

# 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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**A**trial 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

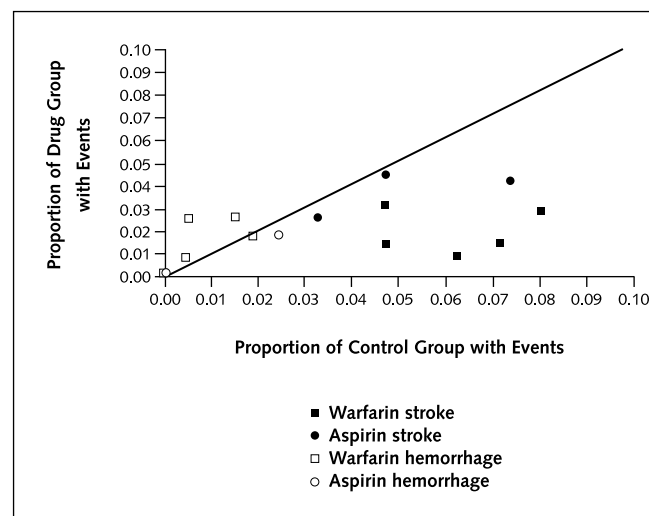
conventional-dose warfarin compared with low-dose warfarin whether the low-dose warfarin was given alone (OR, 0.52 [CI, 0.25 to 1.08];  $P = 0.08$ ) or combined with aspirin (OR, 0.44 [CI, 0.14 to 1.39];  $P = 0.16$ ). Evidence suggested increased bleeding risk with conventional-dose warfarin compared 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-molec-

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



ular-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

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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -blocker may provide additional benefit over either drug alone.

### Acute Conversion

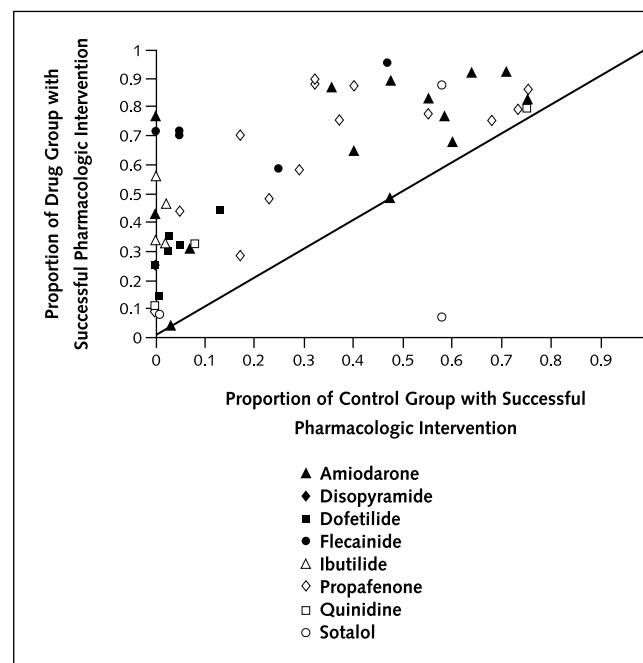
#### What Is the Efficacy of Antiarrhythmic Agents Used for Acute Conversion of Atrial Fibrillation to Sinus Rhythm?

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  $\beta$ -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	
		<i>n</i>				%
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,  $\beta$ -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  $\leq 0.45$ , 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 fle-

cainide (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 post-cardioversion 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,  $\beta$ -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?**

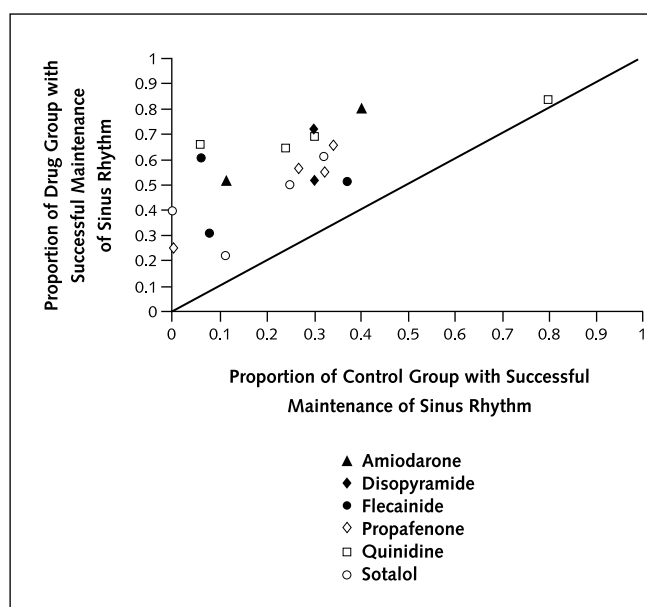
The safety of long-term antiarrhythmic therapy has been questioned. The Cardiac Arrhythmia Suppression Trial (198) found an increased mortality with class IC agents (for example, flecainide) in patients with nonsustained ventricular tachycardia after myocardial infarction. In addition, a meta-analysis 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.

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

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



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.  $\beta$ -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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#### **References**

- Bialy D, Lehmann MH, Schumacher DN, Steinman RT, Meissner MD. Hospitalization for arrhythmias in the United States: importance of atrial fibrillation [Abstract]. *J Am Coll Cardiol*. 1992;19:41A.
- Ostrander LD Jr, Brandt RL, Kjelsberg MO, Epstein FH. Electrocardiographic Findings among the Adult Population of a Total Natural Community, Tecumseh, Michigan. *Circulation*. 1965;31:888-98. [PMID: 14297523]
- Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. *Lancet*. 1987;1:526-9. [PMID: 2881082]
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-8. [PMID: 1866765]
- Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol*. 1994;74:236-41. [PMID: 8037127]
- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-5. [PMID: 11343485]
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*. 1987;147:1561-4. [PMID: 3632164]
- Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*. 1995;98:476-84. [PMID: 7733127]
- Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455-61. [PMID: 9337224]
- Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J*. 1983;106:389-96. [PMID: 6869222]
- Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. *JAMA*. 1985;254:3449-53. [PMID: 4068186]

12. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr, Ilstrup DM, et al. The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med.* 1987;317:669-74. [PMID: 3627174]
13. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology.* 1978;28:973-7. [PMID: 570666]
14. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med.* 1987;147:1561-4. [PMID: 3632164]
15. Levy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation.* 1999;99:3028-35. [PMID: 10368121]
16. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol.* 2000;35:183-7. [PMID: 10636278]
17. Hamer ME, Blumenthal JA, McCarthy EA, Phillips BG, Pritchett EL. Quality-of-life assessment in patients with paroxysmal atrial fibrillation or paroxysmal supraventricular tachycardia. *Am J Cardiol.* 1994;74:826-9. [PMID: 7942563]
18. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med.* 1996;156:1829-36. [PMID: 8790077]
19. Protheroe J, Fahey T, Montgomery AA, Peters TJ. The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysis. *BMJ.* 2000;320:1380-4. [PMID: 10818030]
20. Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in Collaboration With the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol.* 2001;38:1231-66. [PMID: 11583910]
21. McNamara RL, Bass EB, Miller MR, Segal JB, Goodman SN, Kim NL, et al. Evidence Report on Management of New Onset Atrial Fibrillation. Agency for Healthcare Research and Quality publication no. AHRQ 01-E026. Rockville, MD: Agency for Healthcare Research and Quality; January 2001.
22. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining and combining results from several studies in meta-analysis. In: *Systematic Reviews in Health Care: Meta-Analysis in Context.* London: BMJ Books; 2001.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177-88. [PMID: 3802833]
24. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825-33. [PMID: 12466506]
25. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med.* 2002;347:1834-40. [PMID: 12466507]
26. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet.* 2000;356:1789-94. [PMID: 11117910]
27. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med.* 1990;323:1505-11. [PMID: 2233931]
28. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet.* 1993;342:1255-62. [PMID: 7901582]
29. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation.* 1991;84:527-39. [PMID: 1860198]
30. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet.* 1994;343:687-91. [PMID: 7907677]
31. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet.* 1996;348:633-8. [PMID: 8782752]
32. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet.* 1989;1:175-9. [PMID: 2563096]
33. Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med.* 1998;158:1513-21. [PMID: 9679792]
34. Harenberg J, Weuster B, Pfitzer M, Dempfle CE, Stehle G, Kubler W, et al. Prophylaxis of embolic events in patients with atrial fibrillation using low molecular weight heparin. *Semin Thromb Hemost.* 1993;19 Suppl 1:116-21. [PMID: 8395713]
35. Morocutti C, Amabile G, Fattapposta F, Nicolosi A, Matteoli S, Trappolini M, et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA (Studio Italiano Fibrillazione Atriale) Investigators. *Stroke.* 1997;28:1015-21. [PMID: 9158644]
36. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med.* 1992;327:1406-12. [PMID: 1406859]
37. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol.* 1991;18:349-55. [PMID: 1856403]
38. Hellemons BS, Langenberg M, Lodder J, Vermeer F, Schouten HJ, Lemmens T, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ.* 1999;319:958-64. [PMID: 10514159]
39. Pengo V, Zasso A, Barbero F, Banzato A, Nante G, Parissenti L, et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. *Am J Cardiol.* 1998;82:433-7. [PMID: 9723629]
40. Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation. LASAF Pilot Study Group. *Am Heart J.* 1999;138:137-43. [PMID: 10385777]
41. Segal JB, McNamara RL, Miller MR, Powe NR, Goodman SN, Robinson KA, et al. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. *Cochrane Database Syst Rev.* 2001;(1):CD001938. [PMID: 11279741]
42. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs. *J Gen Intern Med.* 2000;15:56-67. [PMID: 10632835]
43. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolic Secondary Prevention Cooperative Study Group. *Stroke.* 2000;31:817-21. [PMID: 10753981]
44. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. The Stroke Prevention in Atrial Fibrillation Investigators. *Ann Intern Med.* 1992;116:6-12. [PMID: 1727097]
45. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med.* 1998;158:1316-20. [PMID: 9645825]
46. Leung DY, Davidson PM, Cranney GB, Walsh WF. Thromboembolic risks of left atrial thrombus detected by transesophageal echocardiogram. *Am J Cardiol.* 1997;79:626-9. [PMID: 9068521]
47. Stollberger C, Chnupa P, Kronik G, Brainin M, Finsterer J, Schneider B, et al. Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT Study Group. Embolism in Left Atrial Thrombi. *Ann Intern Med.* 1998;128:630-8. [PMID: 9537936]
48. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *Ann Intern Med.* 1998;128:639-47. [PMID: 9537937]



49. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. *J Am Coll Cardiol*. 1998;31:1622-6. [PMID: 9626843]
50. Jones EF, Calafiore P, McNeil JJ, Tonkin AM, Donnan GA. Atrial fibrillation with left atrial spontaneous contrast detected by transesophageal echocardiography is a potent risk factor for stroke. *Am J Cardiol*. 1996;78:425-9. [PMID: 8752187]
51. Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 1994;24:755-62. [PMID: 8077549]
52. Lewis RV, Laing E, Moreland TA, Service E, McDevitt DG. A comparison of digoxin, diltiazem and their combination in the treatment of atrial fibrillation. *Eur Heart J*. 1988;9:279-83. [PMID: 3289931]
53. Falk RH, Knowlton AA, Bernard SA, Godlieb NE, Battinelli NJ. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm. A randomized, double-blinded trial. *Ann Intern Med*. 1987;106:503-6. [PMID: 3548521]
54. Wong CK, Lau CP, Leung WH, Cheng CH. Usefulness of labetalol in chronic atrial fibrillation. *Am J Cardiol*. 1990;66:1212-5. [PMID: 2239725]
55. Jordaens L, Trouerbach J, Calle P, Tavernier R, Derycke E, Vertongen P, et al. Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo. *Eur Heart J*. 1997;18:643-8. [PMID: 9129896]
56. Intravenous digoxin in acute atrial fibrillation. Results of a randomized, placebo-controlled multicentre trial in 239 patients. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. *Eur Heart J*. 1997;18:649-54. [PMID: 9129897]
57. Koh KK, Kwon KS, Park HB, Baik SH, Park SJ, Lee KH, et al. Efficacy and safety of digoxin alone and in combination with low-dose diltiazem or betaxolol to control ventricular rate in chronic atrial fibrillation. *Am J Cardiol*. 1995;75:88-90. [PMID: 7801876]
58. Ang EL, Chan WL, Cleland JG, Moore D, Krikler SJ, Alexander ND, et al. Placebo controlled trial of xamoterol versus digoxin in chronic atrial fibrillation. *Br Heart J*. 1990;64:256-60. [PMID: 1977430]
59. Goldenberg IF, Lewis WR, Dias VC, Heywood JT, Pedersen WR. Intravenous diltiazem for the treatment of patients with atrial fibrillation or flutter and moderate to severe congestive heart failure. *Am J Cardiol*. 1994;74:884-9. [PMID: 7977118]
60. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. A placebo-controlled trial of continuous intravenous diltiazem infusion for 24-hour heart rate control during atrial fibrillation and atrial flutter: a multicenter study. *J Am Coll Cardiol*. 1991;18:891-7. [PMID: 1894861]
61. Salerno DM, Dias VC, Kleiger RE, Tschida VH, Sung RJ, Sami M, et al. Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. The Diltiazem-Atrial Fibrillation/Flutter Study Group. *Am J Cardiol*. 1989;63:1046-51. [PMID: 2650517]
62. Lundstrom T, Ryden L. Ventricular rate control and exercise performance in chronic atrial fibrillation: effects of diltiazem and verapamil. *J Am Coll Cardiol*. 1990;16:86-90. [PMID: 2358610]
63. Lundstrom T, Moor E, Ryden L. Differential effects of xamoterol and verapamil on ventricular rate regulation in patients with chronic atrial fibrillation. *Am Heart J*. 1992;124:917-23. [PMID: 1356311]
64. Lewis RV, McMurray J, McDevitt DG. Effects of atenolol, verapamil, and xamoterol on heart rate and exercise tolerance in digitalised patients with chronic atrial fibrillation. *J Cardiovasc Pharmacol*. 1989;13:1-6. [PMID: 2468920]
65. Panidis IP, Morganroth J, Baessler C. Effectiveness and safety of oral verapamil to control exercise-induced tachycardia in patients with atrial fibrillation receiving digitalis. *Am J Cardiol*. 1983;52:1197-201. [PMID: 6359848]
66. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med*. 1997;29:135-40. [PMID: 8998092]
67. Lewis RV, Irvine N, McDevitt DG. Relationships between heart rate, exercise tolerance and cardiac output in atrial fibrillation: the effects of treatment with digoxin, verapamil and diltiazem. *Eur Heart J*. 1988;9:777-81. [PMID: 3169046]
68. Lewis RV, Laing E, Moreland TA, Service E, McDevitt DG. A comparison of digoxin, diltiazem and their combination in the treatment of atrial fibrillation. *Eur Heart J*. 1988;9:279-83. [PMID: 3289931]
69. Pomfret SM, Beasley CR, Challenor V, Holgate ST. Relative efficacy of oral verapamil and digoxin alone and in combination for the treatment of patients with chronic atrial fibrillation. *Clin Sci (Lond)*. 1988;74:351-7. [PMID: 3281786]
