Management of Atrial Fibrillation: Review of the Evidence for the Role of Pharmacologic Therapy, Electrical Cardioversion, and Echocardiography

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Purpose: **This review summarizes the available evidence regarding the efficacy of medications used for ventricular rate control, stroke prevention, acute conversion, and maintenance of sinus rhythm, as well as the efficacy of electrical cardioversion and the use of echocardiography in patients with atrial fibrillation.**

Data Sources: **The Cochrane Collaboration's database of controlled clinical trials and MEDLINE.**

Study Selection: **Primarily randomized, controlled trials of medications.**

Data Extraction: **Paired reviewers obtained data on efficacy and safety. Strength of evidence was assessed.**

Data Synthesis: **Recent clinical trial results showed that most patients with atrial fibrillation have similar outcomes with strategies for controlling ventricular rate compared with strategies for restoring sinus rhythm. For efficacy of primary stroke prevention, compared with placebo, evidence was strong for warfarin and suggestive for aspirin. The evidence for an increased risk for major bleeding was suggestive for warfarin and inconclusive for aspirin. For ventricular rate control, verapamil, diltiazem, atenolol, and metoprolol were qualitatively superior to digoxin and placebo, particularly during exercise. For efficacy of acute conversion, compared with placebo, evidence was strong for ibutilide, flecainide, dofetilide, propafenone, amiodarone, and quinidine. For efficacy of maintenance of sinus rhythm after conversion from atrial fibrillation, evidence was strong for amiodarone, propafenone, disopyramide, and sotalol. Echocardiography was found to be useful in estimating risk for thromboembolism and potentially useful in estimating likelihood of successful cardioversion and maintenance.**

Conclusions: **For several key questions in the pharmacologic management of atrial fibrillation, strong evidence exists to support 1 or more treatment options.**

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Atrial fibrillation is the most common type of arrhythmia in adults, accounting for about one third of hospitalizations for arrhythmia (1). The prevalence increases from less than 1% in persons younger than 60 years of age to more than 8% in those older than 80 years of age (2–6). The incidence ranges from 0.2% per year for men 30 to 39 years of age to 2.3% per year in men 80 to 89 years of age (7, 8). The age-adjusted incidence for women is about half that of men (9).

The cardiac conditions most commonly associated with atrial fibrillation are rheumatic mitral valve disease, coronary artery disease, congestive heart failure, and hypertension (8, 10). Noncardiac causes include hyperthyroidism, hypoxic conditions, surgery, and alcohol intoxication. A predisposing condition exists in more than 90% of cases (5, 11, 12); the remaining cases have what is called *lone atrial fibrillation*. Patients with atrial fibrillation frequently have symptoms of hemodynamic compromise, ranging from irregular palpitations to the more insidious feeling of malaise. They also have an increased risk for thromboembolism. Comparing with age-matched controls, the relative risk for stroke is increased 2- to 7-fold in patients with nonrheumatic atrial fibrillation (3, 8, 13), and the absolute risk for stroke is between 1% and 5% per year, depending on clinical characteristics (3, 12, 14–16).

Quality of life is an important consideration for patients. Paroxysmal atrial fibrillation disrupts the lives of patients (17), but this perception may not be associated with frequency or duration of symptoms. Warfarin therapy affects quality of life because of frequent blood testing and recommendations for limiting some activities. Gage and colleagues (18) found that atrial fibrillation decreases utility, a quantitative assessment of quality of life used in decision analysis, by 1.3%. Protheroe and associates (19) found that only 61% of patients would prefer anticoagulation to no treatment, considerably fewer than those for whom guidelines would recommend treatment. Little is known about the direct effects of antiarrhythmic therapy and rate-control therapy on quality of life.

The American College of Cardiology/American Heart Association/European Society of Cardiology Task Force on Clinical Guidelines for the Management of Atrial Fibrillation classified atrial fibrillation into 4 types (20): first detected episode, paroxysmal (terminates spontaneously), persistent (electrical or pharmacologic termination necessary), and permanent (resistant to electrical or pharmacologic conversion or accepted by the physician).

The purpose of this review was to summarize the evidence that was available during formulation of the guidelines developed by the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) for management of adult patients with nonpostoperative atrial fibrillation. The foundation of this background paper was a systematic review of the pharmacologic management of atrial fibrillation that examined the efficacy of medications used for stroke prevention, ventricular rate control, acute conversion, and maintenance of sinus rhythm, as well as the role of echocardiography in guiding

pharmacologic therapy (21). For this updated version of the systematic review, we considered observational data, consensus statements, decision analyses, and relevant guidelines. This review focused on the evaluation and pharmacologic management of adult patients with nonpostoperative atrial fibrillation. The rapidly advancing field of nonpharmacologic management of atrial fibrillation is outside the scope of this paper.

Methods

A full description of the methods used in the systematic review can be found in a detailed evidence report (21). A brief description of these methods and additional methods specific to this article are given below.

Literature Identification

Whenever possible, we focused our searches for relevant evidence on the strongest study design: randomized, controlled trials (RCTs). For our previous systematic review, we identified controlled trials in the CENTRAL database produced by the Cochrane Collaboration's international efforts, searched MEDLINE from 1966 to 1998 for citations tagged as "randomized controlled trial" or "controlled clinical trial," searched the PubMed "Related Articles" feature, reviewed hand searches submitted to the Baltimore Cochrane Center, scanned the reference lists in relevant publications, and scanned the table of contents of relevant journals. For the current review, we also searched MEDLINE from May 1998 through September 2001 (using the same search terms as in the original review plus terms to identify meta-analyses and decision analyses). For topics without sufficient RCTs, we used observational data, consensus statements, review articles, and decision analyses obtained from our search of MEDLINE from 1966 through September 2001. Although we had to use September 2001 as a cutoff for the systematic searching of the literature in order to generate a report for the ACP–AAFP Guideline group, we included selected studies published after September 2001 on the basis of input from the group.

Article Review Process

Studies were eligible for review if they were randomized trials of adult patients that addressed the management of nonpostoperative atrial fibrillation. In the previous systematic review, 521 citations were identified and 179 articles were eligible for detailed review. The updated search yielded 29 additional articles that met our inclusion criteria.

