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# Atrial fibrillation: Rate control is as good as rhythm control for some, but not all

## ABSTRACT

Four recent trials compared the strategies of rate control vs rhythm control in patients with atrial fibrillation. All of them found a rate control strategy to be equivalent to a rhythm control strategy in terms of primary outcomes, but the findings may not apply equally to all patients.

## KEY POINTS

The studies reinforce the need for continued anticoagulation in both rate and rhythm control strategies in patients with atrial fibrillation and risk factors for stroke.

A rate control strategy is an acceptable alternative to a rhythm control strategy, especially when recurrent atrial fibrillation does not respond well to rhythm control strategies, but individualized treatment remains important.

A rhythm control approach may remain justified in cases of new-onset or first-episode atrial fibrillation, in patients who are younger, or in patients who continue to have symptoms despite rate control.

MANY CLINICIANS are questioning the need to restore or maintain sinus rhythm with antiarrhythmic drugs or electrical cardioversion in patients with atrial fibrillation, after four recent trials suggested that a strategy of merely controlling the ventricular rate produces equivalent results.

However, the results from these studies are not necessarily applicable to all patients with atrial fibrillation. It is vital to analyze these studies critically to determine which patients might benefit from either rate control or rhythm control.

## WHAT WE THOUGHT ABOUT THE TWO STRATEGIES

Before the four studies were performed, rhythm control was thought to have several advantages over rate control: a potential for better improvement in quality of life, greater exercise capacity, more complete relief of symptoms, lower risk of stroke, the possibility of stopping anticoagulation if sinus rhythm is maintained, and the theoretical benefits of potentially reversing atrial structural or electrical remodeling (TABLE 1).

On the other hand, potential benefits of rate control were thought to include a lower risk of adverse effects, such as fatal arrhythmias, and lower cost because the treatment regimen is simpler.

## FOUR RANDOMIZED STUDIES

The four randomized trials of rate control vs rhythm control are summarized in TABLE 2.

**TABLE 1**

**Rate control vs rhythm control for atrial fibrillation: What we thought, what we know now**

| | WHAT WE THOUGHT | WHAT WE KNOW NOW |
|---|---|---|
| **Advantages of rate control** | Lower risk of adverse events?<br>Lower risk of death?<br>Lower cost? | Lower risk of adverse events<br>Trend toward lower risk of death<br>Fewer hospitalizations |
| **Advantages of rhythm control** | Better relief of symptoms?<br>Better exercise tolerance?<br>Lower risk of stroke?<br>Potential to stop anticoagulation?<br>Reverse remodeling? | Comparable relief of symptoms<br>Better exercise tolerance in younger patients<br>Comparable risk of stroke<br>Anticoagulation must be continued<br>Reverse remodeling not yet answered |
| **Bottom line** | Rhythm control is better? | Rate control is an acceptable alternative to rhythm control in many patients |

**None of the four studies found any significant difference in primary end points with rhythm control**

### Pharmacological Intervention in Atrial Fibrillation (PIAF) study

**Patients.** PIAF,[1] a German study, included 252 patients with persistent, symptomatic atrial fibrillation that had lasted 7 to 360 days. The mean age was 61 ± 9 years in the rate control group and 60 ± 10 years in the rhythm control group.

**Treatment.** The rate control strategy aimed at controlling symptoms by controlling the ventricular rate with diltiazem, with additional therapy at the discretion of the physician if further rate control was required. No attempt was made to convert atrial fibrillation to sinus rhythm.

The rhythm control strategy consisted of amiodarone followed by cardioversion, if necessary, and then maintenance amiodarone. Further treatment for recurrences of atrial fibrillation was at the discretion of the physician.

All patients received anticoagulation therapy; the target international normalized ratio (INR) of the prothrombin time was 2.0 to 3.0.

**End points.** The primary end point was improvement in symptoms, including palpitations, dyspnea, and dizziness.

Other outcomes measured were the distance patients could walk in 6 minutes, changes in heart rate in atrial fibrillation, stabilization of sinus rhythm as assessed by Holter monitoring, number of hospital admissions, and quality of life.

Follow-up was for 1 year.

**Results.** At 1 year, 56% of the patients in the rhythm control group were in sinus rhythm, compared with 10% of patients in the rate control group.

