Rate- and Rhythm-Control Therapies in Patients With Atrial Fibrillation
A Systematic Review

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Background: The comparative effectiveness of treatments for atrial fibrillation (AF) is uncertain.

Purpose: To evaluate the comparative effectiveness of rate- and rhythm-control therapies.

Data Sources: English-language studies in PubMed, EMBASE, and the Cochrane Database of Systematic Reviews between January 2000 and November 2013.

Study Selection: Two reviewers independently screened citations to identify comparative studies that assessed rate- or rhythm-control therapies in patients with AF.

Data Extraction: Reviewers extracted data on study design, participant characteristics, interventions, outcomes, applicability, and quality.

Data Synthesis: 200 articles (162 studies) involving 28,836 patients were included. When pharmacologic rate- and rhythm-control strategies were compared, strength of evidence (SOE) was moderate supporting comparable efficacy with regard to all-cause mortality (odds ratio [OR], 1.34 [95% CI, 0.89 to 2.02]), cardiac mortality (OR, 0.96 [CI, 0.77 to 1.20]), and stroke (OR, 0.99 [CI, 0.76 to 1.30]) in older patients with mild AF symptoms. Few studies compared rate-control therapies and included outcomes of interest, which limited conclusions. For the effect of rhythm-control therapies in reducing AF recurrence, SOE was high favoring pulmonary vein isolation versus antiarrhythmic medications (OR, 5.87 [CI, 3.18 to 10.85]) and the surgical maze procedure (including pulmonary vein isolation) done during other cardiac surgery versus other cardiac surgery alone (OR, 7.94 [CI, 3.63 to 17.36]).

Limitation: Studies were heterogeneous in interventions, populations, settings, and outcomes.

Conclusion: Pharmacologic rate- and rhythm-control strategies have comparable efficacy across outcomes in primarily older patients with mild AF symptoms. Pulmonary vein isolation is better than antiarrhythmic medications at reducing recurrences of AF in younger patients with paroxysmal AF and mild structural heart disease. Future research should address uncertainties related to subgroups of interest and the effect of different therapies on long-term clinical outcomes.

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Atrial fibrillation (AF) is a major public health problem in the United States. More than 2.3 million Americans are estimated to have AF (1). The known association between AF and substantial mortality, morbidity, and health care costs compounds the effect of this condition. Not only is the risk for death in patients with AF twice that of patients without it, but AF can result in myocardial ischemia and infarction, exacerbate heart failure (HF), and cause tachycardia-induced cardiomyopathy if the ventricular rate is not well-controlled (2–5).

The most dreaded complication of AF is thromboembolism, especially stroke (6). In some patients, AF or therapies to manage this condition can severely depreciate quality of life (7–10). Furthermore, the management of AF and its complications is responsible for nearly $16 billion in additional costs to the U.S. health care system per year (11).

Despite the substantial public health effect of AF, uncertainties around its management remain. In particular, the comparative safety and effectiveness of different rate- and rhythm-control therapies for patients with AF are unclear. We conducted this systematic review to evaluate the comparative safety and effectiveness of rate- versus rhythm-control strategies; medications used for ventricular rate control; strict versus more lenient rate-control strategies; nonpharmacologic rate-control therapies versus medications; electrical cardioversion and antiarrhythmic medications for restoration of sinus rhythm; and catheter ablation, surgical ablation, and antiarrhythmic medications for maintenance of sinus rhythm.

Methods

We developed and followed a standard protocol for our review. Full details of our methods, search strategies, results, and conclusions are presented in a comparative effectiveness review commissioned by the Agency for Healthcare Research and Quality (AHRQ) and are available at www.effectivehealthcare.ahrq.gov (12).

Data Sources and Searches

We searched PubMed, EMBASE, and the Cochrane Database of Systematic Reviews for studies published between 1 January 2000 and 12 November 2013. Data be-
fore 2000 have been summarized in an AHRQ report on the management of new-onset AF published in 2001 (13–15).

**Study Selection**

We identified randomized, controlled trials (RCTs) published in English that were comparative assessments of pharmacologic or nonpharmacologic rate- or rhythm-control therapies aimed at treating adults with AF. Observational studies were also allowed for comparisons of strict versus lenient rate control or cardiac resynchronization therapy versus other rhythm-control therapies. The following outcomes were considered: restoration of sinus rhythm (conversion), maintenance of sinus rhythm, recurrence of AF at 12 months, development of cardiomyopathy, death (all-cause and cardiac), myocardial infarction, cardiovascular hospitalizations, HF symptoms, control of AF symptoms, quality of life, functional status, stroke and other embolic events, bleeding events, and adverse effects of therapy.