Statistical Analysis

For the quantitative analysis, we stratified the data to obtain an effect measure for each drug. We used Stata, version 7.0 (Stata Corp., College Station, Texas) to calculate the odds ratio (OR) of success of the drug compared with placebo. Respective 95% CIs and P values were also calculated. We used ORs because they provide less heterogeneity of study results than relative risk ratio. Estimates of the relative rates of the outcomes of interest were pooled by using standard methods for combining the OR for the outcomes of conversion to sinus rhythm, maintenance of sinus rhythm, stroke, peripheral embolism, major bleeding, minor bleeding, and death (21). Studies were weighted on the basis of the precision of the estimate within each study. When no heterogeneity was found, meta-analyses used the fixed-effects model (Mantel–Haenszel method for pooling) (22). When heterogeneity was found, the random-effects model was used (DerSimonian and Laird method of pooling) (23). An OR was considered significantly different from 1 if the P value was less than 0.05. Statistical strength of evidence was categorized as strong ($P \leq 0.01$), moderate ($0.01 < P \leq 0.05$), suggestive ($0.05 < P \leq 0.2$), or inconclusive ($P > 0.2$).

Role of the Funding Sources

The initial systematic review was funded through a contract with the Agency for Healthcare Research and Quality (21). Subsequent work was supported by the American College of Physicians. Drafts of the manuscript were reviewed by members of the ACP/AAFP guidelines committee for management of atrial fibrillation.

Data Synthesis

Does Aggressive Rhythm Control Improve Mortality and Morbidity Compared with Rate Control?

Although the relative benefits and risks of rate versus rhythm control are of paramount importance in the management of atrial fibrillation, studies directly addressed this issue only recently. By far the largest, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial was a multicenter RCT that enrolled 4060 patients from more than 200 sites in Canada and the United States (24). Eligibility criteria included documented atrial fibrillation lasting at least 6 hours and at least 1 risk factor for stroke (age >65 years, hypertension, diabetes mellitus, previous stroke, and poor ventricular function). Average age was 70 years. Sixty-one percent of patients were men, 89% were white, 71% had hypertension, 38% had coronary artery disease, and 18% had had failure of antiarrhythmic therapy. After patients were randomly assigned to the rhythm-control or rate-control group, physicians could choose from a list of pharmacologic and nonpharmacologic therapies. Although anticoagulation was continued indefinitely for the rate-control group, discontinuation of anticoagulation was permitted at 1 month or later following conversion in the rhythm-control arm. The mortality rate at 5 years was 23.8% in the rhythm-control group and 21.3% in the rate-control group (hazard ratio, 1.15 [95% CI, 0.99 to 1.34]; $P = 0.08$). Combined central nervous system ischemic strokes and hemorrhagic events occurred in 8.9% of patients in the rhythm-control group and 7.4% of patients in the rate-control group ($P > 0.2$). Eighty-five patients in the rhythm-control group and 79 in the rate-control group had strokes ($P > 0.2$). Of

note, more than 70% of the strokes in both groups occurred in patients who had stopped taking anticoagulant therapy or who had an international normalized ratio less than 2.0. Preliminary analyses of other secondary end points, including quality of life and functional capacity, did not show statistical difference between treatment groups. However, more hospitalizations occurred in the rhythm-control group.

A smaller study conducted in the Netherlands, the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study (25), randomly assigned 522 patients to aggressive rhythm control or rate control only. Mean age was 68 years. Sixty-four percent were men, 49% had hypertension, and 27% had coronary artery disease. The primary composite end point of cardiovascular mortality, heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe side effects of antiarrhythmic drugs occurred in 17.2% of patients in the rate-control group and in 22.6% of patients in the rhythm-control group over a mean of 2.3 years. Thus, rate control was not inferior to rhythm control in this group. In subgroup analysis, the potential benefit of the rate-control strategy was seen only in patients with hypertension; fewer primary end points occurred in the rate-control group (17%) than in the rhythm-control group (31%). Rates were similar for those without hypertension (17% and 13%, respectively).

Another small study, the Pharmacological Intervention in Atrial Fibrillation trial (PIAF), recruited 252 patients with new-onset or permanent symptomatic atrial fibrillation (26). One group of 125 patients received rate control with diltiazem. The other group of 127 patients was aggressively converted from atrial fibrillation, many times if necessary, and received amiodarone to maintain sinus rhythm. Although distance achieved on a 6-minute walking test was improved in the rhythm-control group, relief of atrial fibrillation–related symptoms was similar in both groups. The results indicated that in a patient with atrial fibrillation, controlling ventricular rate could be equivalent to the costly and difficult task of maintaining sinus rhythm.

The pilot study Strategies of Treatment of Atrial Fibrillation (STAF), which has been presented but not yet published, was performed in 11 centers in Germany and included 200 patients with atrial fibrillation. Patients were randomly assigned into 2 groups: short-term anticoagulation after attempted conversion, with antiarrhythmic therapy to prevent atrial fibrillation recurrence, or long-term anticoagulation and rate control. After 19.6 months of follow-up, the annual incidence of death, stroke, transient ischemic attack, cardiopulmonary resuscitation, or thromboembolism was 5.5% in the rhythm-control group and 6.1% in the rate-control group ($P > 0.2$). Only 40% of the patients in the rhythm-control group maintained sinus rhythm at 1 year despite aggressive attempts. Even in the rhythm-control group, all thromboembolic end points occurred in patients while they were in atrial fibrillation.

A meta-analysis of these data was not performed because of the overwhelming influence the AFFIRM trial would exert given its large size compared with other trials. However, all the trials consistently showed no improvement in mortality or morbidity by aggressively controlling rhythm. Certainly, there are subgroups in which an aggressive strategy may be warranted, particularly in combination with aggressive anticoagulation. However, the evidence indicates that a strategy of rate control with antithrombotic therapy is as effective as strategies for rhythm control in many if not most patients with atrial fibrillation.

Anticoagulation

What Is the Evidence for Anticoagulating Patients in Chronic Atrial Fibrillation?

