF ablation by PVI (transcatheter, segmental) (54) Arm 2: AF ablation by PVI (transcatheter, circumferential) (46)	Total: 56 (SD 10) Arm 1: 55 (SD 10) Arm 2: 57 (SD 11)	Total: 0, 51N, 49N Arm 1: 0, 52%, 48% Arm 2: 0, 50%, 50%	Arm 1: 3.3 yr Arm 2: 5.0 yr	None	Arm 1: 19% Arm 2: 22%	NR	Arm 1: 11% Arm 2: 17%	Maintenance of sinus rhythm
Oral, 2006[103]	RCT; Inpatient, Outpatient; US, Europe; Good	Total N: 146 Arm 1: Amiodarone, AF ablation by PVI (transcatheter) (77) Arm 2: Amiodarone, Electrical Cardioversion, AF ablation by PVI (transcatheter) (69)	Arm 1: 55 (SD 9) Arm 2: 58 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 5 yr (SD 4) Arm 2: 4 yr (SD 4)	Persistent AF	NR	Arm 1: 58 (SD 7) Arm 2: 56 (SD 7)	Arm 1: 3N Arm 2: 4N	Maintenance of sinus rhythm All-cause mortality

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Pappone, 2006[104] (APAF) Pappone, 2011[105]	RCT; Outpatient; Europe; Good	Total N: 198 Arm 1: AF ablation by PVI (transcatheter) (99) Arm 2: AAD (99)	Total: 56 (SD 10) Arm 1: 55 (SD 10) Arm 2: 57 (SD 10)	Total: 0, 100%, 0	Total: 6 yr (SD 5) Arm 1: 6 yr (SD 4) Arm 2: 6 yr (SD 6)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 60 (SD 8) Arm 2: 61 (SD 6)	Arm 1: 2% Arm 2: 2%	Maintenance of sinus rhythm Quality of life/ Functional status CV hospitalizations
Sheikh, 2006[106]	RCT; NR; US; Fair	Total N: 100 Arm 1: PVI (50) Arm 2: PVI + 2 linear lesions; 1 between the superior PVs and 1 from the left inferior PV to the mitral valve annulus (50)	Arm 1: 60 (SD 12) Arm 2: 60 (SD 10)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	NR	None	NR	Arm 1: 54 (SD 12) Arm 2: 53 (SD 14)	NR	Control of AF symptoms Maintenance of sinus rhythm
Stabile, 2006[107] (Catheter Ablation For The Cure Of Atrial Fibrillation Study)	RCT; NR; Europe; Good	Total N: 137 Arm 1: AF ablation by PVI (transcatheter), Amiodarone/AAD (68) Arm 2: Amiodarone/AAD (69)	Arm 1: 62.2 (SD 9) Arm 2: 62.3 (SD 10.7)	Arm 1: 0, 42N, 26N Arm 2: 0, 50N, 19N	Arm 1: 5.1 yr (SD 3.9) Arm 2: 7.1 yr (SD 5.9)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 59.1 (SD 6.7) Arm 2: 57.9 (SD 5.8)	Arm 1: 43N Arm 2: 43N	Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Vijayalakshmi, 2006[57]	RCT; NR; UK; Good	Total N: 94 Arm 1: Control (31) Arm 2: Amiodarone (27) Arm 3: Sotalol (36)	Arm 1: 64.8 (SD 9.1) Arm 2: 65.5 (SD 10.5) Arm 3: 62.8 (SD 9.3)	NR	Arm 1: 7 mo (SD 4) Arm 2: 6.6 mo (SD 3.9) Arm 3: 7.3 mo (SD 4.4)	None	Arm 1: 1N Arm 2: 1N Arm 3: 1N	Arm 1: 40 Arm 2: 51 Arm 3: 40	NR	All-cause mortality, Maintenance of sinus rhythm, Restoration of sinus rhythm (conversion)
Willems, 2006[108]	RCT; NR; NR; Good	Total N: 62 Arm 1: PVI + SM (=substrate modification consisting of a roofline connecting both left superior and right superior PV and LA isthmus ablation between left inferior PV and mitral annulus) (32) Arm 2: PVI (30)	Arm 1: 58.3 (SD 11.8) Arm 2: 60.1 (SD 9.3)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: Median 7 mo Arm 1: Median 7 mo Arm 2: Median 7 mo	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	NR	Arm 1: 4N Arm 2: 4N	Stroke Recurrence of AF
Arentz, 2007[109]	RCT; NR; Europe; Fair	Total N: 110 Arm 1: AF ablation by PVI (transcatheter, small area) (55) Arm 2: AF ablation by PVI (transcatheter, large area) (55)	Arm 1: 56 (SD 10) Arm 2: 55 (SD 10)	Total: 0, 67N, 43N Arm 1: 0, 35N, 20N Arm 2: 0, 32N, 23N	Total: 5.5 yr (SD 2.8)	None	NR	NR	NR	Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Blomstrom-Lundqvist, 2007[110] (SWEDMAF)	RCT; Inpatient (surgical patients); Europe; Good	Total N: 65 Arm 1: Concomitant open surgical AF ablation (30) Arm 2: MV surgery alone (35)	Arm 1: 69.5 (SD 7.9) Arm 2: 65.6 (SD 8.8)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 26 mo (SD 33) Arm 2: 33 mo (SD 54)	Permanent AF	Total: 16.92 % Arm 1: 26.7% Arm 2: 8.6%	Arm 1: 53.60 (SD 9.1) Arm 2: 57 (SD 12)	Total: 23.07 % Arm 1: 20% Arm 2: 25.7%	Maintenance of sinus rhythm
Nergardh, 2007[62]	RCT; Outpatient; Europe; Good	Total N: 168 Arm 1: Metoprolol (83) Arm 2: Placebo (85)	Arm 1: 68.2 (SD 10.1) Arm 2: 66.5 (SD 12.2)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 5.3 mo (SD 2.9) Arm 2: 5.1 mo (SD 2.8)	Persistent AF	NR	Arm 1: 48.6 (SD 7.9) Arm 2: 49.7 SD 6.7)	Arm 1: 4N Arm 2: 3N	Control of ventricular rate, Maintenance of sinus rhythm, Restoration of sinus rhythm (conversion), All-cause mortality, Stroke
Turco, 2007[111]	RCT; NR; Europe; Good	Total N: 107 Arm 1: AF ablation by PVI (transcatheter) (54) Arm 2: AF ablation by PVI (transcatheter) + AAD (53)	Total: 57 (SD 10)	Total: 0, 64N, 43N	Total: 4.5 yr (SD 4.2)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Total: 57 (SD 7)	Total: 5N	Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Di Biase, 2008[112]	RCT; NR; US, Canada, Europe; Good	Total N: 103 Arm 1: AF ablation by PVI (transcatheter, PVAI) (35) Arm 2: AF ablation by PVI (transcathter, CFAE) (34) Arm 3: AF ablation by PVI (transcatheter, PVAI+CFAE) (34)	Arm 1: 57 (SD 8.1) Arm 2: 59.9 (SD 8.6) Arm 3: 58.4 (SD 7.5)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0 Arm 3: 0, 100%, 0	Arm 1: 5.3 yr (SD 5.7) Arm 2: 5.1 yr (SD 4.1) Arm 3: 5.3 yr (SD 5)	Paroxysmal AF	NR	Arm 1: 55 (SD 8) Arm 2: 55.5 (SD 6) Arm 3: 54.6 (SD 6)	NR	Maintenance of sinus rhythm Restoration of sinus rhythm (conversion)
Dixit, 2008[113]	RCT; NR; US; Good	Total N: 105 Arm 1: AF ablation by PVI (transcatheter, all veins) (53) Arm 2: AF ablation by PVI (transcatheter, selected veins) (52)	Arm 1: 57 (SD 9) Arm 2: 57 (SD 9)	Arm 1: 0, 77%, 0 Arm 2: 0, 69%, 0	Arm 1: 62 mo (SD 54) Arm 2: 61 mo (SD 53)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	NR	NR	All-cause mortality Maintenance of sinus rhythm Stroke