**Data Extraction and Quality Assessment**

One investigator abstracted and another confirmed data related to study setting and design, patient characteristics, details of treatment, comparators, and relevant outcomes. The quality of individual studies was evaluated using the approach described in AHRQ’s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (16). Investigators also assessed factors that limited applicability of the evidence.

**Data Synthesis and Analysis**

For each treatment comparison and outcome of interest, we determined the feasibility of completing a quantitative synthesis (meta-analysis) based on the volume of relevant literature, conceptual homogeneity of the studies (both in terms of study population and outcomes), and completeness of the reporting of results. We considered meta-analysis for outcomes that at least 3 studies reported.

For our evaluation of rate- versus rhythm-control strategies, we grouped all rate-control strategies together and all rhythm-control strategies together, regardless of the specific medication or procedure. We grouped pharmacologic interventions by class, considering rate-controlling calcium-channel blockers and all β-blockers each to be similar enough to be grouped together. We categorized procedures into electrical cardioversion, atrioventricular node (AVN) ablation, AF ablation by pulmonary vein isolation (PVI) (by open surgical, minimally invasive, or transcatheter procedures), and different types of surgical maze procedures and explored comparisons among these categories. In addition, for the comparisons focusing on medications versus procedures, we also explored grouping all medications together and comparing them with all procedures.

When a meta-analysis was appropriate, we used a random-effects model to synthesize the available evidence quantitatively using Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey). We used a standardized approach to rank the overall strength of evidence (SOE) for each outcome (16).

**Role of the Funding Source**

Primary funding was provided by AHRQ. Neither the technical experts nor AHRQ representatives had a role in the literature search, data analysis, interpretation of the data, or decision to submit the manuscript for publication.

**RESULTS**

We screened 10,495 abstracts, evaluated 570 full-text articles, and included 200 articles representing 162 studies involving 28,836 patients (Figure 1). Tables 1 to 6 of the Supplement (available at www.annals.org) provide details about these studies and their populations for each topic described here. Table 7 of the Supplement lists identified and potential limitations of the studies. The full AHRQ report highlights additional findings (12).

**Rate- Versus Rhythm-Control Strategies**

We included 16 RCTs in this analysis: 13 compared pharmacologic rhythm-control versus rate-control strategies (17–29) and 3 compared a rhythm-control strategy with PVI versus a rate-control strategy that involved AVN ablation and implantation of a pacemaker in 1 study (30) and rate-controlling medications in the other 2 (31, 32).

Ten RCTs (17, 18, 20–22, 24–28) provided information on outcomes of interest and were combined quantitatively (Figure 2). Of these, 5 included only patients with persistent AF (20–22, 25, 28), 1 included only patients with paroxysmal AF (17), and 4 included patients with paroxysmal or persistent AF (18, 24, 26, 27). Two studies (17, 22) compared a single-chamber pacemaker plus AVN ablation versus a dual-chamber pacemaker plus AVN ablation plus an antiarrhythmic medication; all others compared largely unspecified rate-control with rhythm-control strategies.

Data from the included studies showed moderate SOE that pharmacologic rate- and rhythm-control strategies are of comparable efficacy with regard to their effect on all-cause mortality (odds ratio [OR], 1.34 [95% CI, 0.89 to 2.02]; Q = 21.71; P = 0.003) (Figure 2, A) (18, 20–22, 24, 26–28), cardiac mortality (OR, 0.96 [CI, 0.77 to 1.20]; Q = 3.55; P = 0.47) (Figure 2, B) (18, 21, 22, 24, 25), and stroke (OR, 0.99 [CI, 0.76 to 1.30]; Q = 7.02; P = 0.43) (Figure 2, C) (17, 18, 20–22, 24, 27, 28). Although the meta-analysis for all-cause mortality showed a potential benefit, it did not reach statistical significance and 6 of the 8 studies (6069 patients [95%]) had ORs that crossed 1, resulting in a final moderate SOE. For cardiac mortality (Figure 2, B), point estimates were inconsistent and CIs were wide for 2 of the 5 studies (18, 21), but there was no evidence of heterogeneity; therefore, our SOE rating was not affected. For the outcome of stroke, there was no evidence of heterogeneity, but the findings were mostly
Some studies were relevant to more than 1 topic. RCT strategies with rhythm-control strategies using antiarrhythmic medications, which was inconsistent with several of the smaller studies, driven by 1 large, good-quality RCT (4060 patients), which was inconsistent with several of the smaller studies, reducing our confidence in the finding and in the SOE. These studies largely included older patients with mild AF symptoms.