We identified 16 studies for inclusion in our analysis. Eleven (27–37) were reported in our previous systematic review (21). Three additional studies (38–40) were reported in a Cochrane Library review (41), and 1 was reported in a previous meta-analysis (42). For the current review, we identified 1 additional study (43).

All of the studies excluded patients with rheumatic valvular disease, for whom there is strong evidence that anticoagulation is indicated. Three trials were secondary prevention trials, enrolling patients who had already had a stroke or transient ischemic attack (28, 33, 43). The results of these studies were evaluated separately from those of the primary prevention studies. The Stroke Prevention in Atrial Fibrillation (SPAF) III investigators specifically recruited high-risk patients (31), and no trial specifically recruited patients at low risk for events. Several of the studies were terminated prematurely because of early proof of efficacy (27, 29, 31, 32, 37, 43) or publication of relevant results from other trials (33).

Figure 1 illustrates the absolute rates of stroke and hemorrhage for trials comparing warfarin or aspirin with control. In pooled analysis, warfarin was more efficacious than placebo for primary stroke prevention (OR, 0.31 [CI, 0.19 to 0.50]; $P < 0.001$), although suggestive evidence indicated that warfarin increased major bleeding (OR, 1.88 [CI, 0.88 to 4.00]; $P = 0.10$) (**Table 1**). The evidence from studies comparing aspirin with placebo suggested that stroke prevention was better with aspirin (OR, 0.68 [CI, 0.46 to 1.02]; $P = 0.06$); however, the evidence was inconclusive regarding the risk for major bleeding (OR, 0.82 [CI, 0.37 to 1.78]; $P > 0.2$). In direct comparison, moderate evidence indicated that fewer strokes occurred among patients taking warfarin than among those taking aspirin (OR, 0.66 [CI, 0.45 to 0.99]; $P = 0.04$), but evidence regarding bleeding risk was inconclusive (OR, 1.61 [CI, 0.75 to 3.44]; $P > 0.2$).

In general, the evidence did not support the use of low-dose warfarin over several other treatments. Evidence suggested improved efficacy for stroke prevention with

conventional-dose warfarin compared with low-dose warfarin whether the low-dose warfarin was given alone (OR, 0.52 [CI, 0.25 to 1.08]; $P = 0.08$) or combined with aspirin (OR, 0.44 [CI, 0.14 to 1.39]; $P = 0.16$). Evidence suggested increased bleeding risk with conventional-dose warfarin compared with low-dose warfarin alone (OR, 2.21 [CI, 0.67 to 7.25]; $P = 0.19$); however, the risk was not conclusively different when compared with low-dose warfarin combined with aspirin (OR, 1.14 [CI, 0.55 to 2.36]; $P > 0.2$). In the only study that compared low-dose warfarin with aspirin, the evidence was inconclusive regarding warfarin's efficacy (OR, 1.01 [CI, 0.49 to 2.06]; $P > 0.2$) and its bleeding risk (OR, 1.04 [CI, 0.43 to 2.48]; $P > 0.2$) (38).

For secondary prevention, we identified 2 trials evaluating warfarin or aspirin (28, 43). In 1 trial, patients were stratified by their eligibility for warfarin therapy (28). Criteria for ineligibility included chronic controlled or poorly controlled hypertension, chronic alcoholism, hemorrhagic retinopathy, previous intracranial hemorrhage, and poor compliance. Among the warfarin-eligible patients, warfarin was found to be more efficacious for stroke prevention (OR, 0.38 [CI, 0.22 to 0.66]; $P = 0.001$) but led to more episodes of major bleeding (OR, 4.1 [CI, 1.2 to 14]; $P = 0.029$) than placebo. For the warfarin-ineligible patients, no difference in efficacy (OR, 0.91 [CI, 0.66 to 1.3]; $P > 0.2$) or bleeding risk (OR, 1.4 [CI, 0.39 to 5.0]; $P > 0.2$) was demonstrated when aspirin was compared with placebo. Thus, the conclusions from this trial on secondary stroke prevention were consistent with those from the trials on primary prevention.

The other secondary prevention trial evaluated 2 intensities of warfarin anticoagulation (43). This trial was stopped early because the risk for major bleeding was found to be higher in the conventional-intensity warfarin group (international normalized ratio, 2.2 to 3.5) than in the low-intensity group (international normalized ratio, 1.5 to 2.1) (OR, 14.2 [CI, 0.78 to 257]; $P = 0.07$). The evidence for the efficacy of warfarin in ischemic stroke prevention was inconclusive (OR, 0.55 [CI, 0.5 to 6.2]; $P > 0.2$). The low number of participants in this trial precluded definitive conclusions.

Minimal data existed for the use of other antithrombotic regimens. In a single study (34), evidence was inconclusive regarding stroke risk for patients taking low-molecular-weight heparin compared with those receiving placebo (OR, 0.38 [CI, 0.072 to 2.0]; $P > 0.2$). In this small study, neither group had any major hemorrhagic events. In the single study comparing warfarin with indobufen for secondary stroke prevention, evidence suggested that warfarin decreased risk for recurrent stroke (OR, 0.57 [CI, 0.27 to 1.2]; $P = 0.15$) and increased bleeding risk (OR, 5.1 [CI, 0.59 to 44]; $P = 0.14$) (35).

