

# Management of atrial fibrillation

## *Rhythm or rate? That is the question*

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Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al; the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347(23):1825-33.

### Research question

For patients with atrial fibrillation (AF) and at high risk of stroke, which has the better outcome: rate control or rhythm control?

### Type of article and design

Prospective, multicentre, randomized, 3-year trial.

### Relevance to family physicians

Atrial fibrillation is the most common sustained cardiac arrhythmia.<sup>1</sup> Its prevalence is estimated at about 1% of the population,<sup>2</sup> and studies have projected the number of patients with AF will increase 2.5-fold in the next 50 years, directly reflecting the aging population.<sup>1,3</sup>

This is important when we consider that AF and age are both strong risk factors for stroke and that AF can lead to a five-fold increase in incidence of stroke.<sup>3</sup> Cerebrovascular disease is the second leading cause of death worldwide.<sup>4</sup> When patients have AF, strokes are typically larger, are associated with higher early mortality, and occur more often in older patients.<sup>5</sup> As well as suffering symptoms, patients with AF are at risk of serious complications, including cardiomyopathy and congestive heart failure (CHF).<sup>6</sup>

The mainstay of initial therapy for AF has long been directed toward maintenance of sinus rhythm with cardioversion and antiarrhythmic agents, an approach commonly believed superior to rate control only.<sup>1,6,7</sup> Many antiarrhythmic agents, however, have potentially serious side effects and have not been shown to be consistently efficacious. Second-line therapy

is often ventricular rate control with atrioventricular node blockers. This approach appears attractive because it involves use of medications with better safety profiles, but how does it compare with regard to outcomes?

### Overview of study and outcomes

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study was designed to compare outcomes of patients with AF treated with rate control and rhythm control. Patients were recruited from 213 clinics in Canada and the United States; they had to be at least 65 years old or have other risk factors for stroke or death (systemic hypertension, diabetes mellitus, CHF, transient ischemic attack or stroke, left atrial size  $\geq 50$  mm, left ventricular ejection fraction [LVEF]  $< 40\%$ ).

The 4060 patients enrolled in the study were randomly assigned to either rate control ( $n = 2027$ ) or rhythm control ( $n = 2033$ ). About 71% of enrolled subjects had a history of hypertension, and 38% had coronary artery disease. Mean age was  $69.7 \pm 9.0$  years; 39.3% were women; and 11.4% belonged to ethnic minorities. Groups were similar in baseline characteristics, including predominant cardiac diagnoses, history of CHF, duration of AF, and LVEF.

In the rate-control arm, the therapeutic target was heart-rate control at less than 80 beats a minute at rest and less than 110 beats a minute with activity. Acceptable drugs included  $\beta$ -blockers and calcium-channel blockers (verapamil or diltiazem), with or without digoxin. In the rhythm-control group, many agents were allowed, but at least two thirds of patients started with either amiodarone or sotalol.

In the rate-control group, continuous anticoagulation with warfarin (to keep international normalized ratios [INR] between 2.0 and 3.0) was mandated in the protocol. This was encouraged in the rhythm-control arm as well, but could be stopped at physicians' discretion if sinus rhythm appeared to

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have been achieved for at least 4 to 12 consecutive weeks with antiarrhythmic drug therapy. Primary end point was overall mortality. Secondary end point was a composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest.

### Results

The large sample size and randomization produced two well balanced arms. Mean duration of follow-up was 3.5 years; maximum was 6 years.

**Primary end point.** More patients died in the rhythm-control than the rate-control group, but the difference was not statistically significant ( $P = .08$ , risk ratio 1.15, 95% confidence interval [CI], 0.99 to 1.34). The trend to higher risk of death in the rhythm-control group remained unchanged ( $P = .07$ ) after adjustment for covariates that were statistically significant (age, coronary artery disease, CHF, LVEF, and hypertension).

**Secondary end point.** Rates of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest were similar in both arms ( $P = .33$ ).

**Central nervous system.** Similar rates of ischemic stroke were seen in both groups (in 77 rate-control patients and 80 rhythm-control patients); annual rate was about 1% per year in each arm. Most strokes occurred in patients who had stopped warfarin (44%) or who had subtherapeutic INRs (28%).