Three RCTs compared pharmacologic rate-control strategies with rhythm-control strategies using antiarrhythmic medications (17, 18, 22). These RCTs showed fewer cardiovascular hospitalizations with the rhythm-control strategies (17, 18, 22). Although data from 5 RCTs suggest that there is no difference between pharmacologic rate- and rhythm-control strategies in their effect on HF symptoms (17, 22, 24, 26, 46) (Table 1), a prespecified substudy of the Atrial Fibrillation and Congestive Heart Failure study showed that a higher proportion of time spent in sinus rhythm was associated with a greater improvement in New York Heart Association class (29).

Three studies compared a rhythm-control strategy involving catheter ablation with a rate-control strategy involving rate-controlling medications (32) or AVN ablation combined with implantation of a pacemaker (30) or rate-controlling medications (31). One study showed that catheter ablation was better than pharmacologic rate control at improving symptoms, neurohormonal status, and objective physiologic exercise capacity (32). Another study showed that PVI isolation was superior to AVN ablation and pacemaker implantation in improving quality of life, 6-minute walk distance, and ejection fraction (30). Another study showed that PVI resulted in long-term restoration of sinus rhythm in only 50% of patients (compared with none in the medical treatment group) and did not improve ejection fraction compared with a rate-control strategy (31).

**Medications for Ventricular Rate Control**

Sixteen RCTs (47–62) assessed the use of medications for ventricular rate control. Of these, 3 included only patients with permanent AF (59, 61, 62), 1 included only patients with paroxysmal AF (52), and 4 included only patients with persistent AF (50, 53, 54, 56). Most studies compared 2 or more of the following medications: a β-blocker, a calcium-channel blocker, digoxin, or amiodarone.

Although we found evidence that reduction of ventricular response during AF in symptomatic patients benefits patients by reducing the risk for tachycardia-induced cardiomyopathy, HF, and MI and by improving quality of life, data were inconclusive as to whether any 1 medication used for ventricular rate control is safer or more effective than the others (Table 2).

**Strict Versus More Lenient Rate-Control Strategies**

Few studies have evaluated the comparative safety and effectiveness of a strict versus more lenient rate-control strategy; these included 1 good-quality RCT (63) in patients with permanent AF and 2 observational studies (64, 65) that were secondary analyses of RCTs. There were no statistically significant differences in all-cause and cardiovascular mortality, HF symptoms, cardiovascular hospitalizations, bleeding events, quality of life, and control of AF symptoms between strict and lenient rate-control strategies, and evidence was limited by the small number of studies and the imprecision of their findings.

**Nonpharmacologic Rate-Control Therapies Versus Medications**

Six RCTs (22, 66–70) evaluated the comparative effectiveness of a procedural intervention versus a primarily pharmacologic intervention for rate control of AF (22, 66,
67, 70) or of 2 procedural interventions, with pharmacologic therapy used in only 1 group (68, 69).

The studies varied in the types of procedures and pharmacologic interventions evaluated. All studies included at least 1 treatment group with radiofrequency ablation or modification of the AVN or His bundle, most often in conjunction with pacemaker placement. The comparison groups included a pharmacologic intervention whose main...
purpose was to control ventricular heart rate and a procedure that involved a pacemaker implant and AVN ablation in some studies.

Four studies reported outcomes related to heart rate control at approximately 1 year. In the 3 studies that compared a procedural intervention with a pharmacologic intervention, the patients in the procedural intervention group had a lower heart rate at 12 months than those receiving the pharmacologic intervention (66, 67, 70). Three studies compared outcomes related to exercise capacity or duration, and none showed significant differences in these outcomes by treatment group of ventricular demand rate-responsive (VVIR) pacing plus His bundle ablation versus VVIR pacing plus a rate-controlling medication or of AVN ablation plus VVIR pacing versus a rate-controlling medication (66, 67, 69).

Three studies reported outcomes related to mortality and cardiovascular events. No significant differences were found by treatment group in a comparison of AVN ablation plus dual-chamber demand rate-responsive pacing and antiarrhythmic therapy versus AVN ablation plus VVIR pacing alone or in a comparison of AVN ablation plus VVIR pacing versus a rate-controlling medication (22, 67, 69).