70. Ahuja RC, Sinha N, Saran RK, Jain AK, Hasan M. Digoxin or verapamil or metoprolol for heart rate control in patients with mitral stenosis—a randomised cross-over study. *Int J Cardiol*. 1989;25:325-31. [PMID: 2613380]
71. Botto GL, Bonini W, Broffoni T. Modulation of ventricular rate in permanent atrial fibrillation: randomized, crossover study of the effects of slow-release formulations of gallopamil, diltiazem, or verapamil. *Clin Cardiol*. 1998;21:837-40. [PMID: 9825197]
72. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol*. 1999;33:304-10. [PMID: 9973007]
73. Channer KS, James MA, MacConnell T, Rees JR. Beta-adrenoceptor blockers in atrial fibrillation: the importance of partial agonist activity. *Br J Clin Pharmacol*. 1994;37:53-7. [PMID: 7908532]
74. Sweany AE, Moncloa F, Vickers FF, Zupkis RV. Antiarrhythmic effects of intravenous timolol in supraventricular arrhythmias. *Clin Pharmacol Ther*. 1985;37:124-7. [PMID: 3881206]
75. DiBianco R, Morganroth J, Freitag JA, Ronan JA Jr, Lindgren KM, Donohue DJ, et al. Effects of nadolol on the spontaneous and exercise-provoked heart rate of patients with chronic atrial fibrillation receiving stable dosages of digoxin. *Am Heart J*. 1984;108:1121-7. [PMID: 6148872]
76. Lawson-Matthew PJ, McLean KA, Dent M, Austin CA, Channer KS. Xamoterol improves the control of chronic atrial fibrillation in elderly patients. *Age Ageing*. 1995;24:321-5. [PMID: 7484490]
77. Myers J, Atwood JE, Sullivan M, Forbes S, Friis R, Pewen W, et al. Perceived exertion and gas exchange after calcium and beta-blockade in atrial fibrillation. *J Appl Physiol*. 1987;63:97-104. [PMID: 2887542]
78. Lin SK, Morganroth J, Heng M, Rubler S, Baird W, Atwood JE, et al. Effect of orally administered celiprolol in patients with chronic atrial fibrillation. *J Cardiovasc Pharmacol*. 1986;8 Suppl 4:S112-5. [PMID: 2427838]
79. Koh KK, Song JH, Kwon KS, Park HB, Baik SH, Park YS, et al. Comparative study of efficacy and safety of low-dose diltiazem or betaxolol in combination with digoxin to control ventricular rate in chronic atrial fibrillation: randomized crossover study. *Int J Cardiol*. 1995;52:167-74. [PMID: 8749878]
80. Wattanasuwan N, Khan IA, Mehta NJ, Arora P, Singh N, Vasavada BC, et al. Acute ventricular rate control in atrial fibrillation: IV combination of diltiazem and digoxin vs. IV diltiazem alone. *Chest*. 2001;119:502-6. [PMID: 11171729]
81. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med*. 1997;29:135-40. [PMID: 8998092]
82. Brodsky MA, Orlov MV, Capparelli EV, Allen BJ, Iseri LT, Ginkel M, et al. Magnesium therapy in new-onset atrial fibrillation. *Am J Cardiol*. 1994;73:1227-9. [PMID: 8203347]
83. Channer KS, Papouchado M, James MA, Pitcher DW, Rees JR. Towards improved control of atrial fibrillation. *Eur Heart J*. 1987;8:141-7. [PMID: 3552679]
84. Stern EH, Pitchon R, King BD, Guerrero J, Schneider RR, Wiener I. Clinical use of oral verapamil in chronic and paroxysmal atrial fibrillation. *Chest*. 1982;81:308-11. [PMID: 7056105]
85. Lang R, Klein HO, Di Segni E, Gefen J, Sareli P, Libhaber C, et al. Verapamil improves exercise capacity in chronic atrial fibrillation: double-blind crossover study. *Am Heart J*. 1983;105:820-5. [PMID: 6846125]
86. Zoble RG, Brewington J, Olukotun AY, Gore R. Comparative effects of nadolol-digoxin combination therapy and digoxin monotherapy for chronic atrial fibrillation. *Am J Cardiol*. 1987;60:39D-45D. [PMID: 3307366]
87. Smit AJ, Scaf AH, van Essen LH, Lie KI, Wesseling H. Digoxin infusion versus bolus injection in rapid atrial fibrillation: relation between serum level and response. *Eur J Clin Pharmacol*. 1990;38:335-41. [PMID: 2344857]
88. Hays JV, Gilman JK, Rubal BJ. Effect of magnesium sulfate on ventricular rate control in atrial fibrillation. *Ann Emerg Med*. 1994;24:61-4. [PMID: 8010550]
89. Roth A, Kaluski E, Felner S, Heller K, Laniado S. Clonidine for patients with rapid atrial fibrillation. *Ann Intern Med*. 1992;116:388-90. [PMID: 1346564]
90. Scardi S, Humar F, Pandullo C, Poletti A. Oral clonidine for heart rate