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Elayi, 2008[114]	RCT; NR; US, Canada, Europe; Good	Total N: 144 Arm 1: Circumferential PV ablation with a 3.5 mm tip irrigated catheter (47) Arm 2: Pulmonary vein antrum isolation (PVAI) using an open irrigation ablation catheter (48) Arm 3: Ablation of CFAE followed by PVAI (49)	Arm 1: 60.1 (SD 10.1) Arm 2: 58.1 (SD 10.3) Arm 3: 59.2 (SD 11.5)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0 Arm 3: 100%, 0, 0	Arm 1: 6.7 yr (SD 3.2) Arm 2: 5.5 yr (SD 3.5) Arm 3: 6.3 yr (SD 2.5)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Permanent AF	NR	Arm 1: 56 Arm 2: 52 Arm 3: 55	Arm 1: 7N Arm 2: 9N Arm 3: 10N	Restoration of sinus rhythm (conversion) Maintenance of sinus rhythm Stroke
Fiala, 2008[115]	RCT; NR; Europe; Good	Total N: 110 Arm 1: Segmental PVI (54) Arm 2: Circumferential PVI (56)	Total: 52 (SD 11) Arm 1: 51 (SD 11) Arm 2: 53 (SD 10)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Total: 7 yr (SD 6) Arm 1: 7 yr (SD 4) Arm 2: 8 yr (SD 6)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Paroxysmal AF	NR	Total: 60 (SD 6) Arm 1: 59 (SD 7) Arm 2: 60 (SD 4)	NR	Recurrence of AF Maintenance of sinus rhythm All-cause mortality