Electrical Cardioversion and Antiarrhythmic Medications for Restoration of Sinus Rhythm

Forty-four RCTs (33–36, 49, 53, 54, 56, 58, 71–105) assessed the use of antiarrhythmic medications or electrical cardioversion for restoration of sinus rhythm. Four RCTs compared single monophasic waveform with single biphasic waveform for converting AF to sinus rhythm (33–36). All studies were done in patients with persistent AF. Pooling data from these 4 RCTs showed the superiority of a single biphasic waveform over a single monophasic waveform (OR, 4.39 [CI, 2.84 to 6.78]; Q = 2.85; P = 0.42) (Figure 2, D).

Four studies explored the use of anterolateral versus anteroposterior positioning of cardioversion electrodes in patients with persistent AF (75, 82, 86, 99). There was low SOE of no difference in restoration of sinus rhythm.

Few identified studies directly compared similar antiarrhythmic medications. The most frequent comparison was between amiodarone and sotalol, which was evaluated in 4 studies (58, 79, 80, 89) involving patients with paroxysmal or persistent AF. Meta-analysis of these studies showed no statistically significant difference in restoring sinus rhythm (OR, 1.12 [CI, 0.81 to 1.56]) (Table 3).

Catheter Ablation, Surgical Ablation, and Antiarrhythmic Medications for Maintenance of Sinus Rhythm

Ninety studies assessed the comparative safety and effectiveness of new procedural rhythm-control therapies, other nonpharmacologic rhythm-control therapies, and pharmacologic agents for the maintenance of sinus rhythm in patients with AF. We divided these studies into 2 groups by therapy type: procedural and pharmacologic.

Seventy-two RCTs (37–46, 106–167) assessed procedures for rhythm control. Nine RCTs compared transcatheter PVI with antiarrhythmic medications. Of these, 2 included only patients with paroxysmal AF (40, 42), 2 included only patients with persistent AF (39, 45), and 5 included patients with paroxysmal or persistent AF (37, 38, 41, 43, 44). Data from these trials provide high SOE that rhythm control using transcatheter PVI is superior to antiarrhythmic medications in reducing recurrent AF over 12 months of follow-up (OR, 5.87 [CI, 3.18 to 10.85]; Q = 33.82; P < 0.001) (Figure 2, E). This SOE is strongest in younger patients with little to no structural heart
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There was consistent benefit of verapamil or diltiazem compared with digoxin (both *P* < 0.050 across studies) on the maintenance of sinus rhythm. Both studies showed no significant difference between rate- and rhythm-control strategies. Because 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 (OR not reported).

The Appendix Table (available at www.annals.org) presents data on surgical maze procedures (including PVI) at the time of other cardiac surgery. Ten studies evaluated traditional “cut-and-sew” maze procedures versus valvular surgery or coronary artery bypass graft versus valvular surgery or coronary artery bypass graft alone (46, 107, 111, 113, 118, 124, 136, 137, 149, 168). Five studies evaluated traditional “cut-and-sew” maze procedures versus valvular surgery or coronary artery bypass graft alone (127, 138, 142, 146, 154). Four additional studies evaluated unique comparisons (108, 133, 155, 158). Data from 8 RCTs showed high SOE that PVI at the time of other cardiac surgery is superior to cardiac surgery alone in re-