- control in chronic atrial fibrillation [Letter]. *Lancet*. 1993;341:1211-2. [PMID: 8098093]
91. Lok NS, Lau CP. Oxygen uptake kinetics and cardiopulmonary performance in lone atrial fibrillation and the effects of sotalol. *Chest*. 1997;111:934-40. [PMID: 9106572]
  92. Boudonas G, Lefkos N, Efthymiadis AP, Styliadis IG, Tsapas G. Intravenous administration of diltiazem in the treatment of supraventricular tachyarrhythmias. *Acta Cardiol*. 1995;50:125-34. [PMID: 7610735]
  93. Suttrop MJ, Kingma JH, Jessurun ER, Lie-A-Huen L, van Hemel NM, Lie KI. The value of class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. *J Am Coll Cardiol*. 1990;16:1722-7. [PMID: 2123909]
  94. Kingma JH, Suttrop MJ. Acute pharmacologic conversion of atrial fibrillation and flutter: the role of flecainide, propafenone, and verapamil. *Am J Cardiol*. 1992;70:56A-60A. [PMID: 1510000]
  95. Dahlström CG, Edvardsson N, Nasheng C, Olsson SB. Effects of diltiazem, propranolol, and their combination in the control of atrial fibrillation. *Clin Cardiol*. 1992;15:280-4. [PMID: 1563131]
  96. Joshi PP, Deshmukh PK, Salkar RG. Efficacy of intravenous magnesium sulphate in supraventricular tachyarrhythmias. *J Assoc Physicians India*. 1995;43:529-31. [PMID: 8772970]
  97. Gullestad L, Birkeland K, Mølsted P, Høyer MM, Vanberg P, Kjekshus J. The effect of magnesium versus verapamil on supraventricular arrhythmias. *Clin Cardiol*. 1993;16:429-34. [PMID: 8504578]
  98. James MA, Channer KS, Papouchado M, Rees JR. Improved control of atrial fibrillation with combined pindolol and digoxin therapy. *Eur Heart J*. 1989;10:83-90. [PMID: 2702970]
  99. Zehender M, Hohnloser S, Müller B, Meinertz T, Just H. Effects of amiodarone versus quinidine and verapamil in patients with chronic atrial fibrillation: results of a comparative study and a 2-year follow-up. *J Am Coll Cardiol*. 1992;19:1054-9. [PMID: 1552095]
  100. Lee SH, Chen SA, Chiang CE, Tai CT, Wen ZC, Wang SP, et al. Comparisons of oral propafenone and quinidine as an initial treatment option in patients with symptomatic paroxysmal atrial fibrillation: a double-blind, randomized trial. *J Intern Med*. 1996;239:253-60. [PMID: 8772625]
  101. Botto GL, Capucci A, Bonini W, Boriani G, Broffoni T, Barone P, et al. Conversion of recent onset atrial fibrillation to sinus rhythm using a single oral loading dose of propafenone: comparison of two regimens. *Int J Cardiol*. 1997;58:55-61. [PMID: 9021428]
  102. Miller MR, McNamara RL, Segal JB, Kim N, Robinson KA, Goodman SN, et al. Efficacy of agents for pharmacologic conversion of atrial fibrillation and subsequent maintenance of sinus rhythm: a meta-analysis of clinical trials. *J Fam Pract*. 2000;49:1033-46. [PMID: 11093570]
  103. Guo GB, Ellenbogen KA, Wood MA, Stambler BS. Conversion of atrial flutter by ibutilide is associated with increased atrial cycle length variability. *J Am Coll Cardiol*. 1996;27:1083-9. [PMID: 8609325]
  104. Ellenbogen KA, Stambler BS, Wood MA, Sager PT, Wesley RC Jr, Meissner MC, et al. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study. *J Am Coll Cardiol*. 1996;28:130-6. [PMID: 8752805]
  105. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, VanderLugt JT. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study Investigators. *Circulation*. 1996;94:1613-21. [PMID: 8840852]
  106. Abi-Mansour P, Carberry PA, McCowan RJ, Henthorn RW, Dunn GH, Perry KT. Conversion efficacy and safety of repeated doses of ibutilide in patients with atrial flutter and atrial fibrillation. Study Investigators. *Am Heart J*. 1998;136:632-42. [PMID: 9778066]
  107. Suttrop MJ, Kingma JH, Lie-A-Huen L, Mast EG. Intravenous flecainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. *Am J Cardiol*. 1989;63:693-6. [PMID: 2493733]
  108. Barranco F, Sanchez M, Rodriguez J, Guerrero M. Efficacy of flecainide in patients with supraventricular arrhythmias and respiratory insufficiency. *Intensive Care Med*. 1994;20:42-4. [PMID: 8163757]
  109. Donovan KD, Power BM, Hockings BE, Dobb GJ, Lee KY. Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation. *Am J Cardiol*. 1995;75:693-7. [PMID: 7900662]
  110. Capucci A, Lenzi T, Boriani G, Trisolino G, Binetti N, Cavazza M, et al. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. *Am J Cardiol*. 1992;70:69-72. [PMID: 1615873]
  111. Falk RH, Pollak A, Singh SN, Friedrich T. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. Intravenous Dofetilide Investigators. *J Am Coll Cardiol*. 1997;29:385-90. [PMID: 9014993]
  112. Bianconi L, Castro A, Dinelli M, Alboni P, Pappalardo A, Richiardi E, et al. Comparison of intravenously administered dofetilide versus amiodarone in the acute termination of atrial fibrillation and flutter. A multicentre, randomized, double-blind, placebo-controlled study. *Eur Heart J*. 2000;21:1265-73. [PMID: 10924317]
  113. Pedersen OD, Bagger H, Keller N, Marchant B, Køber L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation*. 2001;104:292-6. [PMID: 11457747]
  114. Lindeboom JE, Kingma JH, Crijns HJ, Dunselman PH. Efficacy and safety of intravenous dofetilide for rapid termination of atrial fibrillation and atrial flutter. *Am J Cardiol*. 2000;85:1031-3. [PMID: 10760352]
  115. Nørgaard BL, Wachtell K, Christensen PD, Madsen B, Johansen JB, Christiansen EH, et al. Efficacy and safety of intravenously administered dofetilide in acute termination of atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled trial. Danish Dofetilide in Atrial Fibrillation and Flutter Study Group. *Am Heart J*. 1999;137:1062-9. [PMID: 10347332]
  116. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation*. 2000;102:2385-90. [PMID: 11067793]
  117. Boriani G, Biffi M, Capucci A, Botto GL, Broffoni T, Rubino I, et al. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease. A randomized, controlled trial. *Ann Intern Med*. 1997;126:621-5. [PMID: 9103129]
  118. Boriani G, Capucci A, Lenzi T, Sanguinetti M, Magnani B. Propafenone for conversion of recent-onset atrial fibrillation. A controlled comparison between oral loading dose and intravenous administration. *Chest*. 1995;108:355-8. [PMID: 7634866]
  119. Fresco C, Proclemer A, Pavan A, Buia G, Vicentini A, Pavan D, et al. Intravenous propafenone in paroxysmal atrial fibrillation: a randomized, placebo-controlled, double-blind, multicenter clinical trial. Paroxysmal Atrial Fibrillation Italian Trial (PAFIT)-2 Investigators. *Clin Cardiol*. 1996;19:409-12. [PMID: 8723601]
  120. Stroobandt R, Stieles B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol*. 1997;79:418-23. [PMID: 9052343]
  121. Azpitarte J, Alvarez M, Baún O, García R, Moreno E, Martín F, et al. Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation. Results of a randomized, double-blind, controlled study. *Eur Heart J*. 1997;18:1649-54. [PMID: 9347277]
  122. Bellandi F, Dabizzi RP, Cantini F, Natale MD, Niccoli L. Intravenous propafenone: efficacy and safety in the conversion to sinus rhythm of recent onset atrial fibrillation—a single-blind placebo-controlled study. *Cardiovasc Drugs Ther*. 1996;10:153-7. [PMID: 8842507]
  123. Capucci A, Boriani G, Rubino I, Della Casa S, Sanguinetti M, Magnani B. A controlled study on oral propafenone versus digoxin plus quinidine in converting recent onset atrial fibrillation to sinus rhythm. *Int J Cardiol*. 1994;43:305-13. [PMID: 8181888]
  124. Weiner P, Ganam R, Ganem R, Zidan F, Rabner M. Clinical course of recent-onset atrial fibrillation treated with oral propafenone. *Chest*. 1994;105:1013-6. [PMID: 8162718]
  125. Kochiadakis GE, Igoumenidis NE, Parthenakis FI, Chlouverakis GI, Vardas PE. Amiodarone versus propafenone for conversion of chronic atrial fibrillation: results of a randomized, controlled study. *J Am Coll Cardiol*. 1999;33:966-71. [PMID: 10091823]
  126. Bianconi L, Mennuni M. Comparison between propafenone and digoxin administered intravenously to patients with acute atrial fibrillation. PAFIT-3 In-

