



# Effective Health Care Program

Comparative Effectiveness Review  
Number 119

## Treatment of Atrial Fibrillation



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# ***Comparative Effectiveness Review***

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**Number 119**

## **Treatment of Atrial Fibrillation**

**Prepared for:**

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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.

# Executive Summary

## 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.<sup>1</sup> 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).<sup>1</sup>

It is estimated that more than 2.3 million Americans have AF.<sup>2</sup> The prevalence of AF increases with age and approaches 8 percent in patients older than 80 years of age.<sup>3</sup> 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.<sup>1</sup>

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.<sup>4-7</sup> In some patients, AF can severely deprecate quality of life by causing shortness of breath, intractable fatigue, and near-syncope.<sup>8-11</sup> 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.<sup>12</sup> Importantly, when ischemic stroke occurs in patients with AF, it is either fatal or of moderate to high severity in the majority of patients.<sup>13</sup> The management of AF and its complications is responsible for almost \$16 billion in costs to the U.S. health care system each year.<sup>14</sup>

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.<sup>15</sup>

### 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).<sup>14</sup> 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.<sup>14</sup> 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.<sup>16</sup> 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.”<sup>16</sup> This recommendation was based on the results of the Rate Control Efficacy in Permanent Atrial Fibrillation-II (RACE-II) trial,<sup>17</sup> 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.<sup>17</sup> 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).<sup>14</sup> 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.<sup>14,16,18</sup>

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.<sup>19</sup> 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.<sup>20</sup> 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  $\leq 35$  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.<sup>21,22</sup> 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:

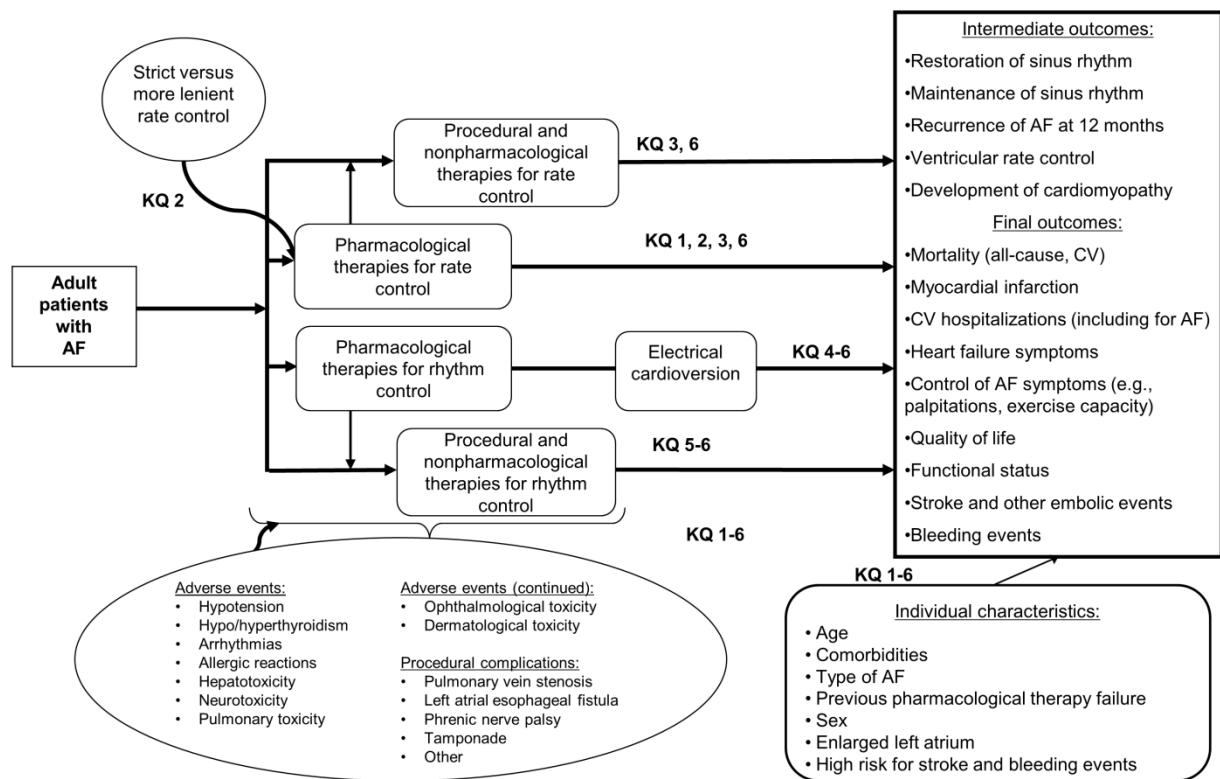
- **KQ 4:** What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?
- **KQ 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).<sup>23</sup>