### Table 1. Summary of SOE and Effect Estimates for Rate- Versus Rhythm-Control Strategies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AADs for Rhythm Control vs. Rate Control</th>
<th>PVI for Rhythm Control vs. Rate Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of sinus rhythm</td>
<td>SOE = High (7 studies, 1473 patients)</td>
<td>SOE = Low (2 studies, 122 patients)</td>
</tr>
<tr>
<td></td>
<td>OR, 0.18 (95% CI, 0.11 to 0.28), favoring rhythm-control strategies</td>
<td>Significantly better in rhythm-control strategies (OR not reported)</td>
</tr>
<tr>
<td>Ventricular rate control</td>
<td>SOE = Low (2 studies, 727 patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significantly better in rhythm-control strategies</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>SOE = Moderate (8 studies, 6372 patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR, 1.34 (95% CI, 0.89 to 2.02), demonstrating a potential benefit of a rhythm-control strategy that did not reach statistical significance. Because 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.</td>
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<tr>
<td>CV mortality</td>
<td>SOE = Moderate (5 studies, 2405 patients)</td>
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</tr>
<tr>
<td></td>
<td>OR, 0.96 (95% CI, 0.77 to 1.20), demonstrating no difference between rate- and rhythm-control strategies</td>
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<tr>
<td>Myocardial infarction</td>
<td>SOE = Low (2 studies, 246 patients)</td>
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</tr>
<tr>
<td></td>
<td>Both studies showed no significant difference between rate- and rhythm-control strategies</td>
<td></td>
</tr>
<tr>
<td>CV hospitalizations</td>
<td>SOE = High (3 studies, 439 patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR, 0.25 (95% CI, 0.14 to 0.43), favoring rate-control strategies</td>
<td></td>
</tr>
<tr>
<td>Heart failure symptoms</td>
<td>SOE = Low (6 studies, 2449 patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR, 1.04 (95% CI, 0.79 to 1.35), demonstrating no difference between rate- and rhythm-control strategies</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>SOE = Insufficient (11 studies, 6607 patients)</td>
<td>SOE = Insufficient (2 studies, 122 patients)</td>
</tr>
<tr>
<td>Stroke</td>
<td>SOE = Moderate (8 studies, 6424 patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR, 0.99 (95% CI, 0.76 to 1.30), demonstrating no difference between rate- and rhythm-control strategies</td>
<td></td>
</tr>
<tr>
<td>Mixed embolic events, including stroke</td>
<td>SOE = Low (3 studies, 866 patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR, 1.24 (95% CI, 0.37 to 4.09), demonstrating a potential benefit of rhythm-control strategies that did not reach statistical significance</td>
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<tr>
<td>Bleeding events</td>
<td>SOE = Moderate (5 studies, 5072 patients)</td>
<td></td>
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<tr>
<td></td>
<td>OR, 1.10 (95% CI, 0.87 to 1.38), demonstrating no difference between rate- and rhythm-control strategies</td>
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</tbody>
</table>

AAD = antiarrhythmic drug; CV = cardiovascular; OR = odds ratio; PVI = pulmonary vein isolation; SOE = strength of evidence.

### Table 2. Summary of SOE and Effect Estimates for Medications Used for Ventricular Rate Control

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Ventricular Rate Control</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers vs. digoxin</td>
<td>SOE = Insufficient (1 study, 47 patients)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>β-Blockers vs. calcium-channel blockers</td>
<td>SOE = Insufficient (2 studies, 100 patients)</td>
<td>SOE = Insufficient (1 study, 60 patients)</td>
</tr>
<tr>
<td>β-Blockers vs. calcium-channel blockers in patients taking digoxin</td>
<td>SOE = Insufficient (1 study, 29 patients)</td>
<td>SOE = Insufficient (1 study, 29 patients)</td>
</tr>
<tr>
<td>Sotalol vs. metoprolol in patients taking digoxin</td>
<td>SOE = Insufficient (1 study, 23 patients)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Amiodarone vs. calcium-channel blockers</td>
<td>SOE = Low (3 studies, 271 patients)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Amiodarone is similar to the calcium-channel blocker diltiazem for rate control</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Amiodarone vs. digoxin</td>
<td>SOE = Low (3 studies, 390 patients)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Amiodarone controlled ventricular rate better than digoxin across 2 studies (both <em>P</em> = 0.020) but did not demonstrate a difference in a third study</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Calcium-channel blockers plus digoxin vs. digoxin alone</td>
<td>SOE = Insufficient (1 study, 52 patients)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Calcium-channel blockers vs. digoxin</td>
<td>SOE = High (4 studies, 422 patients)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>There was consistent benefit of verapamil or diltiazem compared with digoxin (<em>P</em> &lt; 0.050 across studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
</tbody>
</table>

SOE = strength of evidence.
Table 3. Summary of SOE and Effect Estimates for Electrical Cardioversion and Antiarrhythmic Medications for Rhythm Control

