

# Rate Control for AF as Good or Better Than Rhythm Control

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Two studies recently published in the *New England Journal of Medicine* conclude that rate control strategy is at least as good as rhythm control for patients with persistent atrial fibrillation (AF). These landmark trials will substantially change the management of this common arrhythmia. The experts do caution, however, that choosing rate over rhythm control is not a valid option in 25-30% of the population who have refractory symptoms, including palpitations, dyspnea, chest pain, fatigue, and fainting.

This *Heartbeat* will cover AF and some old assumptions about it and updated practical implications based on the results of two trials: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (**AFFIRM**) and Rate Control vs. Electrical Cardioversion for Persistent Atrial Fibrillation (**RACE**) trials.

## Atrial Fibrillation



AF is not a benign condition. It is the most common sustained arrhythmia and has a mortality rate twice as high as those in sinus rhythm. Incidence increases with age, from 0.5% among young adults to 6% among those 80 years of age or older.

Valvular heart disease, heart failure, hypertension and diabetes predispose patients of both sexes to AF. Myocardial infarction is associated with AF in men. Alcohol ingestion and thyrotoxicosis are other conditions that increase risk of AF. Patients with “lone” AF—“idiopathic”, idiotic to the doctor and

pathetic to the patient—account for 17% of all cases with AF. They have no clinical, electrocardiographic, or echocardiographic evidence of these risk factors and have a more benign prognosis.

AF can be paroxysmal, persistent, or chronic (permanent). It is associated with palpitations, decreased exercise tolerance, and dyspnea. Hemodynamic impairment results from loss of synchronous atrial contraction [15-20% decrease in cardiac output (CO)] and rapid irregular ventricular rates. A further decrease in CO can occur in patients with stiff ventricles—diastolic dysfunction (most common), hypertension, mitral stenosis, or hypertrophic or restrictive cardiomyopathy.

Serious complications include thromboembolism and stroke. AF increases the risk of stroke by a factor of 17 in those with rheumatic heart disease or those with dilated congestive cardiomyopathies. Non-rheumatic AF increases the risk to 5% per year (a factor of 5)—independently accounting for 15% of all cases of stroke. Risk factors for stroke are additive and include previous stroke or transient ischemic attack (relative risk, 2.5), diabetes (1.7), hypertension (1.6), and increased age (1.4).

## Old Assumptions

The concept that restoration of sinus rhythm in patients with AF is always an important goal has largely been uncontested. For years, rhythm control was preferable to rate control for AF because this strategy was believed to reduce symptoms, improve exercise tolerance, and lower the risk of stroke. In addition rhythm control can retard or prevent progression to permanent AF. Treatment consisted of using anti-arrhythmic drugs such as amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, or sotalol with cardioversion as necessary. By contrast, intuitively less appealing

ventricular rate control has been considered secondary strategy for AF. Therapies include using atrioventricular (AV) nodal blocking agents (digoxin, beta-blockers, or rate-limiting calcium blockers) or ablation of the AV junction and pacemaker implantation to control ventricular response. Rate control does away with proarrhythmia, but it allows AF to continue and does not eliminate symptoms.

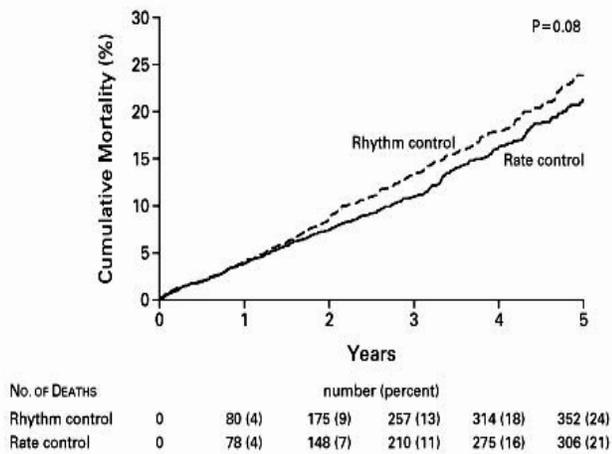
Over time, because of the disappointment with antiarrhythmic drugs (low rate of efficacy, side effects and ventricular proarrhythmia), enthusiasm for antiarrhythmic therapy for cardioversion and maintenance of normal sinus rhythm has decreased. This finally led to two randomized trials comparing the two approaches.