## 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.<sup>24</sup> 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.<sup>25-27</sup> 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.<sup>23</sup> 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.<sup>23,28</sup> 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.<sup>23,29</sup> 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.

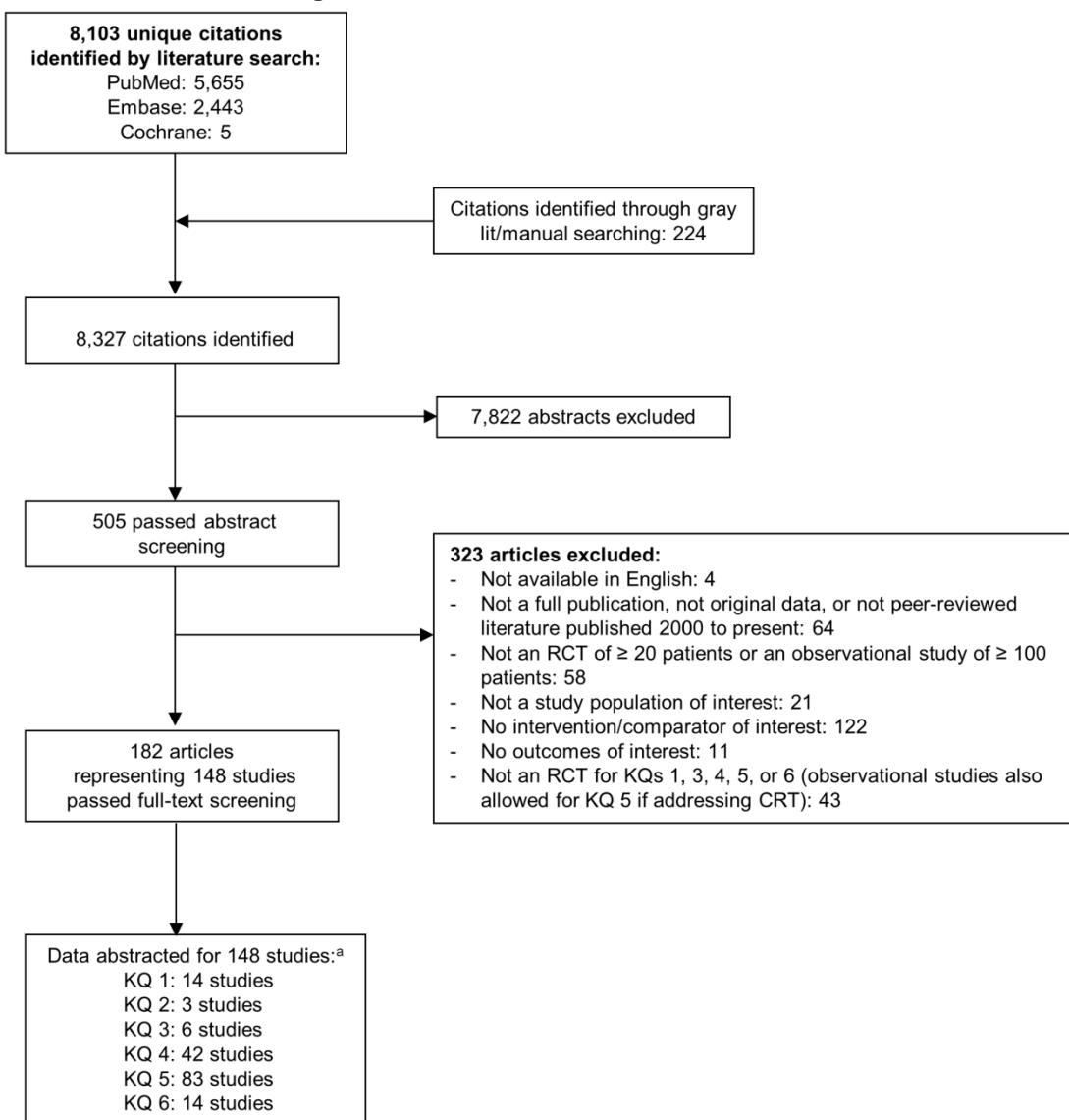