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Restoration of Sinus Rhythm</th>
<th>Maintenance of Sinus Rhythm</th>
<th>Recurrence of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various methods for external electrical cardioversion:</td>
<td>SOE = High (4 studies, 411 patients) OR, 4.39 (95% CI, 2.84 to 6.78), favoring biphasic waveform</td>
<td>SOE = Insufficient (1 study, 83 patients)</td>
<td>SOE = Low (1 study, 216 patients) No difference</td>
</tr>
<tr>
<td>biphasic vs. monophasic waveforms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various methods for external electrical cardioversion:</td>
<td>SOE = Low (4 studies, 393 patients) Potential benefit of anterolateral electrode placement</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>anterolateral vs. anteroposterior cardioversions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various methods for external electrical cardioversion:</td>
<td>SOE = High (3 studies, 432 patients) OR, 0.16 (95% CI, 0.05 to 0.53), favoring 360- vs. 200-Joule monophasic shock</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>energy protocols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug enhancement of external electrical cardioversion vs. no drug enhancement</td>
<td>SOE = Moderate (2 studies, 218 patients) Significant benefit for patients given ibutilide or metoprolol pretreatment (P) values NR</td>
<td>SOE = Moderate (2 studies, 195 patients) Significant benefit for patients given verapamil or metoprolol pretreatment (P) values of 0.040 and 0.027 in the 2 studies</td>
<td>SOE = Low (1 study, 88 patients) Significant benefit of verapamil pretreatment (P = 0.020)</td>
</tr>
<tr>
<td>Drugs for pharmacologic cardioversion: amiodarone vs. sotalol</td>
<td>SOE = Low (4 studies, 736 patients) OR, 1.12 (95% CI, 0.81 to 1.56), demonstrating a potential benefit of amiodarone that did not reach statistical significance</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Drugs for pharmacologic cardioversion: amiodarone vs. rate-control drugs</td>
<td>SOE = High (7 studies, 613 patients) OR, 2.99 (95% CI, 1.64 to 5.44), demonstrating a significant benefit of amiodarone</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Low (1 study, 152 patients) No difference between amiodarone vs. ibutilide within 24 h</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; NR = not reported; OR = odds ratio; SOE = strength of evidence.

Five studies evaluated the use of 1 or more pharmacologic agent, with external electrical cardioversion as a primary component of the tested intervention (53, 54, 78, 104, 180); 1 compared an antiarrhythmic medication with a rate-controlling medication (sotalol vs. bisoprolol) (179); 1 primarily evaluated the effect of the addition of verapamil to either amiodarone or flecainide (174); 1 compared the effect of 2 \(\beta\)-blockers for maintenance of sinus rhythm after cardioversion (169); and 10 compared 2 or more antiarrhythmic medications (79, 80, 170–173, 175–178).

Amiodarone, sotalol, and propafenone were the most commonly studied antiarrhythmic medications in RCTs assessing the pharmacologic maintenance of sinus rhythm (79, 80, 169–179). Only 1 study, a substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, systematically assessed differences in mortality rates between antiarrhythmic medications and found no statistically significant difference between patients receiving amiodarone versus those receiving sotalol (172). Regarding maintaining sinus rhythm and reducing recurrence of AF, amiodarone was better than sotalol and dronedarone but did not differ from propafenone in the few studies that compared the various medications (low SOE).

**Discussion**

This review of 162 studies involving 28 836 patients has 4 main findings. First, in older patients with mild AF...
symptoms, a pharmacologic rate-control strategy has comparable efficacy to a pharmacologic rhythm-control strategy in terms of its effect on all-cause mortality, cardiac mortality, and stroke. Second, we found few studies comparing different rate-controlling medications and reporting on outcomes of interest. The number of clinical trials comparing different antiarrhythmic medications was also small. Third, PVI is superior to antiarrhythmic medications at reducing AF recurrence in younger patients with no substantial structural heart disease. Fourth, the surgical maze procedure done at the time of other cardiac surgery is superior to cardiac surgery alone at reducing AF recurrence. Although our review of all available data in the literature left several unanswered questions, we provide important information on the rigor of evidence that supports or does not support certain interventions and practices.

We found evidence supporting the comparable effectiveness of pharmacologic rate- and rhythm-control strategies in their effect on all-cause mortality, cardiac mortality, and stroke. As the largest analysis to date addressing this issue to our knowledge, our review provides further confirmation that pharmacologic rate-control strategies are of comparable efficacy to pharmacologic rhythm-control strategies in patients similar to those enrolled in the RCTs (namely, older patients with mild symptoms from AF). Follow-up in the included trials ranged from 4 months to 3.5 years. Although a comparative effectiveness study of population-based administrative databases from Québec, Canada, from 1999 to 2007 also found little difference in mortality rates within 4 years of treatment initiation, mortality rates decreased steadily in the rhythm-control group after 5 years (181).