### Trials AFFIRM the Role of Rate

The AFFIRM trial was conducted in 213 centers in the US and Canada.<sup>1</sup> A total of 4060 patients were randomized to rate control therapy using primarily digoxin (51%), beta-blockers (49%), or rate-limiting calcium blockers (41%), or to rhythm control using predominantly amiodarone (39%), sotalol (33%), and propafenone (10%). AV ablation and pacemakers were used in the rhythm arm, if necessary.

All-cause mortality, the primary endpoint of the study, was not significantly different between the two groups, although the survival curves do separate around the second year of follow-up in favor of the rate control group (Fig. 1).

**Fig 1. Cumulative Mortality from any cause in rhythm control group and rate control group. Time zero is the day of randomization. Data truncated at 5 years.**



This makes one suspicious that problems associated with rhythm control might increase over time. Patients with AF often need treatment over decades not years. Also, more rhythm control patients were hospitalized and/or had adverse drug effects and the crossover rate was significantly greater among rhythm control patients, in keeping with the fact that antiarrhythmic drug therapies frequently fail.

The authors saw no differences in several components of secondary endpoint, including functional status, quality of life, or rate of ischemic stroke. However, there was a trend favoring rate control in the occurrence of ischemic stroke (Fig. 2).

**Fig 2. Adverse outcomes in AFFIRM**

End Point	Rate group No. (%)	Rhythm group No. (%)	P *
Death	310 (25.9)	356 (26.7)	0.08
Death, disabling stroke, anoxic encephalopathy, major bleeding	416 (32.7)	445 (32.0)	0.33
Hospitalization after baseline	1220 (73.0)	1374 (80.1)	<0.001

Statistically significant: < 0.05

All patients in this trial were able to tolerate either rate or rhythm control at baseline. It is very important to note that *patients who could not tolerate rate control were excluded from this study*. This is approximately 25-30% of the population. These are the patients who will call the office complaining, “I can’t stand these palpitations” or “I’m short of breath all the time,” even though their ventricular rate is under perfect control.

The authors concluded that the implications of these findings are that *in an elderly population with stroke and risk factors, the rate control strategy, which up until now has been considered by most physicians as second best, is at least as good as the rhythm control strategy and should be elevated to the status of a primary approach*. The caveat here is that the results of AFFIRM only relate to the type of patients who were in the study. So if rate control doesn’t provide symptom relief, which it doesn’t 25-30% of the time, those patients are not candidates to stay in AF with rate control.

In a rhythm control sub-study of AFFIRM amiodarone is associated with the best short term outcomes and is one of the best at maintaining sinus rhythm. Because of its long-term side effects, decisions regarding usage are determined by the prognosis of the patient.

### **Rate not a loser in RACE**

The RACE trial showed that the primary endpoint of CV death, heart failure, thromboembolic complications, bleeding, pacemaker implantation, or severe drug effects occurred in 60 out of 266 patients randomized to rhythm control, compared to 44 out of 256 in the rate control group.<sup>2</sup> The rate of death was similar in the two groups of RACE patients, but thromboembolic complications and adverse drug reactions were greater in the rhythm control group. A higher event rate was seen among female patients and patients with hypertension. A strong trend toward increased mortality with hypertension was also seen in the rhythm control arm of AFFIRM.

The RACE trial confirms that *rate control is an acceptable, and in some cases the preferred, approach to therapy for persistent AF. Anticoagulant therapy should be maintained for either therapy.*

### **Summary/Conclusions/Implications**

In the AFFIRM and RACE trials, with a sum of more than 4500 patients with AF, who were randomly assigned to rhythm control or rate control, the results show that rhythm control had no advantage over rate control with respect to survival.