- investigators. The Propafenone in Atrial Fibrillation Italian Trial. *Am J Cardiol*. 1998;82:584-8. [PMID: 9732884]
127. **Ganau G, Lenzi T.** Intravenous propafenone for converting recent onset atrial fibrillation in emergency departments: a randomized placebo-controlled multicenter trial. FAPS Investigators Study Group. *J Emerg Med*. 1998;16:383-7. [PMID: 9610964]
128. **Stroobandt R, Stiels B, Hoebrechts R.** Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol*. 1997;79:418-23. [PMID: 9052343]
129. **Baroffio R, Tisi G, Guzzini F, Milvio E, Annoni P.** A randomized study comparing digoxin and propafenone in the treatment of recent onset atrial fibrillation. *Clin Drug Invest*. 1995;9:277-83.
130. **Kochiadakis GE, Igoumenidis NE, Simantirakis EN, Marketou ME, Parthenakis FI, Mezilis NE, et al.** Intravenous propafenone versus intravenous amiodarone in the management of atrial fibrillation of recent onset: a placebo-controlled study. *Pacing Clin Electrophysiol*. 1998;21:2475-9. [PMID: 9825370]
131. **Noc M, Stajer D, Horvat M.** Intravenous amiodarone versus verapamil for acute conversion of paroxysmal atrial fibrillation to sinus rhythm. *Am J Cardiol*. 1990;65:679-80. [PMID: 2178386]
132. **Cowan JC, Gardiner P, Reid DS, Newell DJ, Campbell RW.** A comparison of amiodarone and digoxin in the treatment of atrial fibrillation complicating suspected acute myocardial infarction. *J Cardiovasc Pharmacol*. 1986;8:252-6. [PMID: 2422461]
133. **Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, et al.** Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J*. 1995;16:521-8. [PMID: 7671898]
134. **Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN.** Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation*. 1998;98:2574-9. [PMID: 9843465]
135. **Joseph AP, Ward MR.** A prospective, randomized controlled trial comparing the efficacy and safety of sotalol, amiodarone, and digoxin for the reversal of new-onset atrial fibrillation. *Ann Emerg Med*. 2000;36:1-9. [PMID: 10874228]
136. **Kochiadakis GE, Igoumenidis NE, Marketou ME, Solomou MC, Kanoupakis EM, Vardas PE.** Low-dose amiodarone versus sotalol for suppression of recurrent symptomatic atrial fibrillation. *Am J Cardiol*. 1998;81:995-8. [PMID: 9576159]
137. **Vardas PE, Kochiadakis GE, Igoumenidis NE, Tsatsakis AM, Simantirakis EN, Chlouverakis GI.** Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. *Chest*. 2000;117:1538-45. [PMID: 10858380]
138. **Peuhkurinen K, Niemelä M, Ylitalo A, Linnaluoto M, Lilja M, Juvonen J.** Effectiveness of amiodarone as a single oral dose for recent-onset atrial fibrillation. *Am J Cardiol*. 2000;85:462-5. [PMID: 10728951]
139. **Galve E, Rius T, Ballester R, Artaza MA, Arnau JM, García-Dorado D, et al.** Intravenous amiodarone in treatment of recent-onset atrial fibrillation: results of a randomized, controlled study. *J Am Coll Cardiol*. 1996;27:1079-82. [PMID: 8609324]
140. **Cotter G, Blatt A, Kaluski E, Metzkor-Cotter E, Koren M, Litinski I, et al.** Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm: the effect of no treatment and high-dose amiodarone. A randomized, placebo-controlled study. *Eur Heart J*. 1999;20:1833-42. [PMID: 10581142]
141. **Galperin J, Elizari MV, Chiale PA, Molina RT, Ledesma R, Scapin AO, et al.** Efficacy of amiodarone for the termination of chronic atrial fibrillation and maintenance of normal sinus rhythm: a prospective, multicenter, randomized, controlled, double blind trial. *J Cardiovasc Pharmacol Ther*. 2001;6:341-50. [PMID: 11907636]
142. **Singh S, Saini RK, DiMarco J, Kluger J, Gold R, Chen YW.** Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation. The Sotalol Study Group. *Am J Cardiol*. 1991;68:1227-30. [PMID: 1951086]
143. **Sung RJ, Tan HL, Karagounis L, Hanyok JJ, Falk R, Platia E, et al.** Intravenous sotalol for the termination of supraventricular tachycardia and atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled study. Sotalol Multicenter Study Group. *Am Heart J*. 1995;129:739-48. [PMID: 7900626]
144. **Baldi N, Russo VA, Lenti V, Marasco G, Polimeni G, Conserva R, et al.** Relation between plasma levels and efficacy of flecainide and propafenone for treatment of atrial fibrillation of recent onset. *New Trends Arrhythmias*. 1993;9:899-906.
145. **Martínez-Marcos FJ, García-Garmendia JL, Ortega-Carpio A, Fernández-Gómez JM, Santos JM, Camacho C.** Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol*. 2000;86:950-3. [PMID: 11053705]
146. **Reisinger J, Gatterer E, Heinze G, Wiesinger K, Zeindlhofer E, Gattermeier M, et al.** Prospective comparison of flecainide versus sotalol for immediate cardioversion of atrial fibrillation. *Am J Cardiol*. 1998;81:1450-4. [PMID: 9645896]
147. **Madrid AH, Moro C, Marín-Huerta E, Mestre JL, Novo L, Costa A.** Comparison of flecainide and procainamide in cardioversion of atrial fibrillation. *Eur Heart J*. 1993;14:1127-31. [PMID: 8404944]
148. **Vos MA, Golitsyn SR, Stangl K, Ruda MY, Van Wijk LV, Harry JD, et al.** Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation. The Ibutilide/Sotalol Comparator Study Group. *Heart*. 1998;79:568-75. [PMID: 10078083]
149. **Volgman AS, Carberry PA, Stambler B, Lewis WR, Dunn GH, Perry KT, et al.** Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. *J Am Coll Cardiol*. 1998;31:1414-9. [PMID: 9581743]
150. **Bertini G, Conti A, Fradella G, Francardelli L, Giglioli C, Mangialavori G, et al.** Propafenone versus amiodarone in field treatment of primary atrial tachydysrhythmias. *J Emerg Med*. 1990;8:15-20. [PMID: 2351794]
151. **Hohnloser SH, van de Loo A, Baedeker F.** Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. *J Am Coll Cardiol*. 1995;26:852-8. [PMID: 7560608]
152. **Halinen MO, Huttunen M, Paakkinen S, Tarssanen L.** Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the Sotalol-Digoxin-Quinidine Trial). *Am J Cardiol*. 1995;76:495-8. [PMID: 7653451]
153. **Roden DM.** Risks and benefits of antiarrhythmic therapy. *N Engl J Med*. 1994;331:785-91. [PMID: 8065408]
154. **Falk RH.** Proarrhythmia in patients treated for atrial fibrillation or flutter. *Ann Intern Med*. 1992;117:141-50. [PMID: 1605429]
155. **Maisel WH, Kuntz KM, Reimold SC, Lee TH, Antman EM, Friedman PL, et al.** Risk of initiating antiarrhythmic drug therapy for atrial fibrillation in patients admitted to a university hospital. *Ann Intern Med*. 1997;127:281-4. [PMID: 9265427]
156. **Prystowsky EN.** Inpatient versus outpatient initiation of antiarrhythmic drug therapy for patients with supraventricular tachycardia. *Clin Cardiol*. 1994;17:117-10. [PMID: 7882612]
157. **Zimetbaum PJ, Schreckengost VE, Cohen DJ, Lemery R, Love D, Epstein LM, et al.** Evaluation of outpatient initiation of antiarrhythmic drug therapy in patients reverting to sinus rhythm after an episode of atrial fibrillation. *Am J Cardiol*. 1999;83:450-2. [PMID: 10072241]
158. **Blanc JJ, Voinov C, Maarek M.** Comparison of oral loading dose of propafenone and amiodarone for converting recent-onset atrial fibrillation. PARSIFAL Study Group. *Am J Cardiol*. 1999;84:1029-32. [PMID: 10569658]
159. **Alp NJ, Bell JA, Shahi M.** Randomised double blind trial of oral versus intravenous flecainide for the cardioversion of acute atrial fibrillation. *Heart*. 2000;84:37-40. [PMID: 10862585]
160. **Levi G, Proto C, Rovetta A.** Double-blind evaluation of practolol and quinidine in the treatment of chronic atrial fibrillation. *Cardiology*. 1973;58:364-8. [PMID: 4608474]
161. **Innes GD, Vertesi L, Dillon EC, Metcalfe C.** Effectiveness of verapamil-quinidine versus digoxin-quinidine in the emergency department treatment of paroxysmal atrial fibrillation. *Ann Emerg Med*. 1997;29:126-34. [PMID: 8998091]
162. **Lown B, Perloth MG, Kaidbey S, Abe T, Harken DE.** "Cardioversion" of atrial fibrillation. A report on the treatment of 65 episodes in 50 patients. *N Engl J Med*. 1963;269:325-31. [PMID: 13931297]
163. **Scott ME, Geddes JS, Patterson GC.** The long term prognosis of atrial fibrillation following direct current conversion. *Ulster Med J*. 1968;37:155-61. [PMID: 5700240]