Our review found a lack of definitive evidence for better rate control with β-blockers compared with verapamil or diltiazem. Amiodarone and diltiazem are similar options for rate control, and the available evidence suggests that amiodarone or verapamil is a better option for rate control than digoxin (47, 53). For patients presenting to the emergency department with AF, metoprolol or diltiazem produces similar results for rate control. However, there is a general lack of information on comparative safety of the agents overall and within specific patient subgroups. Our findings underscore the importance of conducting studies comparing the effectiveness, tolerability, and safety of different β-blockers and in different patient populations.

Although few studies have suggested that lenient rate control may be as good as strict rate control, this finding needs to be confirmed.

Studies that explored the effect of AVN ablation and pacemaker implantation versus AVN blockers on ventricular rate control showed a significantly lower heart rate in patients who had a procedure. Studies of other outcomes found no difference by treatment group or were inconsistent. There is a need for well-designed studies comparing final outcomes in patients receiving rate-controlling medications versus those having rate-controlling procedures.

We found that biphasic waveform cardioversion was superior to monophasic waveform cardioversion. Showing no significant difference in restoration of sinus rhythm with use of anterolateral versus anteroposterior positioning of cardioversion electrodes is important and clinically helpful because health care providers often debate the superiority of 1 positioning of cardioversion electrodes over another. Although data suggest that pretreatment enhances electrical cardioversion in terms of restoration and maintenance of sinus rhythm, our review does not support 1 antiarrhythmic medication as superior to others in such pretreatment. These findings call for studies comparing the effectiveness and safety of medication pretreatments in enhancing restoration of sinus rhythm.

Although additional data are needed on final outcomes, evidence is strong in support of the use of PVI versus antiarrhythmic medications for reducing recurrences of AF in younger patients with paroxysmal AF who have mild structural heart disease or mild left atrial enlargement. These studies mostly examined PVI as second-line therapy. One recent study compared PVI with antiarrhythmic medications as first-line therapy in patients with paroxysmal AF. It found no significant difference in the burden of AF over 2 years (182). More studies are needed on PVI as first-line therapy.

The effect of PVI on final outcomes, including mortality, is being assessed by the ongoing National Heart, Lung, and Blood Institute–funded Catheter Ablation Versus Antiarrhythmic Drug Therapy for AF trial. Less evidence supports the use of PVI versus antiarrhythmic medications in similar types of patients with persistent AF. Unlike previous studies, we found that CFAE ablation in addition to PVI did not increase maintenance of sinus rhythm compared with PVI only. Although it is unclear whether this finding is due to including more patients with persistent AF in our review, the influence of AF type and duration on the effectiveness of CFAE ablation should be considered. Our findings underscore the importance of conducting well-powered and well-designed RCTs to address this issue definitively, especially as it relates to appropriate patient selection for CFAE ablation.

We found that the surgical maze procedure or PVI done at the time of cardiac surgery is superior to cardiac surgery only in reducing AF recurrence over 12 months of follow-up in patients with persistent or permanent AF. However, data on final outcomes, such as all-cause mortality, are largely absent. Therefore, our findings support exploring these interventions further in regard to their effect on final outcomes and in different patient populations.

In RCTs that examined the comparative effectiveness of different antiarrhythmic medications in maintaining sinus rhythm, we found that amiodarone, sotalol, and propafenone were the most frequently studied agents. Amiodarone did not differ from propafenone in the few studies.
that compared these medications. Our findings highlight the importance of future research to compare different antiarrhythmic medications in specific patient populations.

Our review has limitations. By using narrow eligibility criteria, the included studies may not be representative of the full clinical spectrum of patients and settings. Although understanding racial and sex differences in the effectiveness of rhythm control versus rate control is of interest, these data do not exist. Trials of procedures typically use highly selected operators and may not apply to less experienced operators. Our review was limited to English-language publications. In this analysis, we had to rely on the description of the papers’ authors about the techniques that they used and the extent of ablation. Because of the heterogeneity and inherent difficulties in monitoring patients for recurrence of AF, findings related to this outcome should be interpreted with this limitation in mind.

As the largest analysis examining pharmacologic rate versus rhythm control to our knowledge, our review provides confirmation that pharmacologic rate- and rhythm-control strategies are of comparable efficacy in older patients with mild symptoms from AF. Although more data are needed on final outcomes, robust evidence supports the use of PVI versus antiarrhythmic medications for reducing recurrences of AF in younger patients with paroxysmal AF and mild structural heart disease. Uncertainties still exist within specific subgroups of interest, among therapies within each strategic approach, and about the effect of strategies on long-term clinical outcomes. Our review highlights areas for future research needed for clinical decision making in the treatment of AF.

