

# Rhythm Versus Rate Control for Atrial Fibrillation and Flutter

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Cordina J, Mead G. Pharmacologic conversion for atrial fibrillation and flutter (Cochrane review). Chichester, UK: Cochrane Library; 2005; issue 4.

The *Annals'* EBEM editors helped prepare the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

To assess the effects of pharmacologic cardioversion of atrial fibrillation and flutter on future risk of stroke, peripheral embolism, and mortality.

## DATA SOURCES

The Cochrane Stroke Group Trials Register was searched up to August 2002, as well as the following electronic databases: MEDLINE (2000 to 2002), EMBASE (1998 to 2002), CINAHL (1982 to 2002), and Web of Science (1981 to 2002). The following journals were hand searched: *Circulation* (1997 to 2002), *Heart* (1997 to 2002), *European Heart Journal* (1997 to 2002), and the *Journal of the American College of Cardiology* (1997 to 2002). Selected abstracts from the following conference proceedings from 1997 to 2002 were also reviewed: British Cardiac Society, European Congress of Cardiology, Scientific sessions of the American Heart Association, American College of Cardiology annual meetings, and scientific sessions of the North American Society of Pacing and Electrophysiology (2001 to 2002). No language restriction was applied.

## STUDY SELECTION

Studies were included if they were randomized controlled clinical trials of rhythm versus rate control for acute atrial fibrillation or flutter in adults. The atrial fibrillation or flutter could be paroxysmal or sustained, of any duration, a result of any cause, and of any length of follow-up. Drugs used for rate control included digoxin,  $\beta$ -blockers, and calcium-channel blockers. Drugs used for rhythm control included oral and intravenous class Ia antiarrhythmics (eg, quinidine, procainamide, disopyramide), class Ic antiarrhythmics (eg,

flecainide, propafenone, moricizine), class II drugs (eg, propranolol, acebutolol, atenolol, bisoprolol, esmolol, metoprolol, nadolol, oxprenolol, sotalol), class III drugs (eg, amiodarone, sotalol, ibutilide, dofetilide, azimilide).

Primary outcome variables were annual risk of stroke, peripheral embolism, and death. Secondary outcome variables were cognitive decline, quality of life, use of anticoagulants, cardiac functional status, and rehospitalization rates.

## DATA EXTRACTION

One author searched the data sources listed above (JC). The quality of the trials in terms of methodology was independently assessed by each of the reviewers. The same author entered the data from these trials into RevMan.

Relative risk (RR) was assessed with 95% confidence intervals (CIs), and  $P < .05$  was considered statistically significant. Heterogeneity of trial data was assessed using the  $I^2$  statistic.

## MAIN RESULTS

From review of the titles and abstracts of the 4,521 identified citations, 4,476 were deemed irrelevant. The 45 remaining citations were retrieved and the full manuscript used to identify 8 articles for potential inclusion. After excluding ongoing trials, retrospective trials, and outcomes not analyzed as intention to treat, a total of 2 trials involving 4,312 patients were included. The majority of the data arose from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.<sup>1</sup> The Table provides a summary of the RRs for the primary and secondary outcomes.

**Table.** Combined meta-analysis (n=4,312).

Outcome Measures	RR (95% CI)	Odds in Favor of
Death	1.14 (1.00–1.31), $P = .06$	Rate control but nonsignificant
Hospitalization rate	1.16 (1.11–1.22), $P < .00001$	Rate control
Drug withdrawal and adverse events (AE)	Not possible to statistically combine data, but individual studies each show statistically significant higher rates of AE in the rhythm control group	Rate control
Risk of stroke or thromboembolism	Meta-analysis not possible because outcomes were reported in only a single study	

## CONCLUSIONS

Meta-analysis of the pooled data does not favor either rate or rhythm control, although there is a trend in favor of rate control. Patients whose atrial fibrillation or flutter is treated with pharmacologic rhythm control do appear to have a higher morbidity compared with patients treated with pharmacologic rate control.