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Gaita, 2008[116]	RCT; Outpatient; Europe; Fair	Total N: 204 Arm 1: AF ablation by PVI (transcatheter) (67) Arm 2: AF ablation by PVI (transcatheter, left linear) (137)	Arm 1: 53.3 (SD 9) Arm 2: 56 (SD 9.9)	Arm 1: 0, 61%, 0 Arm 2: 0, 61%, 0 (remaining 39% patients were classified as having permanent or persistent AF)	Total: 5.2 yr (SD 4) Arm 1: 5.7 yr (SD 4.5) Arm 2: 4.9 yr (SD 3.8)	None	NR	NR	NR	Maintenance of sinus rhythm
Jais, 2008[117] (A4 Study)	RCT; Outpatient; Canada, Europe; Fair	Total N: 112 Arm 1: RF ablation (53) Arm 2: AAD use (59)	Total: 51.1 (SD 11.1) Arm 1: 49.7 (SD 10.7) Arm 2: 52.4 (SD 11.4)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	NR	Paroxysmal AF	NR	Total: 64.3 (SD 9.4) Arm 1: 63.1 (SD 11.0) Arm 2: 65.6 (SD 7.2)	Total: 9N Arm 1: 3N Arm 2: 6N	Maintenance of sinus rhythm, Control of ventricular rate, Control of AF symptoms (e.g., palpitations, exercise capacity), Quality of life/ Functional status
Oral, 2008[118]	RCT; NR; US; Fair	Total N: 85 Arm 1: Left atrial RFA (19) Arm 2: No right atrial RTA (33) Arm 3: Left atrial + right atrial RFA (33)	Total: 59 (SD 10) Arm 1: 58 (SD 9) Arm 2: 58 (SD 10) Arm 3: 60 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100%	Total: 4 yr (SD 5) Arm 1: 4 yr (SD 4) Arm 2: 5 yr (SD 6) Arm 3: 4 yr (SD 5)	Persistent AF	NR	Total: 53 (SD 10) Arm 1: 52 (SD 11) Arm 2: 51 (SD 10) Arm 3: 55 (SD 10)	Total: 8% Arm 1: 16% Arm 2: 6% Arm 3 6%	Restoration of sinus rhythm Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Srivastava, 2008[119]	RCT; NR; Asia; Good	Total N: 160 Arm 1: Control (40) Arm 2: Surgical Maze procedure (biatrial) (40) Arm 3: Surgical Maze procedure (left atrial) (40) Arm 4: AF ablation by PVI (transcatheter) (40)	Arm 1: 36.74 (SD 9.79) Arm 2: 37.11 (SD 11.12) Arm 3: 36.03 (SD 7.99) Arm 4: 40.95 (SD 11.41)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0 Arm 3: 100%, 0, 0 Arm 4: 100%, 0, 0	Arm 1: 12.17 mo Arm 2: 9.83 mo Arm 3: 12.48 mo Arm 4: 12.56 mo	Permanent AF	NR	NR	NR	All-cause mortality Restoration of sinus rhythm (conversion)
Wang, 2008[120]	RCT; NR; Asia; Poor	Total N: 106 Arm 1: CPVI (54) Arm 2: CPVI + SVCI (52)	Arm 1: 66.6 (SD 8.8) Arm 2: 65.4 (SD 8.9)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 42.9 mo (SD 24.2) Arm 2: 44.4 mo (SD 24.3)	Paroxysmal AF	NR	Total: 54 (SD 8)	Arm 1: 5.6% Arm 2: 7.7%	Recurrence of AF
Albrecht, 2009[121]	RCT; NR; S. America; Fair	Total N: 60 Arm 1: Surgical PVI (20) Arm 2: Concomitant surgical Maze procedure (20) Arm 3: MV surgery alone (20)	Total: 53 (SD 14.2) Arm 1: 55.1 (SD 9.2) Arm 2: 51.7 (SD 12.4) Arm 3: 51.3 (SD 14.7)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0 Arm 3: 100%, 0, 0	Total: 30.6 mo (SD 35.7) Arm 1: 31.78 mo (SD 31.6) Arm 2: 35.4 mo (SD 38.5) Arm 3: 24.6 mo (SD 32)	Permanent AF	Total: 98.3% Arm 1: 100% Arm 2: 100% Arm 3: 95%	Total: 63.2 (SD 8.5) Arm 1: 62.1 (SD 11.3) Arm 2: 64.3 (SD 7.1) Arm 3: 63.3 (SD 7)	NR	Restoration of sinus rhythm (conversion) Maintenance of sinus rhythm Recurrence of AF Recurrence of AF All-cause mortality Bleeding events (including hemorrhagic stroke)

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Chevalier, 2009[122] (SAFIR)	RCT; Inpatient; Europe; Good	Total N: 43 Arm 1: Concomitant AF ablation (21) Arm 2: MV surgery alone (22)	Arm 1: 69.1 (SD 6.2) Arm 2: 66.31 (SD 9.7)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 161 mo Arm 2: 89.2 mo	Persistent AF	Arm 1: 63.6% Arm 2: 75%	Arm 1: 59.8 (SD 8.5) Arm 2: 61.3 (SD 9.45)	NR	Restoration of sinus rhythm (conversion) Maintenance of sinus rhythm All-cause mortality Stroke Bleeding events (including hemorrhagic stroke) Composite outcome (Recurrence of AF (specify time period) : 12 months, All-cause mortality, Stroke, adverse surgical events)
Deisenhofer, 2009[123]	RCT; NR: Europe; Good	Total N: 98 Arm 1: AF ablation by PVI (transcatheter) (48) Arm 2: AF ablation by PVI (transcatheter, CFAE) (50)	Total: 57 (SD 10) Arm 1: 58 (SD 10) Arm 2: 55 (SD 10)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 4 yr (SD 3) Arm 2: 4 yr (SD 4)	Paroxysmal AF	NR	NR	NR	Maintenance of sinus rhythm Composite outcome (Mixed embolic events including stroke, Pulmonary vein stenosis, pericardial tamponade)
Forleo, 2009[124]	RCT; NR; Europe; Good	Total N: 70 Arm 1: AF ablation by PVI (transcatheter) (35) Arm 2: Amiodarone, propafenone, sotalol (35)	Arm 1: 63.2 (SD 8.6) Arm 2: 64.8 (SD 6.5)	Arm 1: 0, 16N, 19N Arm 2: 0, 13N, 22N	Arm 1: Median 41 mo (IQR, 18 to 66) Arm 2: Median 36 mo (IQR, 17 to 55)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 54.6 (SD 7) Arm 2: 52.6 (SD 8.6)	Arm 1: 20% Arm 2: 20%	Maintenance of sinus rhythm Recurrence of AF CV hospitalizations Mixed embolic events including stroke Quality of life/ Functional status