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### Appendix Table. Summary of SOE and Effect Estimates for Procedural Rhythm-Control Therapies

<table>
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<tr>
<th>Treatment Comparison</th>
<th>Restoration of Sinus Rhythm</th>
<th>Maintenance of Sinus Rhythm</th>
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<th>Stroke (and Mixed Embolic Events, Including Stroke)</th>
<th>Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcatheter PVI vs. AADs</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Moderate (2 studies, 268 patients) Both studies demonstrated significant increase in CV hospitalizations in the AAD group vs. PVI AF: SOE = Insufficient (1 study, 249 patients)</td>
<td>SOE = Insufficient (6 studies, 647 patients) Stroke: SOE = Insufficient (1 study, 245 patients) Mixed: SOE = Low (2 studies, 140 patients) No embolic events in either the PVI or AAD group</td>
<td>Stroke: SOE = Insufficient (1 study, 245 patients) Mixed: SOE = Low (2 studies, 140 patients) No embolic events in either the PVI or AAD group</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (1 study, 82 patients) Mixed: SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Transcatheter PVI using different types of ablation catheters</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Low (3 studies, 264 patients) No difference between different types of ablation catheters</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>Stroke: SOE = Insufficient (1 study, 82 patients) Mixed: SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Transcatheter circumferential PVI vs. transcather segmental PVI</td>
<td>SOE = Insufficient (1 study, 80 patients)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
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<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Transcatheter PVI with CFAE ablation vs. without CFAE ablation</td>
<td>SOE = Insufficient (no studies)</td>
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</tr>
<tr>
<td>Transcatheter PVI vs. PV antrum radial linear ablation</td>
<td>SOE = Insufficient (1 study, 86 patients)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
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<td>SOE = Insufficient (no studies)</td>
<td>Stroke: SOE = Insufficient (1 study, 82 patients) Mixed: SOE = Insufficient (no studies)</td>
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</tr>
<tr>
<td>Transcatheter PVI vs. transcather PVI with additional ablation sites other than CTI and CFAE and transcather PVI involving all 4 PVs vs. transcather PVI involving arrhythmogenic PVs only</td>
<td>SOE = Insufficient (2 studies, 384 patients)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>All-cases: SOE = Insufficient (3 studies, 612 patients) Cardiac: SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>Stroke: SOE = Insufficient (1 study, 207 patients) Mixed: SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (1 study, 207 patients)</td>
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</tbody>
</table>
### Appendix Table—Continued

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<tbody>
<tr>
<td>Transcatheter PVI alone vs. transcatheter PVI plus postablation AADs</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (2 studies, 217 patients)</td>
<td>SOE = Insufficient (no studies)</td>
<td>CV: SOE = Insufficient (no studies)</td>
<td>AF: SOE = Low (1 study, 110 patients)</td>
<td>No difference between groups</td>
<td>SOE = Insufficient (no studies)</td>
<td>SOE = Insufficient (no studies)</td>
</tr>
<tr>
<td>Surgical maze (including PVI and mitral valve surgery) or AADs</td>
<td>SOE = High (3 studies, 181 patients)</td>
<td>OR, 12.30 (95% CI, 1.31 to 115.29), demonstrating statistically significant benefit of PVI at time of cardiac surgery</td>
<td>SOE = Insufficient (1 study, 64 patients)</td>
<td>All-cause: SOE = Low (7 studies, 537 patients)</td>
<td>OR, 1.06 (95% CI, 0.44 to 2.55), demonstrating no difference between groups</td>
<td>Cardiac: SOE = Insufficient (1 study, 97 patients)</td>
<td>SOE = Insufficient (no studies)</td>
<td>Stroke: SOE = Moderate (3 studies, 456 patients)</td>
<td>SOE = Insufficient (3 studies, 325 patients)</td>
</tr>
</tbody>
</table>

AAD = antiarrhythmic drug; AF = atrial fibrillation; CFAE = complex fractionated atrial electrogram; CTI = cavotricuspid isthmus; CV = cardiovascular; OR = odds ratio; PV = pulmonary vein; PVI = pulmonary vein isolation; SOE = strength of evidence.