**Other.** Scores on the Mini-Mental State Examination, a cognition test, and certain measures of quality of life were similar in both groups. More patients in the rhythm-control group required hospitalization, however (1374 [80.1%] vs 1220 [73.0%],  $P < .001$ ), and the difference was statistically significant. There were also more adverse drug effects in the rhythm-control group, especially a prolonged QT interval.

### Analysis of methodology

This well designed, ambitious study successfully randomized a large number of patients to rate-control and standard-care (rhythm-control) groups. Of the 4060 patients enrolled, only 71 withdrew consent during the study, and only 26 were lost to follow up. The study demonstrated a trend toward survival advantage for rate-control patients that manifested itself clearly at the end of 2 years. Since mean follow-up time was only 3.5 years, this divergence between the two arms could become even more pronounced. Analysis of specific causes of death is ongoing.

One possible limitation of this study lies in the choice of antiarrhythmic medication used in the rhythm-control group. Choice of drug was left to treating physicians, but antiarrhythmic drugs are a heterogeneous group with potentially very different side effects. If the study protocol had mandated a few specific medications, results might have been different. Also, it would be useful to see survival analyses for specific medications, but that was beyond the scope of this study.

Some patients in both arms had paroxysmal AF and were, therefore, in sinus rhythm for periods during the study. Maintenance of sinus rhythm was not itself a primary end point. Prevalence of sinus rhythm in rate-control patients at 5 years was 35% and in rhythm-control patients was 82% at 1 year and 63% at 5 years. The relatively high prevalence of sinus rhythm in the rate-control arm and low maintenance of sinus rhythm in the rhythm-control arm could have been confounding factors.

Patients had a mean age of 69.7 years; younger patients were included only if they were at high risk of stroke. This limits the ability to generalize results to younger patients not at risk of stroke, such as those with solitary paroxysmal AF. Stroke is the most serious direct consequence of AF, and rates of stroke were similar in both arms. Most strokes in both groups occurred in patients who had either stopped taking warfarin or were using subtherapeutic levels of medication, confirming that anticoagulation therapy should be continued, regardless of rhythm.

### Application to clinical practice

This very important trial should mark a turning point in management of AF. It had an excellent design, a large sample size, and an important primary end point of overall mortality.

A previous, smaller trial, the Pharmacological Intervention in Atrial Fibrillation trial<sup>1</sup> compared rate control with rhythm control in 252 patients for 1 year. No statistically significant difference in symptoms was seen between the two arms (76 vs 70 responders,  $P = .317$ ), although more patients in the rhythm-control group were admitted to hospital (69% vs 24%,  $P = .001$ ).

A smaller Dutch study,<sup>8</sup> published at the same time as AFFIRM, had similar results. Its composite primary end point included cardiovascular death, heart failure, thromboembolic complications, bleeding, need for pacemaker implantation, and severe drug side effects. There was no statistically significant difference between rate and rhythm control with respect to primary end point (17.2% vs 22.6%,

absolute difference -5.4), although the trend again favoured rate control.

Other small studies have been published,<sup>9,10</sup> but none have been as large or lengthy in follow up as AFFIRM. Patients studied in AFFIRM are representative of most patients with AF: elderly or at increased risk of stroke and similar to patients seen in family practice.

The AFFIRM study suggests, despite conventional favour for maintaining sinus rhythm, that rate control is as effective as rhythm control in prevention of overall mortality, and appears better with respect to adverse side effects. Also, AFFIRM makes a strong case for anticoagulation regardless of rhythm in patients with AF or at risk of stroke. ❖

### Bottom line

- There was no significant difference between rate control and rhythm control of AF with respect to overall mortality.
- In general, patients taking antiarrhythmic medications had more adverse effects than those who were not.
- Risk for stroke was similar in both rate- and rhythm-control groups and was related to absence of adequate anticoagulation.
- It might now be preferable to manage AF with rate control and anticoagulation.

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### Points saillants

- Il n'y avait pas de différence significative entre le contrôle du taux et le contrôle du rythme de la FA en ce qui a trait à la mortalité globale.
- En général, les patients qui prenaient des médicaments contre l'arythmie avaient plus d'effets secondaires que ceux qui n'en prenaient pas.
- Le risque d'accident vasculaire cérébral dans les deux groupes témoins, dont le contrôle se basait sur le taux et sur le rythme, était semblable et associé à l'absence d'une anticoagulation suffisante.
- Il pourrait maintenant être préférable de prendre en charge la FA avec le contrôle du taux et l'anticoagulation.

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