We conclude that while insufficient evidence exists to support the use of low-dose warfarin, low-molecular-weight heparin, or newer antiplatelet agents to manage atrial fibrillation, evidence is sufficient to support the use of warfarin or aspirin, depending on patients' risks for stroke and bleeding. The evidence strongly supports the use of warfarin in patients with atrial fibrillation who have average or greater risk for stroke, unless there is a specific increased risk for bleeding. For patients with atrial fibrillation who have a lower risk for stroke, the evidence suggests that aspirin may be useful. For perspective, if a patient's baseline risk for stroke is 45 per 1000 patient-years, warfarin compared with placebo could prevent 30 strokes at the expense of only 6 additional major bleeding episodes. At that same stroke risk, aspirin compared with placebo could prevent 17 strokes without increasing the number of major

Figure 1. **Absolute rates of stroke and hemorrhage for trials comparing warfarin or aspirin with control.**

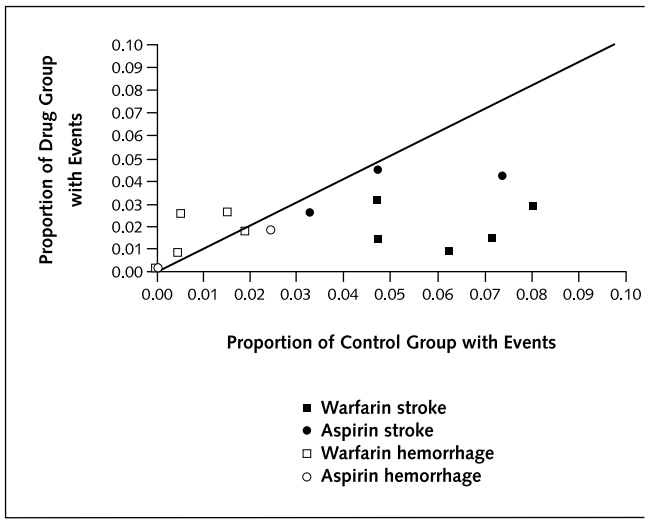


Table 1. **Meta-Analysis of Primary Prevention of Stroke in Atrial Fibrillation**

Comparison	Studies, *n*	Stroke		Major Bleeding	
		Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Conventional-dose warfarin vs. placebo	5	0.31 (0.19–0.50)	<0.001	1.88 (0.88–4.00)	0.10
Aspirin vs. placebo	3	0.68 (0.46–1.02)	0.06	0.82 (0.37–1.78)	>0.2
Conventional-dose warfarin vs. aspirin	5	0.66 (0.45–0.99)	0.04	1.61 (0.75–3.44)	>0.2
Conventional-dose warfarin vs. low-dose warfarin	3	0.52 (0.25–1.08)	0.08	2.21 (0.67–7.25)	0.19
Conventional-dose warfarin vs. low-dose warfarin with aspirin	2	0.44 (0.14–1.39)	0.16	1.14 (0.55–2.36)	>0.2
Low-dose warfarin vs. aspirin	1	1.01 (0.49–2.06)	>0.2	1.04 (0.43–2.48)	>0.2

hemorrhages. In patients with a lower risk for stroke, the absolute reduction in stroke rate with warfarin may not offset an increased risk for major bleeding.

What Is the Role of Transthoracic and Transesophageal Echocardiography in Identifying Patients in Permanent Atrial Fibrillation Who Should Receive Anticoagulation?

In our systematic review, we found no RCTs that directly assessed strategies for identifying appropriate candidates for antithrombotic therapy. However, indirect evidence is available from data in a few trials that were designed to address other questions. In the SPAF study, both left ventricular function and size of the left atrium on transthoracic echocardiography were independent predictors of thromboembolism (44). A strategy of stratification of thromboembolic risk including these 2 echocardiographic variables would alter therapy in 18% of the entire cohort and in 38% of those without clinical risk factors, compared with clinical risk factor stratification alone. In another study, investigators pooled individual patient results from 3 trials and showed that abnormal left ventricular function in otherwise low-risk patients increased the risk for stroke from 0.4% per year to 9.3% per year (45). In patients with high risk for stroke, abnormal left ventricular function increased the risk for stroke from 4.4% per year to greater than 15% per year. In contrast, left atrial size on M-mode echocardiography did not predict stroke.

Transesophageal echocardiography has been shown to identify features correlating with high thromboembolic risk, including left atrial thrombus (46–49), left atrial appendage size (47), left atrial appendage peak velocities (48, 49), spontaneous echocardiographic contrast (often called "smoke") (47, 50, 51), left ventricular dysfunction (50), left ventricular hypertrophy (50), and complex aortic plaque (47–50). The SPAF III trial prospectively assessed the ability of transesophageal echocardiography to stratify patients with atrial fibrillation by risk (48). Independent risk factors for stroke included complex aortic plaque and left atrial abnormality, such as thrombus in the left atrial appendage, spontaneous echocardiographic contrast in the left atrium or left atrial appendage, or peak antegrade flow from the left atrial appendage. The stroke rates were 1.3% per year if neither risk factor was present, 7.8% per year if a left atrial abnormality was present, 12.0% per year if a complex aortic plaque was present, and 20.5% per year if both were present. Thus, transthoracic echocardiography can be used to stratify patients by risk on the basis of left ventricular function. Transesophageal echocardiography can also stratify patients by risk on the basis of left atrial abnormalities and aortic plaque.

Rate Control

What Is the Efficacy of Each Agent in the Control of Ventricular Rate in Atrial Fibrillation?

Our systematic review identified 54 trials assessing 17 agents used for rate control in atrial fibrillation (21). We concentrated on studies evaluating digoxin, calcium-channel blockers, and β-blockers. Methods and outcome measures of these studies were deemed too heterogeneous for a quantitative summary. Main outcome measures included mean heart rate at rest, maximum heart rate with exercise, and distance or time walked on an exercise test. In addition to the heterogeneity of outcome measures, 2 other methodologic considerations were noted: The studies were small, ranging from 6 to 239 patients, and follow-up varied, ranging from 15 minutes to 8 weeks.

Comparisons of digoxin with placebo were inconsistent, particularly when tests were done during exercise (52–58). The nondihydropyridine calcium-channel blockers diltiazem and verapamil were effective compared with placebo (52, 59–65) or digoxin (64–72) in reducing the ventricular rate both at rest and during exercise in patients with atrial fibrillation. The efficacy of β-blockers in the control of resting ventricular rate was agent specific. Atenolol (64, 72, 73), metoprolol (70), timolol (74), pindolol (73), and nadolol (75) were effective. The evidence on xamoterol (58, 60, 64, 76) was inconsistent. Celiprolol (77, 78) and labetalol (54) were ineffective. However, all β-blockers tested were more effective than placebo in controlling ventricular rate during exercise in patients with atrial fibrillation (54, 58, 63, 64, 70, 77, 78). Of note, the evidence on exercise tolerance in patients taking β-blockers compared with those taking placebo was inconsistent, indicating increased (58, 65, 70), decreased (74, 78), or similar (63) exercise tolerance. Combination therapy with digoxin–diltiazem (52, 57, 79–81), digoxin–verapamil (69, 82–85), digoxin–xamoterol (76), digoxin–nadolol (86), and digoxin–betaxolol (57, 79) was effective both at rest and with exercise. Labetalol, even in combination with digoxin, was ineffective at rest but effective with exercise (54). Other studies compared less common agents or were not placebo-controlled trials (87–101).