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Khaykin, 2009[125]	RCT; Inpatient, Outpatient; US, Canada, UK, Europe; Good	Total N: 60 Arm 1: PVI (30) Arm 2: Circumferential PVI with CFAE ablation (30)	Arm 1: 54 (SD 7) Arm 2: 57 (SD 9)	Arm 1: 0, 25N, 5N Arm 2: 0, 23N, 7N	Arm 1: 8 yr (SD 8) Arm 2: 7 yr (SD 6)	None	Arm 1: 2N Arm 2: 3N	NR	NR	Maintenance of sinus rhythm Quality of life/ Functional status
Oral, 2009[126]	RCT; Outpatient; US; Fair	Total N: 100 Arm1: Antral PVI targeting CFAEs (50) Arm 2: Antral PVI targeting CFAEs followed by additional ablation of CFAE in left atrium or coronary sinus (50)	Arm 1: 58 (SD 10) Arm 2: 62 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 6 yr (SD 5) Arm 2: 5 yr (SD 4)	Persistent AF	NR	Arm 1: 53 (SD 12) Arm 2: 54 (SD 9)	Arm 1: 16% Arm 2: 18%	Maintenance of sinus rhythm
Pontoppidan, 2009[127]	RCT; NR; Europe; Good	Total N: 149 Arm 1: AF ablation by PVI (transcatheter) (76) Arm 2: AF ablation by PVI (transcatheter, CTI) (73)	Arm 1: 56 (SD 8) Arm 2: 56 (SD 8)	Arm 1: 0, 55%, 45% Arm 2: 0, 52%, 48%	Arm 1: Median 44 mo (6 to 240) Arm 2: Median 60 mo (4 to 300)	None	Arm 1: 22% Arm 2: 21%	Arm 1: 64 (SD 9) Arm 2: 60 (SD 10)	Arm 1: 3N Arm 2: 4N	Recurrence of AF
Roux, 2009[128] (5A) Leong-Sit, 2011[129]	RCT; Inpatient; US; Good	Total N: 110 Arm 1: AAD (53) Arm 2: No AAD (57)	Arm 1: 56 (SD 8) Arm 2: 55 (SD 9)	NR	Arm 1: 71 mo (SD 68) Arm 2: 81 mo (SD 65)	None	NR	Arm 1: 61 (SD 8) Arm 2: 62 (SD 7)	Arm 1: 13% Arm 2: 12%	Composite outcome (Maintenance of sinus rhythm, AF Hospitalizations, Other adverse drug reaction) Maintenance of sinus rhythm AF Hospitalizations

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Tamborero, 2009[130]	RCT; NR; Europe; Good	Total N: 120 Arm 1: AF ablation by PVI (transcatheter, anterolateral) (60) Arm 2: AF ablation by PVI (transcatheter, posterolateral) (60)	Arm 1: 52.5 (SD 10.9) Arm 2: 52.9 (SD 10.8)	Arm 1: 12N, 37N, 11N Arm 2: 12N, 35N, 13N	Arm 1: 60.8 mo (SD 55.7) Arm 2: 67.1 mo (SD 48.2)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 59.8 (SD 9.8) Arm 2: 59.5 (SD 10.1)	NR	Maintenance of sinus rhythm
von Oppell, 2009[131]	RCT; Inpatient; UK; Good	Total N: 49 Arm 1: Concomitant AF ablation by PVI (24) Arm 2: Cardiac surgery alone (25)	Arm 1: 66 (SD 8) Arm 2: 68 (SD 9)	Arm 1: 22N, 0, 2N Arm 2: 22N, 0, 3N	Arm 1: 7 yr (SD 10) Arm 2: 5 yr (SD 4)	None	Arm 1: 10N Arm 2: 12N	NR	Arm 1: 10N Arm 2: 14N	Restoration of sinus rhythm
Wang, 2009[132]	RCT; NR; Asia; Good	Total N: 299 Arm 1: AF ablation by PVI (transcatheter, left atrial + CTI) (149) Arm 2: AF ablation by PVI (transcatheter, biatrial) (150)	Total: 53 Arm 1: 54.2 (SD 10.1) Arm 2: 53.4 (SD 10.8)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 37 mo (SD 46) Arm 2: 35 mo (SD 37)	Permanent AF	Total: 160N Arm 1: 83N Arm 2: 77N	Total: 59 (SD 9) Arm 1: 59.3 (SD 8.9) Arm 2: 59 (SD 8.7)	NR	Maintenance of sinus rhythm All-cause mortality Restoration of sinus rhythm (conversion) Stroke