## Results

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**



<sup>a</sup>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 Drugs** Key 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)

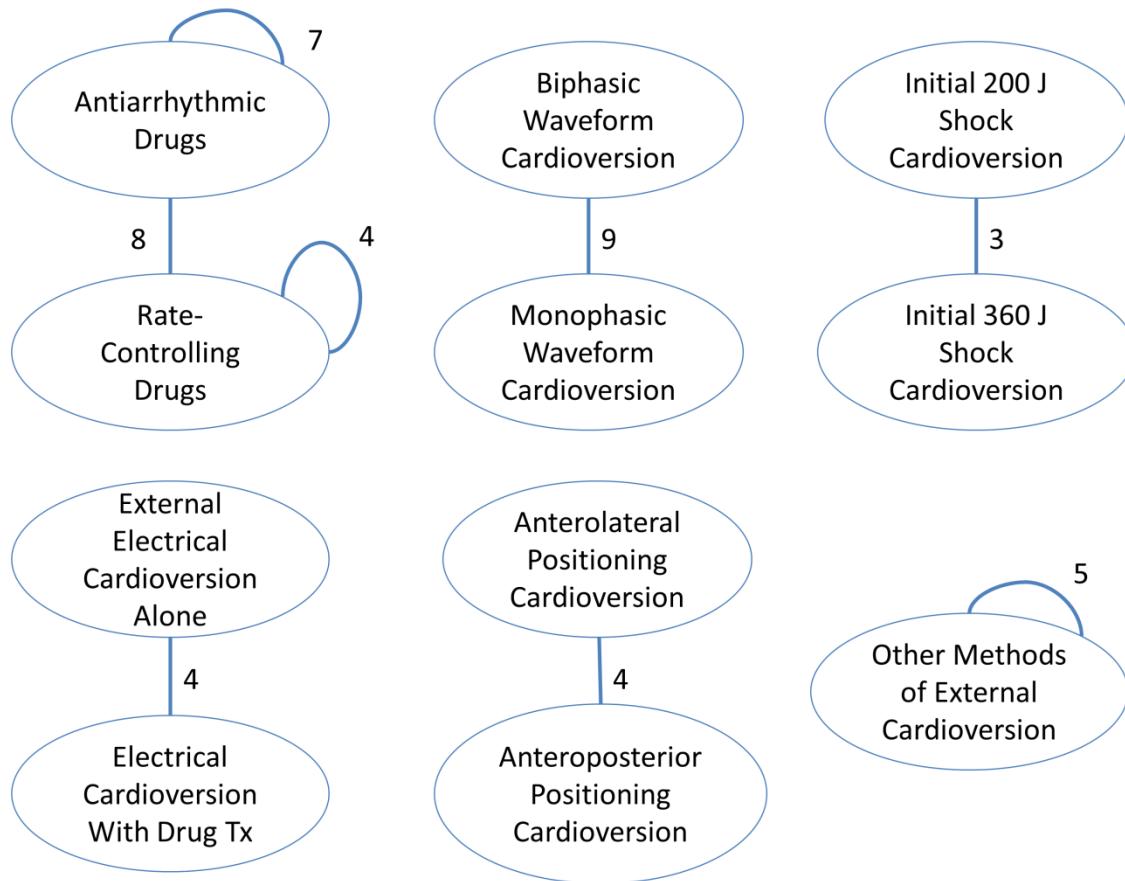
and decrease recurrence of AF (one poor-quality study, 88 patients, low strength of evidence).