The side effects of rate-control agents were reported inconsistently. Most studies reported having a single patient or no patients with side effects. However, in 1 study, 3 of 14 patients given diltiazem experienced clinically significant side effects, including chest pain, dyspnea, and edema (52). In another, 3 of 18 patients receiving verapamil required drug withdrawal for liver toxicity or pneumonia (60). In a third study, 5 of 15 patients receiving atenolol required drug withdrawal, but the reasons were not given (62). Finally, 1 trial stopped digoxin therapy in 2 of 117 patients because of clinically significant arrhythmias (56). Since congestive heart failure was an exclusion criterion in many of the studies, the side effect profile in patients with congestive heart failure was not directly addressed.

Thus, the nondihydropyridine calcium-channel blockers, such as verapamil or diltiazem, and β-blockers, such as atenolol and metoprolol, have been shown to control ventricular rate at rest and with exercise. Although patients' ability to tolerate these medications must be considered,

both drug classes seem to have superior efficacy compared with digoxin. The evidence suggests that adding digoxin to a nondihydropyridine calcium-channel blocker or a β-blocker may provide additional benefit over either drug alone.

Acute Conversion

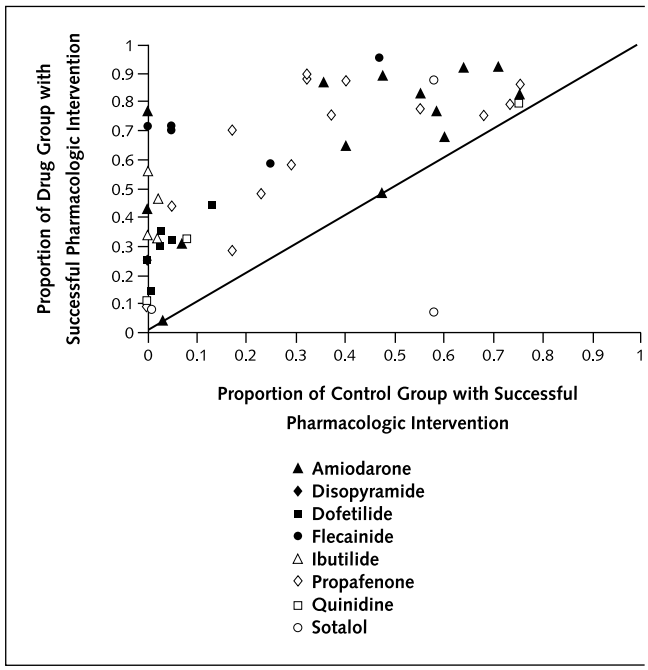
What Is the Efficacy of Antiarrhythmic Agents Used for Acute Conversion of Atrial Fibrillation to Sinus Rhythm?

Our meta-analysis included 60 randomized clinical trials evaluating the use of 8 antiarrhythmic agents for acute conversion of nonpostoperative atrial fibrillation (21, 102). Because digoxin lacked efficacy compared with placebo (53, 55, 56) and β-blockers and calcium-channel blockers were not definitely proven to be superior to placebo, studies that involved these agents or placebo were treated as having control arms. The studies evaluated heterogeneous patient samples, reflected by the conversion rates in the control groups, which ranged from 0% to 76%. Thus, the difference in absolute conversion rates among different antiarrhythmic agents is difficult to determine across studies.

Figure 2 illustrates the absolute rates of conversion for the 43 studies with control arms. In pooled analyses, we found strong evidence of efficacy for acute conversion of atrial fibrillation compared with controls for ibutilide (103–106), flecainide (94, 107–110), dofetilide (111–116), propafenone (94, 101, 117–130), and amiodarone (109, 112, 125, 128, 131–141), with moderate evidence for quinidine (94, 123) (**Table 2**). Insufficient evidence of efficacy was found for disopyramide (92) and sotalol (135, 142, 143).

When we included 5 studies that also contained control arms, 22 studies directly compared antiarrhythmic agents. Because few studies had identical comparisons and most studies were small, the ability to construct a hierarchical order of efficacy was limited. However, the general tendency of the results paralleled those of the meta-analysis of studies with control arms. The evidence showed greater efficacy for flecainide compared with propafenone (OR, 3.5 [CI, 1.8 to 6.7]; $P < 0.01$) (94, 144, 145), sotalol

Figure 2. **Proportions of patients who had successful pharmacologic intervention.**



(OR, 3.5 [CI, 1.4 to 9.1]; $P = 0.002$) (146), and procainamide (OR, 7.4 [CI, 1.7 to 42.9]; $P < 0.01$) (147). Similarly, ibutilide was more efficacious than sotalol (OR, 13.7 [CI, 5.8 to 35.4]; $P < 0.01$) (148) and procainamide (OR, 6.2 [CI, 2.5 to 15.8]; $P < 0.01$) (149). In other studies, propafenone was more efficacious than amiodarone (OR, 13.1 [CI, 2.1 to 79.6]; $P < 0.002$) (150), amiodarone was more efficacious than quinidine (OR, 4.5 [CI, 1.2 to 17.4]; $P < 0.02$) (99), and quinidine was more efficacious than sotalol (OR, 5.8 [CI, 2.4 to 14.2]; $P < 0.01$) (151, 152).