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Bulava, 2010[133]	RCT; Outpatient; Europe; Good	Total N: 102 Arm 1: PVI using a multipolar circular ablation catheter (PVAC group) (51) Arm 2: Point-by-point PV isolation using an irrigated-tip ablation catheter (51)	Arm 1: 56.5 (SD 9.9) Arm 2: 59.8 (SD 11.9)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	NR	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Paroxysmal AF	NR	Arm 1: 69.8 (SD 6.2) Arm 2: 67.6 (SD 7.9)	Arm 1: 2N Arm 2: 3N	Recurrence of AF Maintenance of sinus rhythm
Chen, 2010[134]	RCT; NR; Asia; Fair	Total N: 118 Arm 1: AF ablation by PVI (transcatheter, circumferential) (24) Arm 2: AF ablation by PVI (transcatheter, CFE) (35) Arm 3: AF ablation by PVI (transcathter, circumferential + CFE) (58) 1 patient had acute procedural failure and was not included in analyses	Total: 56 (SD 11.2) Arm 1: 52.2 (SD 13.2) Arm 2: 57.6 (SD 9.1) Arm 3: 56.4 (SD 11.2)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0 Arm 3: 0, 100%, 0	Total: 53.1 mo (SD 46.3) Arm 1: 52.9 mo (SD 42.2) Arm 2: 53.5 mo (SD 43.5) Arm 3: 51.8 mo (SD 46.5)	Paroxysmal AF	NR	Arm 1: 66.2 (SD 4.1) Arm 2: 65.9 (SD 4.7) Arm 3: 64.5 (SD 3.3)	Arm 1: 1N Arm 2: 3N Arm 3: 2N	Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Corrado, 2010[135]	RCT; NR; Europe; Fair	Total N: 294 Arm 1: AF ablation by PVI (transcatheter, ICE) (160) Arm 2: AF ablation by PVI (transcatheter ICE + superior vena cava isolation [SVCI]) (134)	Arm 1: 57 (SD 9) Arm 2: 55 (SD 10)	Arm 1: 28%, 46%, 26% Arm 2: 29%, 46%, 25%	Arm 1: 7.1 yr (SD 4) Arm 2: 6.5 yr (SD 5)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 53 (SD 7) Arm 2: 54 (SD 6)	NR	Maintenance of sinus rhythm
Kim, 2010[136]	RCT; Outpatient; Asia; Fair	Total N: 102 Arm 1: AF ablation by PVI (transcatheter, additional ablation) (49) Arm 2: AF ablation by PVI (transcatheter) (53)	Arm 1: 52.3 (SD 9.8) Arm 2: 54.2 (SD 11.6)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 4.6 yr (SD 3.5) Arm 2: 4.3 yr (SD 4)	Paroxysmal AF	NR	Arm 1: 54 (SD 8.4) Arm 2: 56 (SD 5.5)	NR	Recurrence of AF Maintenance of sinus rhythm
Knaut, 2010[137]	RCT; NR; Europe; Fair	Total N: 45 Arm 1: Concomitant AF ablation by PVI (open surgical) (24) Arm 2: Cardiac surgery alone (21)	Arm 1: 74 (SD 4.4) Arm 2: 74.8 (SD 5.8)	Total: 100%, 0, 0 Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	Arm 1: 5.9 yr (SD 4.4) Arm 2: 4.3 yr (SD 8.0)	Permanent AF	NR	Arm 1: 55.8 (SD 13.6) Arm 2: 54.2 (SD 5.5)	Arm 1: 83.3% Arm 2: 71.4%	All-cause mortality Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Liu, 2010[138]	RCT; Inpatient; Asia; Fair	Total N: 99 Arm 1: AF ablation by PVI (transcatheter), Amiodarone (49) Arm 2: Concomitant surgical Maze procedure, Amiodarone (50)	Arm 1: 55 (SD 12) Arm 2: 54 (SD 10)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 74 mo (SD 46) Arm 2: 67 mo (SD 47)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy, Persistent AF	NR	Arm 1: 61.4 (SD 9.9) Arm 2: 65.1 (SD 10.9)	NR	Maintenance of sinus rhythm
Le Heuzey, 2010[139] (DIONYSOS)	RCT; NR: US, Canada, Europe, S. America, C. America, Asia, Australia/NZ; Good	Total N: 504 Arm 1: Dronedarone (249) Arm 2: Amiodarone (255)	Total: 64 (SD 10.7) Arm 1: 64.4 (SD 10.8) Arm 2: 63.7 (SD 10.6)	Total: 3%, 4.4%, 62.9% Arm 1: 2%, 4.4%, 61.8% Arm 2: 3.9%, 4.3%, 63.9%	Total: Median 49 days (IQR, 3 to 368) Arm 1: Median 47.5 day (IQR, 3 to 368) Arm 2: Median 54 days (IQR, 4 to 352)	None	Total: 21.6% Arm 1: 22.5% Arm 2: 20.8%	NR	Total: 17.9% Arm 1: 18.9% Arm 2: 16.9%	Recurrence of AF, Composite outcome (Recurrence of AF, Other adverse drug reaction), Mortality

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Pires, 2010[140]	RCT; Inpatient; S. America; Fair	Total N: 22 Arm 1: Concomitant AF ablation by PVI (open surgical, incisions) (10) Arm 2: Concomitant AF ablation by PVI (open surgical, radiofrequency) (12)	Arm 1: 62.1 (SD 8.3) Arm 2: 56.5 (SD 11.5)	Arm 1: 100%, 0, 0 Arm 2: 100%, 0, 0	NR	Permanent AF	Arm 1: 8N Arm 2: 11N	Arm 1: 62.8 (SD 10.8) Arm 2: 59.3 (SD 15.3)	Arm 1: 1N Arm 2: 1N	Restoration of sinus rhythm (conversion) Recurrence of AF
Sawhney, 2010[141]	RCT; NR; NR; Fair	Total N: 66 Arm 1: PVI (33) Arm 2: CPVA + LALA (33)	Arm 1: 55.2 (SD 11.7) Arm 2: 58.6 (SD 9.6)	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 5.2 yr (SD 5) Arm 2: 6.0 yr (SD 5.7)	Paroxysmal AF	NR	Arm 1: 61.8 (SD 5.8) Arm 2: 61.1 (SD 4.3)	NR	Maintenance of sinus rhythm Recurrence of AF
Wilber, 2010[142] (ThermoCool AF) Reynolds, 2010[143]	RCT; Inpatient, Outpatient; US, Canada, Europe, C. America Good	Total N: 167 Arm 1: AAD (61) Arm 2: AF ablation by PVI (transcatheter) (106)	Arm 1: 55.8 (SD 13.1) Arm 2: 55.5 (SD 9.4)	NR	NR	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NYHA class I or II Arm 1: 54N Arm 2: 92N	Arm 1: 62.7 Arm 2: 62.3	NR	Quality of life/ Functional status, Control of AF symptoms