164. McCarthy C, Varghese PJ, Barritt DW. Prognosis of atrial arrhythmias treated by electrical counter shock therapy. A three-year follow-up. *Br Heart J*. 1969;31:496-500. [PMID: 5791131]
165. Gunning JF, Kristinsson A, Miller G, Saunders K. Long-term follow-up of direct current cardioversion after cardiac surgery with special reference to quinidine. *Br Heart J*. 1970;32:462-6. [PMID: 4914821]
166. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. *Am J Cardiol*. 1969;23:208-16. [PMID: 4180019]
167. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344:1411-20. [PMID: 11346805]
168. Page RL, Kerber RE, Russell JK, Trouton T, Waktare J, Gallik D, et al. Biphasic versus monophasic shock waveform for conversion of atrial fibrillation: the results of an international randomized, double-blind multicenter trial. *J Am Coll Cardiol*. 2002;39:1956-63. [PMID: 12084594]
169. Lévy S, Lauribe P, Dolla E, Kou W, Kadish A, Calkins H, et al. A randomized comparison of external and internal cardioversion of chronic atrial fibrillation. *Circulation*. 1992;86:1415-20. [PMID: 1423954]
170. Alt E, Ammer R, Schmitt C, Evans F, Lehmann G, Pasquantonio J, et al. A comparison of treatment of atrial fibrillation with low-energy intracardiac cardioversion and conventional external cardioversion. *Eur Heart J*. 1997;18:1796-804. [PMID: 9402455]
171. Mittal S, Ayati S, Stein KM, Schwartzman D, Cavlovich D, Tchou PJ, et al. Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. *Circulation*. 2000;101:1282-7. [PMID: 10725288]
172. Niebauer MJ, Chunk MK, Wilkoff BL, Schweikert RA, Saliba WI, Jaeger FJ, et al. Success rate of the rectilinear biphasic waveform in atrial cardioversion in a large cohort of patients [Abstract]. *Circulation*. 2000;102:II574f.
173. Rasmussen K, Wang H, Fausa D. Comparative efficiency of quinidine and verapamil in the maintenance of sinus rhythm after DC conversion of atrial fibrillation. A controlled clinical trial. *Acta Med Scand Suppl*. 1981;645:23-8. [PMID: 7015799]
174. Byrne-Quinn E, Wing AJ. Maintenance of sinus rhythm after DC reversion of atrial fibrillation. A double-blind controlled trial of long-acting quinidine bisulfate. *Br Heart J*. 1970;32:370-6. [PMID: 4911757]
175. Hillestad L, Bjerkelund C, Dale J, Maltau J, Storstein O. Quinidine in maintenance of sinus rhythm after electroconversion of chronic atrial fibrillation. A controlled clinical study. *Br Heart J*. 1971;33:518-21. [PMID: 4934041]
176. Bianconi L, Mennuni M, Lukic V, Castro A, Chieffi M, Santini M. Effects of oral propafenone administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. *J Am Coll Cardiol*. 1996;28:700-6. [PMID: 8772759]
177. Bianconi L, Mennuni M, Lukic V, Tassoni G, Santini M. Pretreatment with oral propafenone in electrical cardioversion of chronic atrial fibrillation. *New Trends Arrhythmias*. 1993;9:1017-20.
178. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med*. 1999;340:1849-54. [PMID: 10369847]
179. Moreyra E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. *Am Heart J*. 1995;129:71-5. [PMID: 7817928]
180. Klein AL, Murray RD, Grimm RA. Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation. *J Am Coll Cardiol*. 2001;37:691-704. [PMID: 11693739]
181. Goldman MJ. The management of chronic atrial fibrillation: indications for and method of conversion to normal rhythm. *Progress in Cardiovascular Diseases*. 1960;2:465-79.
182. Leung DY, Davidson PM, Cranney GB, Walsh WF. Thromboembolic risks of left atrial thrombus detected by transesophageal echocardiogram. *Am J Cardiol*. 1997;79:626-9. [PMID: 9068521]
183. Stöllberger C, Chnupa P, Kronik G, Brainin M, Finsterer J, Schneider B, et al. Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT Study Group. *Embolism in Left Atrial Thrombi*. *Ann Intern Med*. 1998;128:630-8. [PMID: 9537936]
184. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. *J Am Coll Cardiol*. 1994;23:307-16. [PMID: 8294679]
185. Stoddard MF, Dawkins PR, Prince CR, Longaker RA. Transesophageal echocardiographic guidance of cardioversion in patients with atrial fibrillation. *Am Heart J*. 1995;129:1204-15. [PMID: 7754955]
186. Harjai K, Mobarek S, Abi-Samra F, Gilliland Y, Davison N, Drake K, et al. Mechanical dysfunction of the left atrium and the left atrial appendage following cardioversion of atrial fibrillation and its relation to total electrical energy used for cardioversion. *Am J Cardiol*. 1998;81:1125-9. [PMID: 9605054]
187. Hirsh J, Dalen J, Guyatt G. The sixth (2000) ACCP guidelines for antithrombotic therapy for prevention and treatment of thrombosis. *American College of Chest Physicians*. *Chest*. 2001;119(1 Suppl):1S-2S. [PMID: 11157638]
188. Hwang JJ, Chen JJ, Lin SC, Tseng YZ, Kuan P, Lien WP, et al. Diagnostic accuracy of transesophageal echocardiography for detecting left atrial thrombi in patients with rheumatic heart disease having undergone mitral valve operations. *Am J Cardiol*. 1993;72:677-81. [PMID: 8249844]
189. Manning WJ, Weintraub RM, Waksmanski CA, Haering JM, Rooney PS, Maslow AD, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med*. 1995;123:817-22. [PMID: 7486462]
190. Fatkin D, Scalia G, Jacobs N, Burstow D, Leung D, Walsh W, et al. Accuracy of biplane transesophageal echocardiography in detecting left atrial thrombus. *Am J Cardiol*. 1996;77:321-3. [PMID: 8607421]
191. Manning WJ, Silverman DI, Gordon SP, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *N Engl J Med*. 1993;328:750-5. [PMID: 8437595]
192. Seidl K, Rameken M, Drögemüller A, Vater M, Brandt A, Schwacke H, et al. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. *J Am Coll Cardiol*. 2002;39:1436-42. [PMID: 11985904]
193. Seto TB, Taira DA, Tsevat J, Manning WJ. Cost-effectiveness of transesophageal echocardiography-guided cardioversion: a decision analytic model for patients admitted to the hospital with atrial fibrillation. *J Am Coll Cardiol*. 1997;29:122-30. [PMID: 8996304]
194. Bellandi F, Cantini F, Pedone T, Palchetti R, Bamoshmoosh M, Dabizzi RP. Effectiveness of intravenous propafenone for conversion of recent-onset atrial fibrillation: a placebo-controlled study. *Clin Cardiol*. 1995;18:631-4. [PMID: 8590531]
195. Tommaso C, McDonough T, Parker M, Talano JV. Atrial fibrillation and flutter. Immediate control and conversion with intravenously administered verapamil. *Arch Intern Med*. 1983;143:877-81. [PMID: 6679229]
196. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913-20. [PMID: 10738049]
197. Kochiadakis GE, Marketou ME, Igoumenidis NE, Chrysostomakis SI, Mavrakis HE, Kaleboubas MD, et al. Amiodarone, sotalol, or propafenone in atrial fibrillation: which is preferred to maintain normal sinus rhythm? *Pacing Clin Electrophysiol*. 2000;23:1883-7. [PMID: 11139949]
198. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med*. 1989;321:406-12. [PMID: 2473403]
199. Copley SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation*. 1990;82:1106-16. [PMID: 2144796]
200. Naccarelli GV, Dorian P, Hohnloser SH, Coumel P. Prospective comparison of flecainide versus quinidine for the treatment of paroxysmal atrial fibrillation/flutter. The Flecainide Multicenter Atrial Fibrillation Study Group. *Am J Cardiol*. 1996;77:53A-59A. [PMID: 8607392]
201. van Wijk LM, den Heijer P, Crijns HJ, van Gilst WH, Lie KI. Flecainide