- 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

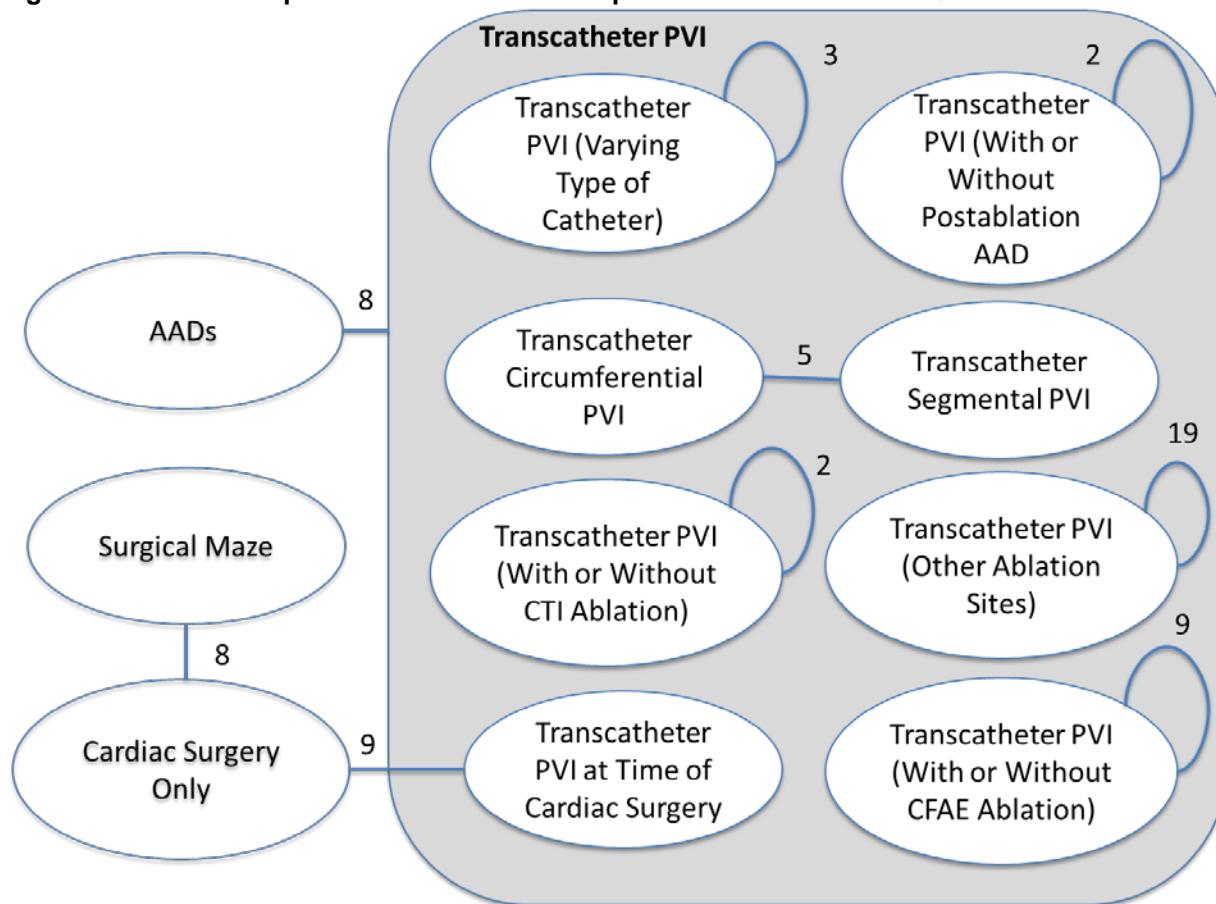
We identified 65 studies enrolling 6,739 patients that evaluated procedures for rhythm control that were relevant to this KQ. All of these studies were RCTs. Thirty-one studies were rated as good quality, 32 as fair quality, and 2 as poor quality.

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 = cavoatrial 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 Hospitalizations	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 hospitalizations 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 Hospitalizations	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)	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 Hospitalizations	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 Hospitalizations	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 = cavoatrial 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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