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Van Breugel, 2010[144]	RCT; Inpatient; Europe; Good	Total N: 132 Arm 1: Cardiac surgery alone (67) Arm 2: Concomitant AF ablation by PVI (open surgical) (65)	Total: 68.2 (SD 9.1) Arm 1: 71 (IQR, 38.8 to 85.0) Arm 2: 61.9 (IQR, 46.6 to 81.0)	Total: 43N, 57N, 30N Arm 1: 21N, 30N, 15N Arm 2: 22N, 27N, 15N	Total: 81.0 mo (SD 102.4) Arm 1: 84.1 mo (IQR, 3 to 618) Arm 2: 78.0 mo (IQR, 33 to 403)	None	NR	Total: 52.6 (SD 7.5) Arm 1: 56.5 (IQR, 30 to 80) Arm 2: 48.8 (IQR, 18 to 79)	NR	Quality of life/ Functional status Maintenance of sinus rhythm
Verma, 2010[145] (STAR AF)	RCT; Inpatient, Outpatient; Canada, Europe; Good	Total N: 101 Arm 1: AF ablation by PVI (transcatheter, CFE) (34) Arm 2: AF ablation by PVI (transcatheter, PVAI) (32) Arm 3: AF ablation by PVI (transcatheter, PVAI+CFE) (34) Note one patient randomized to PVI did not end up undergoing ablation	Total: 57 (SD 10) Arm 1: 57 (SD 9) Arm 2: 55 (SD 11) Arm 3: 59 (SD 10)	Arm 1: 0, 21N, 13N Arm 2: 0, 21N, 11N Arm 3: 0, 22N, 12N	Total: 7 yr (SD 7) Arm 1: 6.4 yr (SD 6.0) Arm 2: 6.4 yr (SD 6.6) Arm 3: 7.6 yr (SD 9.4)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	Total: 3N Arm 1: 1N Arm 2: 2N Arm 3: 0N	Total: 62 (SD 10) Arm 1: 64 (SD 10) Arm 2: 62 (SD 7) Arm 3: 59 (SD 12)	Total: 7N Arm 1: 3N Arm 2: 1N Arm 3: 3N	Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Bittner, 2011[146]	RCT; NR; Europe; Good	Total N: 80 Arm 1: PVI using a new circular ablation catheter (40) Arm 2: PVI using a point by point conventional ablation catheter (40)	Arm 1: 57 (SD 11) Arm 2: 59 (SD 9)	Arm 1: 0, 21N, 19N Arm 2: 0, 23N, 17N	Arm 1: 78 mo (SD 76) Arm 2: 104 mo (SD 91)	None	NR	NR	NR	Maintenance of sinus rhythm
Dixit, 2011[147] (RASTA)	RCT; NR; US; Good	Total N: 156 Arm 1: AF ablation by PVI (transcatheter) (55) Arm 2: AF ablation by PVI (transcatheter, PV triggers) (50) Arm 3: AF ablation by PVI (transcatheter, CFE) (51)	Total: 58 (SD 9) Arm 1: 59 (SD 8) Arm 2: 57 (SD 10) Arm 3: 60 (SD 9)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100% Arm 3: 0, 0, 100%	Arm 1: 56 mo (SD 65) Arm 2: 44 mo (SD 44) Arm 3: 43 mo (SD 40)	Persistent AF	Arm 1: 18% Arm 2: 18% Arm 3: 16%	Arm 1: 56 (SD 90) Arm 2: 57 (SD 10) Arm 3: 56 (SD 14)	NR	Maintenance of sinus rhythm Recurrence of AF Mixed embolic events including stroke
Boersma, 2012[148] (FAST)	RCT; NR; Europe; Good	Total N: 124 Arm 1: AF ablation by PVI (transcatheter) (63) Arm 2: AF ablation by PVI (minimally invasive surgical PVI) (61)	Total: 56 (SD 8) Arm 1: 56 (SD 7.2) Arm 2: 56.1 (SD 8)	Total: 0, 67%, 33% Arm 1: 0, 37N, 26N Arm 2: 0, 45N, 16N	Arm 1: 6.8 yr (SD 5.3) Arm 2: 7.4 yr (SD 6.3)	Previously failed a rate- or rhythm-control pharmaco-logical therapy strategy	NR	Arm 1: 55.5 (SD 8.2) Arm 2: 57.7 (SD 6.8)	NR	Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Gavin, 2012[149]	RCT; Outpatient; Australia/NZ; Fair	Total N: 42 Arm 1: AF ablation by PVI (transcatheter) (22) Arm 2: AF ablation by PVI (transcatheter, coronary sinus) (20)	Arm 1: 68 Arm 2: 67	Total: 0, 100%, 0 Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 19 mo Arm 2: 17 mo	Paroxysmal AF	NR	Arm 1: 63.5 Arm 2: 64.8	NR	Maintenance of sinus rhythm
Mun, 2012[150]	RCT; Outpatient; Asia; Fair	Total N: 156 Arm 1: CPVI (52) Arm 2: CPVI + RL (52) Arm 3: CPVI + PostBox (52)	Total: 55.8 (SD 11.5) Arm 1: 54.88 (SD 12.66) Arm 2: 58.25 (SD 10.78) Arm 3: 54.27 (SD 10.62)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0 Arm 3: 0, 100%, 0	NR	Previously failed a rate- or rhythm-control pharmacological therapy strategy, Paroxysmal AF	Arm 1: 1.9% Arm 2: 1.9 % Arm 3: 1.9 %	Arm 1: 64.7 (SD 5.98) Arm 2: 63.8 (SD 7.6) Arm 3: 63.7 (SD 6.6)	NR	Recurrence of AF Composite Outcome (Maintenance of sinus rhythm, All-cause mortality)

Abbreviations: AF=atrial fibrillation; CAD=coronary artery disease; CV=cardiovascular; IQR=interquartile range; KQ=Key Question; LVEF=left ventricular ejection fraction; MI=myocardial infarction; mo=month(s); N=number of patients; NR=not reported; RCT=randomized controlled trial; SD=standard deviation