Quality of life and symptoms improved over time in both groups, with no significant differences between the two groups. Exercise tolerance, as measured by the 6-minute walk test, was better in the rhythm control group.

On the other hand, significantly more patients were admitted to the hospital in the rhythm control group (69% vs 24%, $P = .001$). Treatment was stopped due to medication side effects in 25% of the rhythm control patients, compared with 14% of the rate control patients.

### Strategies of Treatment of Atrial Fibrillation (STAF) pilot study

**Patients.** STAF,[2,3] another German study, included 200 patients with one or more of the following: atrial fibrillation lasting more than 4 weeks, left atrial size greater than 45 mm, congestive heart failure (New York Heart Association functional class II or greater), left ventricular ejection fraction less than 45%, or one or more cardioversions with recurrence of atrial fibrillation. The mean age was 65 in the rhythm control group and 66 years in the rate control group.

**Treatment.** The rate control strategy

**TABLE 2**

## Randomized trials of rate vs rhythm control for atrial fibrillation

| TRIAL* | N | MEAN AGE (YEARS) | FOLLOW-UP | PRIMARY END POINT | RATE CONTROL | RHYTHM CONTROL | *P* VALUE |
|---|---|---|---|---|---|---|---|
| **PIAF**[1] | 252 | 61 | 1 year | Symptom improvement | 60.8% | 55.1% | .317 |
| **STAF**[2,3] | 200 | 66 | 19.6 months | Composite‡ | 9% | 10% | NS |
| **RACE**[4] | 522 | 68 | 2.3 years | Composite§ | 17.2% | 22.6% | .11 |
| **AFFIRM**[5] | 4,060 | 69.7 | 3.5–6 years | Overall mortality | 25.9%† | 26.7%† | .08 |

*PIAF = Pharmacological Intervention in Atrial Fibrillation, STAF = Strategies of Treatment of Atrial Fibrillation pilot study, RACE = Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation, AFFIRM = Atrial Fibrillation Follow-Up Investigation of Rhythm Management; see text for entry criteria and findings of the studies other than the primary end points

†Derived from Kaplan-Meier analyses

‡Death from any cause, cerebrovascular event, cardiopulmonary resuscitation, systemic embolism

§Cardiovascular death, heart failure hospitalization, thromboembolic complications, severe bleeding, pacemaker implantation, severe adverse effects of therapy

included anticoagulation, digoxin, beta-blockers, calcium channel blockers, or atrioventricular (AV) node ablation and a pacemaker, if necessary. The rhythm control strategy included anticoagulation, electrical cardioversion, amiodarone, or a class I antiarrhythmic drug.

**End points.** The primary end point was a composite of death from any cause, cerebrovascular events (stroke, transient ischemic attack), need for cardiopulmonary resuscitation, or systemic embolism.

Follow up was for at least 1 year, with a mean of approximately 19.5 months.

**Results.** In the preliminary results,[2] the composite primary end point occurred in 9 patients in the rate control group and 10 in the rhythm control group, which was not significantly different. All but 1 of the 19 patients who reached an end point were in atrial fibrillation at the time.

There were also no significant differences in the incidences of syncope, bleeding, or worsening heart failure or in quality of life measures. Rhythm control patients had more hospitalizations and longer lengths of stay, primarily due to repeated cardioversions and antiarrhythmic drug loading.

At 3 years, only 23% of the patients who had undergone cardioversion were still in sinus rhythm.

### Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study

**Patients.** RACE,[4] a Dutch trial, enrolled 522 patients with persistent atrial fibrillation or flutter that had lasted between 24 hours and 1 year. To enter, all had to have undergone one or two electrical cardioversions over the prior 2 years and be on oral anticoagulation.

The mean age was 68 years. Risk factors for stroke were present in 90% of the rate control group and 91% of the rhythm control group.

**Treatment.** Patients in the rate control group received beta-blockers, calcium channel blockers, or digitalis, with a target heart rate of less than 100 beats per minute. If they had continuing symptoms, intolerable side effects, or progressive left ventricular dysfunction, they underwent electrical cardioversion or AV junction ablation with implantation of a permanent pacemaker.