Both studies underscore the importance of hypertension as a risk factor for AF and the need to *consider hypertension when choosing a treatment strategy. It appears to be a marker of worse outcome in the rhythm control group* and may indicate that hypertensive patients may do better with rate control (further study is needed). A possible explanation is that hypertension is the most common cause of left ventricular hypertrophy, which is associated with an increased risk of drug-related arrhythmic events.<sup>3</sup> Hypertension, even if treated, is a risk factor for embolic stroke among patients with AF and inadequate anticoagulation.<sup>4</sup>

An important secondary finding was that attempted maintenance of sinus rhythm did not reduce the incidence of stroke. In fact there was a trend (not

statistically significant) toward increased stroke events, even with a high prevalence of sinus rhythm. A well-known high incidence of transient asymptomatic AF, even in post-cardioversion patients on antiarrhythmic therapy,<sup>5</sup> raises the possibility that such episodes were responsible for many of the ischemic strokes in this AF population (not proven). *Both studies focused on older higher-risk patients, and in this setting anticoagulation should be used for both strategies.*

In addition, the costs of the drugs and follow-up care necessary for rate control are far cheaper than those used for rhythm control.

“On the basis of these data, *rate control can now be considered a primary approach to the treatment of AF, and rhythm control if used, can be abandoned early if it is not successful,*” comments Dr Cain in an accompanying perspective article.<sup>6</sup> “These options are important to physicians who treat AF. It is no longer necessary to prescribe a drug with borderline benefit-risk ratio for an individual patient because of the belief that rate control therapy does the patient a greater disservice.” This conclusion assumes patients are asymptomatic with the rate control strategy.

### **Plan of Action**

A reasonable approach to the first episode of AF is to do a careful assessment of symptoms and the underlying cardiac disease (history and physical examination and an echocardiogram). Rate control is a perfectly reasonable first option strategy while completing the assessment to determine need for anticoagulation. As compared to rhythm control, rate control has advantages previously unappreciated.

In patients 65 and above or those who have predisposing disease states, who are asymptomatic on rate control, nothing more is necessary other than careful attention to anticoagulation.

In younger patients who don't convert, or those who remain symptomatic on rate control, cardioversion may be performed initially without the use of antiarrhythmic drugs, thereby avoiding potential side effects—following anticoagulation guidelines. If AF recurs and/or symptoms persist despite rate control, repeated cardioversion with the addition of antiarrhythmic drugs should be considered. Dr Rodney H Falk adds a “word of caution,” saying,

“There remains a substantial proportion of patients in whom, AF causes symptoms despite pharmacologic attempts to control heart rate.” For these patients, Falk says, “The goal is still maintenance of sinus rhythm, and the quest for better drugs and techniques to achieve this goal will and should continue.”<sup>7</sup>

Non-pharmacologic AV ablation with a permanent pacemaker is an option in patients who remain symptomatic despite adequate rate control or in those refractory to or intolerant to rhythm control. If a patient has an asymptomatic recurrence of persistent AF, rate control is certainly an option, especially if hypertensive.

Pulmonary vein ablation (PVA), which is not covered in these two studies, is a new mode of therapy and is

gaining more and more acceptance as a strategy for the possible “cure” of patients with paroxysmal AF. It may be considered for a lot of younger people as one of the early options. If successful, these patients won’t require any medication including anticoagulation. Utilization will depend on further study.

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<sup>1</sup> 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* December 5 2002; 347: 1825-33.

<sup>2</sup> Van Gelder IC et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* December 5 2002; 347: 1834-40.

<sup>3</sup> Reiffel JA. Impact of structural heart disease on the selection of class III antiarrhythmics for the prevention of atrial fibrillation and flutter. *Am Heart J* 1998; 135: 551-5.

<sup>4</sup> Hart RG et al. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. *STROKE* 1999; 30: 1223-29.

<sup>5</sup> Fetsch T et al. How reliable are symptoms for detection of atrial fibrillation in clinical routine? Results of PAFAC trial. *Eur Heart J* 2002; 4: Suppl: 662-662. abstract.

<sup>6</sup> Cain ME. Atrial fibrillation: rhythm control or rate control. *N Engl J Med* December 5 2002; 347: 1822-23.

<sup>7</sup> Falk RH. Management of atrial fibrillation – Radical reform or modest modification. *N Eng J Med* December 5 2002; 347: 1883-84.