Appendix Table F-6. Study characteristics—KQ 6

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Hohnloser, 2000[151] (PIAF) Gronefeld, 2003[152]	RCT; NR; Europe; Good	Total N: 252 Arm 1: Rhythm control (amiodarone) (127) Arm 2: Rate control (diltiazem) (125)	Arm 1: 60 (SD 10) Arm 2: 61 (SD 9)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 103 days (SD 91) Arm 2: 118 days (SD 105)	Persistent AF	NR	NR	Total: 23.41 Arm 1: 20 Arm 2: 26	Control of AF symptoms, Restoration of sinus rhythm, Quality of life/functional status
Brignole, 2002[153] (PAF 2)	RCT; Outpatient; Europe; Fair	Total N: 137 Arm 1: Rate control with AVN ablation and pacemaker only (69) Arm 2: AVN ablation with pacemaker implantation and rhythm control with pharmacological therapy (68)	Arm 1: 69 (SD 8) Arm 2: 67 (SD 8)	Arm 1: 0, 100%, 0 Arm 2: 0, 100%, 0	Arm 1: 9 yr (SD 7) Arm 2: 8 yr (SD 7)	Paroxysmal AF	NR	NR	Arm 1: 16% Arm 2: 16%	Heart failure symptoms, CV hospitalizations, Stroke, Myocardial infarction, Quality of life/functional status, Recurrence of AF

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Van Gelder, 2002[154] (RACE) Hagens, 2004[155] Hagens, 2006[156] Hagens, 2005[157] Rienstra, 2007[158] Rienstra, 2005[159]	RCT; Outpatient; Europe; Good	Total N: 522 Arm 1: Rate control (256) Arm 2: Rhythm control (266)	Arm 1: 68 (SD 9) Arm 2: 68 (SD 8)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: Median 337 days Arm 2: Median 309 days	Persistent AF	Arm 1: 51% Arm 2: 49%	NR	Arm 1: 29% Arm 2: 26%	Composite outcome (Cardiac mortality, Mixed embolic events including stroke, Bleeding events including hemorrhagic stroke), Cardiac mortality, Mixed embolic events including stroke, Bleeding events, Maintenance of sinus rhythm, Control of ventricular rate, Quality of life/functional status
Wyse, 2002[160] (AFFIRM) Bush, 2006[161] Chung, 2005[162] Curtis, 2005[163] Guglin, 2010[164] Jenkins, 2005[165] Sherman, 2005[166] Steinberg, 2004[167]	RCT; Outpatient; US, Canada; Good	Total N: 4060 Arm 1: Rate control (2027) Arm 2: Rhythm control (2033)	Total: 69.7 (SD 9) Arm 1: 69.8 (SD 8.9) Arm 2: 69.7 (SD 9)	NR	Total: 2808 days (SD 69.2) Arm 1: 1406 days (SD 69.4) Arm 2: 1402 days (SD 69)	None	Total: 23.1% Arm 1: 23.4% Arm 2: 22.8%	Total: 54.7 (SD 13.5) Arm 1: 54.9 (SD 13.1) Arm 2: 54.6 (SD 13.8)	Total: 26.1% Arm 1: 24.5% Arm 2: 27.6%	All-cause mortality, Composite outcome (All-cause mortality, Stroke, Bleeding events including hemorrhagic stroke,Other adverse drug reaction), Stroke, Other embolic events excluding stroke, Bleeding events, Quality of lifefunctional status

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Carlsson, 2003[168] (STAF) Carlsson, 2003[169]	RCT; Outpatient; Europe; Good	Total N: 200 Arm 1: Rhythm control (100) Arm 2: Rate control (100)	Arm 1: 65.3 (SD 9.4) Arm 2: 66.2 (SD 7.6)	NR	Arm 1: 6 mo (SD 2) Arm 2: 6 mo (SD 3)	None	Arm 1: 9N Arm 2: 16N	NR	Arm 1: 34N Arm 2: 53N	Composite outcome (All-cause mortality, Stroke, Other embolic events, excluding stroke), All-cause mortality, Cardiac mortality, Stroke, Bleeding events, CV hospitalizations, Maintenance of sinus rhythm, Quality of life/functional status
Okcun, 2004[170]	RCT; Inpatient; Europe; Fair	Total N: 154 Arm 1: Rhythm control (amiodarone, electrical cardioversion) (70) Arm 2: Rate control (digoxin or metoprolol) (84)	Arm 1: 61 (SD 10) Arm 2: 58 (SD 12)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 11 mo (SD 7) Arm 2: 13 mo (SD 6)	Persistent AF	NR	Arm 1: 31 (SD 8) Arm 2: 33 (SD 15)	NR	Mixed embolic events including stroke, All-cause mortality, Stroke
Opolski, 2004[171] (HOT CAFÉ) Opolski, 2003[172] Pietrasik, 2007[173] Szulc, 2006[174]	RCT; Outpatient; Europe; Good	Total N: 205 Arm 1: Rate control (101) Arm 2: Rhythm control (104)	Total: 60.8 (SD 11.2) Arm 1: 61.4 (SD 17.6) Arm 2: 60.4 (SD 7.9)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: 273.7 days (SD 112.4) Arm 1: 243.2 days (SD 137.3) Arm 2: 220.4 days (SD 148.6)	Persistent AF	NR	NR	Arm 1: 37.6% Arm 2: 50%	Composite outcome (All-cause mortality, Mixed embolic events including stroke, Bleeding events including hemorrhagic stroke), All-cause mortality, Cardiac mortality, Stroke, Bleeding events, Maintenance of sinus rhythm, Control of ventricular rate, Quality of life/functional status