Three methodologic problems were noted in these studies. First, the studies were small, ranging from 11 to 239 patients. Second, the follow-up was short, usually less

Table 2. **Pooled Results for the Efficacy and Adverse Effects of Drugs Used in Acute Conversion of Atrial Fibrillation**

Level of Evidence	Drug	Trials with Control Group				Range of Sustained Ventricular Arrhythmia in All Trials that Reported Side Effects
		Trials	Patients in Drug Group	Odds Ratio of Conversion Compared with Control (95% CI)*	*P* Value	
		n				%
Strong	Ibutilide	4	552	30.7 (10.9–86)	<0.01	0–9
	Flecainide	5	128	13.2 (6.4–27.4)	<0.01	0–2
	Dofetilide	6	716	6.7 (4.5–10)	<0.01	1–12
	Propafenone	14	680	3.9 (2.3–6.8)	<0.01	0–2
	Amiodarone	15	484	3.2 (2.5–5.1)	<0.01	0
Moderate	Quinidine	3	99	2.9 (1.2–6.9)	0.02	0–12
Inconclusive	Disopyramide	1	13	7.0 (0.3–153)	0.10	Not reported
	Sotalol	3	115	1.1 (0.1–6.9)	>0.2	0–2

* Control indicates placebo, calcium-channel blockers, β-blockers, or digoxin.

than 24 hours. Third, the duration of atrial fibrillation was variable. Some studies required an upper limit for duration as short as 24 hours, while other studies had no upper limit. These last 2 factors accounted for much of the heterogeneity of spontaneous conversion; the studies in which patients had shorter duration of atrial fibrillation and were followed for longer periods were more likely to have high spontaneous conversion rates. In the limited subgroup analyses possible, relative efficacy of the antiarrhythmic agents did not differ on the basis of duration of atrial fibrillation or length of follow-up.

What Is the Safety of Antiarrhythmic Therapy for Conversion of Atrial Fibrillation?

The major concern with starting antiarrhythmic therapy for atrial fibrillation is the potential to induce polymorphic ventricular tachycardia, often called torsades de pointes. The precise mechanism of induction of this arrhythmia is not clear, but it is associated with a marked prolongation of the cardiac action potential, which can be measured by the QT interval on the electrocardiogram (153). However, different agents can prolong the QT interval to similar degrees with different risks for torsades de pointes. The risk for torsades de pointes increases for patients with structural heart disease, hypokalemia, and bradycardia (153, 154).

Estimating the risk for ventricular arrhythmia is particularly important in deciding whether to initiate antiarrhythmic therapy under close inpatient monitoring or on an outpatient basis. Two studies investigating this question found the greatest incidence of arrhythmia within the first 24 hours (155) or 3 days (156) of therapy. Most patients in these studies had structural heart disease. Another study followed 172 patients, 82% of whom had normal ejection fractions; the researchers found no cases of significant arrhythmia in the first 4 days of therapy (157). Thus, current recommendations include a 1- to 3-day inpatient observation period after starting most antiarrhythmic agents for patients with atrial fibrillation (155, 156). Two exceptions were noted in a recent guideline (156): First, amiodarone can usually be given safely on an outpatient basis, and second, outpatient initiation of sotalol and disopyramide may be reasonable in patients without structural heart disease (left ventricular ejection fraction ≤ 0.45, coronary artery disease, valvular heart disease, or left ventricular hypertrophy), abnormal conduction system (sick sinus syndrome, atrioventricular conduction disturbances, or bundle-branch blocks), or long QT.

In our systematic review of RCTs, only 39 of the 60 clinical trials on the pharmacologic conversion of atrial fibrillation reported the incidence of ventricular arrhythmia, limiting the usefulness of these data (**Table 2**). Of those reported, no ventricular arrhythmias occurred with amiodarone (110, 125, 126, 128, 135–141, 147, 150, 158) or procainamide (149). The incidence was 3% or less for flecainide (94, 110, 124, 145–147, 159), propafenone (94, 117, 122, 126, 128, 136, 145, 150, 158), and sotalol (143, 146). Ventricular arrhythmias were noted in up to 9% of patients with ibutilide (104–106, 148, 149), and up to 12% of patients for quinidine (94, 152, 160, 161) and dofetilide (111–116).

What Are the Efficacy and Safety of Direct-Current Cardioversion?

Direct-current cardioversion of atrial fibrillation was first reported by Bernard Lown in 1963 (162). The efficacy of traditional, external, monophasic direct-current cardioversion in consecutive patients has consistently been found to be 80% to 85% (163–168). Applying direct-current cardioversion directly in the right atrium through percutaneous catheter has been shown to increase the efficacy to more than 90% (169, 170); however, the invasive nature of this procedure limits applicability. Biphasic defibrillators, which use less energy but apply both positive and negative currents, have also been shown to increase the efficacy of transthoracic cardioversion to more than 90% (168, 171, 172).

Ventricular tachycardia occurs rarely and was noted in only 1 patient in the trials in this review (170). In 1 study (169), transient atrioventricular node dysfunction occurred in 7 of 112 patients but lasted less than 15 seconds. One study found that moderate skin burns (with tenderness) occurred in about 40% of patients after external monophasic electrical cardioversion and severe burns (blistering) occurred in 2% (168). Biphasic waveforms decreased the incidence and severity of these burns.

What Is the Efficacy of Pharmacologic Treatment of Atrial Fibrillation before Electrical Cardioversion?

Of the 8 RCTs evaluating the efficacy of administering antiarrhythmic agents before direct-current cardioversion compared with direct-current cardioversion alone, 7 demonstrated no increased efficacy with the addition of quinidine, propafenone, or sotalol (128, 142, 173–177). One study demonstrated improved efficacy with use of ibutilide (178). Although starting an antiarrhythmic agent before direct-current cardioversion in an attempt to maintain sinus rhythm after cardioversion may be appropriate, the data do not support the routine use of an antiarrhythmic agent before direct-current cardioversion to improve the efficacy of restoring sinus rhythm.

What Is the Usefulness of Transesophageal Echocardiography in the Acute Conversion of Atrial Fibrillation?

In a pooled analysis of observational data, Moreyra and coworkers (179) estimated the risk for thromboembolism after cardioversion to be 0.33% in those who had received anticoagulation before cardioversion and 2.00% in those who had not. The risk for thromboembolism does not seem to differ between electrical cardioversion and

pharmacologic conversion (180). At least 2 mechanisms may be responsible for the thromboembolic risk associated with conversion of atrial fibrillation. First, thrombi in the left atrium or the left atrial appendage that are present before conversion may embolize once atrial contraction resumes (181–183). Second, because both left atrial function and left atrial appendage function are impaired shortly after conversion, thrombus may develop after conversion (184–186).