versus quinidine in the prevention of paroxysms of atrial fibrillation. *J Cardiovasc Pharmacol.* 1989;13:32-6. [PMID: 2468933]

202. Aliot E, Denjoy I. Comparison of the safety and efficacy of flecainide versus propafenone in hospital out-patients with symptomatic paroxysmal atrial fibrillation/flutter. The Flecainide AF French Study Group. *Am J Cardiol.* 1996;77:66A-71A. [PMID: 8607394]

203. Van Gelder IC, Crijns HJ, Van Gilst WH, Van Wijck LM, Hamer HP, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. *Am J Cardiol.* 1989;64:1317-21. [PMID: 2511744]

204. Crijns HJ, Gosselink AT, Lie KI. Propafenone versus disopyramide for maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation: a randomized, double-blind study. PRODIS Study Group. *Cardiovasc Drugs Ther.* 1996;10:145-52. [PMID: 8842506]

205. Lee SH, Chen SA, Tai CT, Chiang CE, Wen ZC, Chen YJ, et al. Comparisons of oral propafenone and sotalol as an initial treatment in patients with symptomatic paroxysmal atrial fibrillation. *Am J Cardiol.* 1997;79:905-8. [PMID: 9104904]

206. A randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. UK Propafenone PSVT Study Group. *Circulation.* 1995;92:2550-7. [PMID: 7586356]

207. Reimold SC, Cantillon CO, Friedman PL, Antman EM. Propafenone versus sotalol for suppression of recurrent symptomatic atrial fibrillation. *Am J Cardiol.* 1993;71:558-63. [PMID: 8438741]

208. Bellandi F, Simonetti I, Leoncini M, Frascarelli F, Giovannini T, Maioli M, et al. Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *Am J Cardiol.* 2001;88:640-5. [PMID: 11564387]

209. de Paola AA, Veloso HH. Efficacy and safety of sotalol versus quinidine for the maintenance of sinus rhythm after conversion of atrial fibrillation. SOCESP Investigators. The Cardiology Society of São Paulo. *Am J Cardiol.* 1999;84:1033-7. [PMID: 10569659]

210. Benditt DG, Williams JH, Jin J, Deering TF, Zucker R, Browne K, et al. Maintenance of sinus rhythm with oral d,l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. d,l-Sotalol Atrial Fibrillation/Flutter Study Group. *Am J Cardiol.* 1999;84:270-7. [PMID: 10496434]

211. Juul-Möller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. *Circulation.* 1990;82:1932-9. [PMID: 2242519]

212. Pritchett EL, Page RL, Connolly SJ, Marcello SR, Schnell DJ, Wilkinson WE. Antiarrhythmic effects of azimilide in atrial fibrillation: efficacy and dose-response. Azimilide Supraventricular Arrhythmia Program 3 (SVA-3) Investigators. *J Am Coll Cardiol.* 2000;36:794-802. [PMID: 10987602]

213. Södermark T, Jonsson B, Olsson A, Orö L, Wallin H, Edhag O, et al. Effect of quinidine on maintaining sinus rhythm after conversion of atrial fibrillation or flutter. A multicentre study from Stockholm. *Br Heart J.* 1975;37:486-92. [PMID: 1093559]

214. Bellandi F, Dabizzi RP, Niccoli L, Cantini F. Propafenone and sotalol in the prevention of paroxysmal atrial fibrillation: long-term safety and efficacy study. *Current Therapeutic Research.* 1995;56:1154-68.

215. Antonielli E, Pizzuti A, Pálincás A, Tanga M, Gruber N, Michelassi C, et al. Clinical value of left atrial appendage flow for prediction of long-term sinus rhythm maintenance in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol.* 2002;39:1443-9. [PMID: 11985905]

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