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## COMMENTARY: CLINICAL IMPLICATION

Atrial fibrillation/flutter is the most common sustained cardiac dysrhythmia and is frequently observed in patients presenting to the emergency department (ED). The prevalence is approximately 2.3 million in the United States.<sup>2</sup> According to the Framingham Heart Study,<sup>3</sup> the lifetime risk for development of atrial fibrillation is 1 in 4 for men and women 40 years of age and older, although it is far more prevalent in the age group older than 65 years. Data from the National Hospital Discharge Survey (from 1996 to 2001) on cases that included atrial fibrillation as a primary discharge diagnosis showed that hospitalizations with atrial fibrillation as the first listed diagnosis increased by 34%.<sup>3</sup>

Atrial fibrillation increases the risk of stroke approximately 5-fold and is responsible for about 15% to 20% of all strokes;<sup>4</sup> most important, the cardioembolic subtype of stroke tends to have higher morbidity and mortality,<sup>5</sup> and stroke prevention is a key component of disease management. Anticoagulation of patients with atrial fibrillation has been shown to decrease the risk of subsequent stroke.<sup>6</sup> Antiplatelets are also effective in decreasing risk of future stroke and have been recommended in patients younger than 65 years and without cardiac risk factors. The disadvantage of anticoagulants is their associated increased morbidity as a result of falls and trauma and the fact that a sizeable proportion will be ineligible for such therapy because of history of bleeding. A recent report showed people who had atrial fibrillation and were not treated with anticoagulants had a 2.1-fold increase in risk for recurrent stroke and a 2.4-fold increase in risk for recurrent severe stroke.<sup>1</sup>

The mainstay of treatment for atrial fibrillation is rate or rhythm control, with or without concurrent anticoagulation or antiplatelet therapy. Therapeutic rate control options include drugs (digoxin, calcium channel blockers,  $\beta$ -blockers) or atrioventricular node ablation. Treatment strategies for rhythm control include direct current or pharmacologic cardioversion or an implantable defibrillator. Often, the patient must be treated with long-term antiarrhythmic therapy to maintain sinus rhythm. This review evaluated all the published clinical trial literature that compared rate to rhythm control. Using weak methods to avoid selection bias, yet strong methods to avoid

publication bias, the authors identified 1 large and 1 small trial to date involving approximately 4,500 patients. From these data, there appears to be no clear difference between the 2 approaches. In fact, the rate-control group appears to fare *better* than the rhythm-control group, though this is not conclusive.

The mechanism behind the trend toward increased mortality in the rhythm-control groups is unclear. Possible explanations include inherent cardiotoxicity of the pharmacologic agents used for rhythm control (greater sudden cardiac death, prolonged QT, and torsade de pointes), drug-drug interactions and dosing errors of rhythm control agents, or greater variability in use of anticoagulant therapy in the rhythm-control groups. The fear that selection bias (sicker or more symptomatic patients are randomized to the rhythm control arm) is unlikely, given the balanced groups, large numbers, and randomization methods in the individual studies.

What, then, should emergency physicians do? The most important limitations in the application of these results include that they are based on only 2 studies, the estimates are influenced by the size (and weight) of the AFFIRM trial,<sup>1</sup> AFFIRM patients were older than 65 years and had multiple comorbidities, and most of these patients were in long-term atrial fibrillation. Thus, the issue of rate versus rhythm control in younger patients and those who present acutely with new-onset atrial fibrillation remains unresolved.

## TAKE HOME MESSAGE

With an aging population, emergency physicians can expect to encounter more elderly patients with chronic atrial fibrillation, most of whom are receiving warfarin and a simple rate-control agent. According to this review, there is insufficient survival evidence for emergency physicians to convert this rate-control approach to rhythm control. Moreover, pharmacologic rhythm treatment does appear to increase associated morbidity compared with rate control. These studies do not shed light on the treatment of acutely symptomatic patients with new-onset atrial fibrillation who present to the ED. Indeed, there may be a subset of patients in whom rhythm control is superior to rate control; however, a large ED-based randomized controlled trial conducted in this patient population is urgently needed to answer this question.

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**EBEM TEACHING POINT**

*Intention-to-treat analysis:* Intention-to-treat analysis is the reporting of results from all patients assigned to each of the randomized groups, regardless of whether a given subject in a given group completed or even partook in the intervention. For example, let us assume a study randomized patients into placebo and drug-treatment groups. Suppose one third of patients in the drug group failed to receive the recommended amount of the study drug. This failure is common in effectiveness trials in which nonadherence, dropouts, and adverse effects may result in lower rates of drug use than expected. Although it may be tempting to exclude these patients from further analysis, doing so would bias the results in favor of the study drug, even when a true benefit does not exist. The primary problem in doing so is that these same postrandomization exclusion criteria have not been applied to the control group, and failure to receive the drug may be related to important confounders (eg, disease severity, compliance with other healthy behaviors, comorbidities). Consequently, high-quality studies always analyze patients in the groups they were originally assigned to, regardless of their adherence (partial or complete), dropout status, or adverse effects. When a randomized clinical trial is read, it is important to determine whether all patients assigned

to a treatment arm were actually analyzed—an intention-to-treat analysis.<sup>5</sup>

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