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Vora, 2004[175] (CRRAFT) Vora, 2004[176]	RCT; Outpatient; Asia; Fair	Total N: 144 Arm 1: Placebo (48) Arm 2: Rhythm control (amiodarone) (48) Arm 3: Rate control (diltiazem, electrical cardioversion) (48)	Total: 38.6 (SD 10.3) Arm 1: 38 Arm 2: 39.5 Arm 3: 38.4	NR	Total: 6.1 yr (SD 5.4)	None	Arm 1: 3N Arm 2: 5N Arm 3: 2N	Arm 1: 56 Arm 2: 55 Arm 3: 56.6	NR	Restoration of sinus rhythm, Maintenance of sinus rhythm, Control of AF symptoms, Heart failure symptoms, Quality of life/functional status, All-cause mortality, Bleeding events
Petrac, 2005[25]	RCT; Outpatient; Europe; Good	Total N: 102 Arm 1: Rate control with AVN ablation and VVI-R pacemaker (52) Arm 2: Rate control with AVN ablation and DDD-R pacemaker and an antiarrhythmic drug (50)	Arm 1: 62 (SD 10) Arm 2: 60 (SD 11)	Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	NR	Persistent AF	Arm 1: 23.1% Arm 2: 12%	NR	Arm 1: 23.1% Arm 2: 16%	Cardiac mortality, Stroke, All-cause mortality, CV hospitalizations, Recurrence of AF, Heart failure symptoms, Myocardial infarction, Composite outcome (Cardiac mortality, Stroke)
Khan, 2008[177] (PABA-CHF)	RCT; Outpatient; NR; Good	Total N: 81 Arm 1: Rhythm control (AF ablation by PVI, transcatheter) (41) Arm 2: Rate control (AVN ablation and PPM) (40)	Arm 1: 60 (SD 8) Arm 2: 61 (SD 8)	Arm 1: 0, 49%, 51% Arm 2: 0, 54%, 46%	Arm 1: 4 yr (SD 2.4) Arm 2: 3.9 yr (SD 2.8)	Heart failure	Total: 100% Arm 1: 100% Arm 2: 100%	Arm 1: 27 (SD 8) Arm 2: 29 (SD 7)	Arm 1: 73% Arm 2: 68%	Composite outcome (Quality of life/functional status), Quality of life/functional status, Maintenance of sinus rhythm

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
Yildiz, 2008[178]	RCT; NR; Europe; Poor	Total N: 221 Arm 1: Rhythm control (155) Arm 2: Rate control (66)	Arm 1: 61 (SD 9) Arm 2: 57 (SD 11)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 11 mo (SD 7) Arm 2: 13 mo (SD 6)	Persistent AF	NR	Arm 1: 60 (SD 11) Arm 2: 63 (SD 9)	NR	Maintenance of sinus rhythm, Mixed embolic events including stroke, Stroke, All-cause mortality, Quality of life/functional status
Shelton, 2009[179] (CAFÉ-II)	RCT; Outpatient; UK; Good	Total N: 61 Arm 1: Rate control (digoxin or beta blockers) (31) Arm 2: Rhythm control (amiodarone, electrical cardioversion) (30)	Total: 72.4 (SD 7.1) Arm 1: 72.7 (SD 8.3) Arm 2: 72 (SD 5.4)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Total: Median 14 mo (IQR, 6 to 32) Arm 1: Median 15 mo (IQR, 8 to 34) Arm 2: Median 14 mo (IQR, 5 to 31)	Heart failure, Persistent AF	Total: 100% Arm 1: 100% Arm 2: 100%	NR	Total: 50% Arm 1: 55% Arm 2: 44%	Quality of life/ Functional status
Talajic, 2010[180] (AF-CHF) Roy, 2008[181]	RCT; Outpatient; US, Canada, S. America, Israel; Good	Total N: 1376 Arm 1: Rhythm control (electrical cardioversion, AAD) (682) Arm 2: Rate control (beta blockers, digoxin) (694)	Arm 1: 66 (SD 11) Arm 2: 67 (SD 11)	Arm 1: 0, 33%, 67% Arm 2: 0, 30%, 70%	NR	Heart failure	Arm 1: 100% Arm 2: 100%	Arm 1: 27 (SD 6) Arm 2: 27 (SD 6)	Arm 1: 48% Arm 2: 48%	Cardiac mortality, All-cause mortality, Heart failure symptoms, Stroke, Composite outcome (All-cause mortality, Heart failure symptoms, Stroke), AF hospital-izations

Study	Study Design; Setting; Location; Quality	Total N; Interventions (N)	Mean Age	Type of AF: (Permanent, Paroxysmal, Persistent)	Mean Duration of AF	Special Popula-tion	HF	Mean LVEF (%)	CAD	Outcomes Assessed
MacDonald, 2011[182]	RCT; Outpatient; UK; Poor	Total N: 41 Arm 1: Rate control (19) Arm 2: Rhythm control (AF ablation by PVI, transcatheter) (22)	Arm 1: 64.4 (SD 8.3) Arm 2: 62.3 (SD 6.7)	Total: 0, 0, 100% Arm 1: 0, 0, 100% Arm 2: 0, 0, 100%	Arm 1: 64 mo (SD 47.6) Arm 2: 44 mo (SD 36.5)	Heart failure, Persistent AF	Arm 1: 100% Arm 2: 100%	Arm 1: 19.6 (SD 5.5) Arm 2: 16.1 (SD 7.1)	Arm 1: 10N Arm 2: 11N	Maintenance of sinus rhythm, Quality of life/ Functional status

Abbreviations: AAD9(s)=antiarrhythmic drug(s); AF=atrial fibrillation; CAD=coronary artery disease; CV=cardiovascular; IQR=interquartile range; KQ=Key Question; LVEF=left ventricular ejection fraction; MI=myocardial infarction; mo=month(s); N=number of patients; NR=not reported; PVI=pulmonary vein isolation; RCT=randomized controlled trial; SD=standard deviation

References to Appendix F

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