Conventional recommendations include treating patients experiencing atrial fibrillation with warfarin, with a goal international normalized ratio of 2.0 to 3.0, for 3 weeks before cardioversion and for 4 weeks after conversion (187). From a pathophysiologic standpoint, this strategy could stabilize preexisting thrombi and prevent new thrombus formation. However, no clinical trials have directly compared this strategy with no anticoagulation or with anticoagulation of varying intensities or duration.

Given the high sensitivity and specificity of transesophageal echocardiography (TEE) to detect left atrial and left atrial appendage thrombus (188–190), this procedure could be used to stratify patients by risk before cardioversion. Initial experience using TEE to identify patients who could safely undergo cardioversion without anticoagulation found an unacceptably high embolic risk of 1.34% (179). However, no thromboembolic events occurred in 1 study of 236 patients that used a strategy of short-term anticoagulation (approximately 48 hours) and TEE for identification of existing thrombi before cardioversion with postcardioversion anticoagulation (191). The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) study was a randomized clinical trial comparing a TEE-guided strategy with the conventional strategy in patients with atrial fibrillation lasting longer than 2 days (167). In the TEE-guided group, thrombus in the left atrium, left atrial appendage, or right atrium was identified in 76 of 619 patients (14%). These patients received at least 4 weeks of anticoagulation before any cardioversion attempt. The remaining patients without thrombus identified on TEE were converted immediately and received anticoagulation for at least 4 weeks afterward. The primary end point of stroke, transient ischemic attack, or peripheral embolism did not differ between the TEE-guided group and the conventional group (0.81% vs. 0.50%, respectively; $P > 0.2$). However, there was a significant difference in the composite end point of major and minor bleeding (2.9% for the TEE-guided group and 5.5% for the conventional group; $P = 0.02$). The low incidence of the primary end point in each arm of this trial underscores the efficacy of anticoagulation in settings with close monitoring of anticoagulation surrounding conversion. The recent Ludwigshafen Observational Cardioversion Study reproduced these low embolic rates and found no difference between patients treated with the TEE-guided approach and patients treated conventionally (0.8% for both groups) (192). Analysis of observational studies suggests that the TEE-guided approach may be cost-effective (193); however, the cost-effectiveness analysis of the ACUTE trial has not been published.

Overall, the literature suggests that TEE-guided conversion using short-term preconversion anticoagulation and at least 3 weeks of appropriate postconversion anticoagulation may be an effective, safe alternative to the conventional approach.

What Is the Role of Transthoracic Echocardiography in Identifying Likelihood of Successful Conversion of Atrial Fibrillation?

We addressed the ability of echocardiography to predict the likelihood of successful conversion by reviewing randomized clinical trials that reported outcomes relative to left atrial diameter. Of the 46 studies evaluating acute pharmacologic conversion that we identified in our comprehensive search (21), only 6 gave information relating left atrial diameter on echocardiography to success of conversion. Five of these studies found an inverse relation between left atrial size and success of conversion (99, 105, 128, 194, 195). The final study in this group found no difference in left atrial size between patients with successful and unsuccessful conversion (94). The fact that the left atrium was smaller and conversion less likely in the placebo group compared with the treatment groups may have confounded this last study. Because the methods for relating left atrial size to cardioversion success were not consistent across the studies, combining the data is not helpful. Qualitatively, the evidence suggests that the likelihood of successful pharmacologic cardioversion is related to left atrial size as measured by echocardiography.

Maintenance of Sinus Rhythm

What Is the Efficacy of Each Antiarrhythmic Agent for the Maintenance of Sinus Rhythm after Successful Conversion of Atrial Fibrillation to Sinus Rhythm?

Our meta-analysis identified 30 RCTs evaluating 7 antiarrhythmic agents used for maintenance of sinus rhythm in patients with paroxysmal or persistent atrial fibrillation. Our previous meta-analysis included 28 of these trials (21). In the 18 trials with a control arm, we found strong evidence of efficacy for amiodarone, propafenone, disopyramide, and sotalol (**Table 3** and **Figure 3**). Moderate evidence was found for flecainide, quinidine, and azimilide.

Our search identified 15 studies that directly compared antiarrhythmic agents. Only 3 studies showed a statistically significant difference between agents. Two trials showed superior efficacy for amiodarone compared with sotalol or propafenone (196, 197). In 1 trial, propafenone had greater efficacy than quinidine (100).

As with the studies evaluating acute conversion, 3 methodologic problems were noted. First, the studies were relatively small, ranging from 12 to 289 patients. Second, the duration of atrial fibrillation in the selected patients

Table 3. **Pooled Results of Randomized, Controlled Trials of Drugs for Maintenance of Sinus Rhythm after Conversion of Atrial Fibrillation**

Level of Evidence	Drug	Trials with Control Group				All Trials That Reported Side Effects	
		Trials	Patients in Drug Group	Odds Ratio Compared with Control (95% CI)*	*P* Value	Range of Sustained Ventricular Arrhythmia	Range of Cessation or Decreased Dose of Drug
		n				%	
Strong	Amiodarone	2	173	6.8 (4.0–11.4)	<0.01	0	0–9
	Propafenone	4	228	3.0 (2.0–4.7)	<0.01	0–3	3–25
	Disopyramide	2	62	2.9 (1.4–6.1)	<0.01	0	0–55
	Sotalol	4	363	2.5 (1.7–3.7)	<0.01	0–5	5–13
Moderate	Flecainide	3	102	4.3 (1.3–14.1)	0.01	0	0–20
	Quinidine	4	218	2.7 (1.1–6.8)	0.02	0–12	4–58
	Azimilide	1	291	1.6 (1.2–2.2)	0.01	1	5

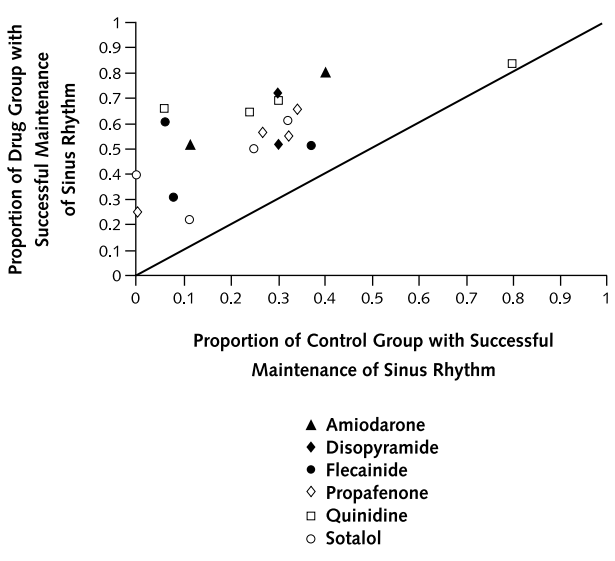
* Control indicates placebo, calcium-channel blockers, β-blockers, or digoxin.

varied. Precise information on this duration is limited. Some studies excluded patients who had had atrial fibrillation for more than 48 hours, whereas other studies had no upper limit for duration. Third, the length of follow-up was short, ranging from 1 to 18 months. While subgroup analyses found only minimal differences in relative efficacy based on length of follow-up, these analyses were limited by the small number of studies for each comparison.

What Is the Long-Term Safety of Antiarrhythmic Therapy?

The safety of long-term antiarrhythmic therapy has been questioned. The Cardiac Arrhythmia Suppression Trial (198) found an increased mortality with class IC agents (for example, flecainide) in patients with nonsustained ventricular tachycardia after myocardial infarction. In addition, a meta-analysis of RCTs found increased mortality associated with quinidine (199). More recently, as discussed previously, the AFFIRM trial found a nonsignificant increase in mortality in the rhythm-control group compared with the rate-control group (hazard ratio, 1.15 [CI, 0.99 to 1.34]; $P = 0.08$). The relatively short follow-up in the clinical trials (<3.5 years) limits any longer-term risk–benefit evaluations of safety and efficacy.

Figure 3. **Proportions of patients who had successful maintenance of sinus rhythm.**



Antiarrhythmic therapy may induce serious ventricular tachycardia, in particular torsades de pointes. Only 18 of 30 studies evaluating maintenance of sinus rhythm reported the incidence of ventricular arrhythmia (**Table 3**). There were no reported ventricular arrhythmias in studies evaluating amiodarone (134, 137, 196, 197), flecainide (200–203), or disopyramide (204). Ventricular arrhythmias were noted in 0% to 3% of patients receiving propafenone (100, 128, 196, 202, 204–206, 207, 208), 0% to 5% of those receiving sotalol (151, 196, 197, 205, 208, 209–211), 0% to 12% of those receiving quinidine (100, 151, 174, 200, 201, 209, 211), and 1% of those receiving azimilide (212).

These trials had a widely varying incidence of other side effects that prompted cessation or decreased dosage of the antiarrhythmic agent. Such side effects occurred in up to 58% of patients taking quinidine (213), 55% of those taking disopyramide (204), 20% of those taking flecainide (201), 18% of those taking propafenone (202), and 13% of those taking sotalol (142). Although the risk for torsades de pointes associated with amiodarone is small, this drug often raises concern because of its potential for causing other adverse effects. In the 201 patients assigned to receive amiodarone in the Canadian Trial of Atrial Fibrillation Investigators (196), other cardiac side effects included unacceptable prolongation of the QT interval (1 patient), heart failure (2 patients), and serious bradyarrhythmias (6 patients). Incidences were similar among the patients treated with propafenone or sotalol. In this trial, amiodarone was discontinued more frequently for noncardiac side effects, including suspected pulmonary toxicity (4 patients), hypothyroidism (2 patients), hyperthyroidism (1 patient), and other reasons (2 patients). Noncardiac side

effects prompted discontinuation of sotalol or propafenone in only 3 patients.

Thus, safety and side effects are critical factors when considering whether to start or maintain antiarrhythmic therapy. Amiodarone appears to be relatively safe from a cardiac perspective but has a substantial profile of noncardiac side effects. The other antiarrhythmic agents require careful consideration in patients with structural heart disease because of the risk for proarrhythmia. In particular, flecainide is not indicated in patients with coronary artery disease.

What Is the Role of Echocardiography in Identifying the Likelihood of Successful Maintenance of Sinus Rhythm?

Of the 30 studies evaluating maintenance of sinus rhythm in our original review, only 2 reported on the relation between left atrial size and efficacy. Bellandi and colleagues (214) found a statistically significant relationship between recurrent atrial fibrillation and left atrial size in all 3 treatment groups (propafenone, sotalol, and placebo). Van Gelder and associates (203) reported that, after controlling for New York Heart Association class and flecainide treatment, the predictive power of left atrial size for efficacy did not reach statistical significance. Overall, the paucity of evidence precludes strong conclusions regarding the association between left atrial size and maintenance of sinus rhythm after conversion of atrial fibrillation.

Little evidence exists regarding the role of TEE in identifying patients with a high likelihood of maintaining sinus rhythm. One study found high left atrial appendage velocities on TEE to be the only echocardiographic variable predictive of patients remaining in sinus rhythm for 1 year after cardioversion (215).

Conclusion

Substantial evidence exists to provide guidance in management of patients with atrial fibrillation. Recent trials have shown similar outcomes for patients treated with a rhythm-control strategy or a rate-control strategy. Warfarin significantly reduces stroke risk in patients unless the embolic risk is low or a contraindication to anticoagulation exists. β-Blockers and calcium-channel blockers are superior to digoxin for rate control when patients do not have contraindications to these therapies. Many antiarrhythmic agents are superior to placebo for acute conversion. Some agents are efficacious for maintenance of sinus rhythm, but side effect profile should be considered in deciding whether to use antiarrhythmic therapy and in choosing an agent. Finally, echocardiography is useful in stratifying risk for thromboembolism and may be useful in predicting success for conversion of atrial fibrillation and maintenance of sinus rhythm.

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