In the rhythm control group, patients underwent cardioversion and then started sotalol. If atrial fibrillation recurred late (ie,

**Even after cardioversion, patients at risk of stroke must continue warfarin**

after 6 months), electrical cardioversion was repeated. If atrial fibrillation recurred sooner, sotalol was changed to flecainide or propafenone. Then similarly, if atrial fibrillation recurred late after starting flecainide, electrical cardioversion was again performed; if it recurred early, the drug was changed to amiodarone and cardioversion was performed. If atrial fibrillation recurred late after starting amiodarone, electrical cardioversion was again performed; for early recurrences on amiodarone, atrial fibrillation could be accepted or AV junction ablation could be performed.

Anticoagulant therapy consisted of oral acenocoumarol or phenprocoumon (both of which are similar to warfarin), with a target INR of 2.5 to 3.5. However, patients in the rate control group could take aspirin instead of these drugs if they were younger than 65 years and if they had no underlying cardiac disease (ie, if they had "lone" atrial fibrillation). All other rate control patients received the oral anticoagulant drugs.

Patients in the rhythm control group could stop oral anticoagulation or take aspirin 80 to 100 mg daily instead if they achieved long-term sinus rhythm, although oral anticoagulation was required at least 1 month before and after electrical cardioversions.

**AFFIRM: No survival advantage with rhythm control vs rate control in atrial fibrillation**

**End points.** The primary end point was a composite of cardiovascular death, heart failure requiring hospitalization, thromboembolic complications, severe bleeding, pacemaker implantation, or severe adverse effects of therapy.

**Results.** After a mean follow up of 2.3 years, 39% of the rhythm control group were in sinus rhythm vs 10% of the rate control group. Half of the patients in sinus rhythm had undergone spontaneous conversion and half had undergone electrical cardioversion for intolerable symptoms.

The primary end point occurred in 17.2% of the rate control group and 22.6% of the rhythm control group, which was not significantly different.

More rhythm control patients experienced adverse effects of antiarrhythmic drugs than did rate control patients (4.5% vs 0.8%), but there were no other significant differences in other components of the composite end point. In addition, thromboembolic complications were more frequent in the rhythm control group, although most events occurred after stopping oral anticoagulant therapy or with a subtherapeutic INR.

### Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study

The AFFIRM trial[5–7] was the largest study to date that compared rate vs rhythm control strategies, and the only one of the four studies with sufficient statistical power to detect a difference in mortality.

**Patients.** The study enrolled 4,060 patients from sites in the United States and Canada. All were at least 65 years old (mean age 69.7 years) or had a risk factor for stroke or death. Risk factors included hypertension; diabetes mellitus; congestive heart failure; prior transient ischemic attack, cerebral vascular accident, or systemic embolus; a left atrial size of 50 mm or larger; a left ventricular shortening fraction less than 25%; or a left ventricular ejection fraction less than 40%.

Patients had atrial fibrillation that, in the clinical judgment of the investigators, was likely to recur, likely to cause illness or death, and warranted long-term treatment. They also had to be candidates for anticoagulation therapy. Cardioversion was allowed before randomization; however, if the cardioversion was unsuccessful, the patient was excluded.

**Treatment.** In the rate control group, beta-blockers, calcium channel blockers (verapamil or diltiazem), digoxin, or a combination of drugs was used. Heart rate control was usually assessed by a 6-minute walk test. The target heart rates were less than 80 beats per minute at rest and 110 beats per minute or less during the 6-minute walk test.

In the rhythm control group, antiarrhythmic drugs were selected by the treating physician according to guidelines; the drugs used were amiodarone, disopyramide, dofetilide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, and combinations of these drugs. Cardioversion was performed as needed.

After pharmacologic trials of at least two agents in either group, patients were allowed to undergo nonpharmacologic therapies, including radiofrequency ablation, the maze

procedure, or pacing. However, ablative therapies were used only rarely.

Anticoagulation with warfarin was mandatory in the rate control group, with a target INR of 2.0 to 3.0. Anticoagulation was recommended for the rhythm control group but could be stopped if the patient had been in sinus rhythm for at least 4 consecutive weeks (preferably 12 weeks) with antiarrhythmic drug therapy.

**End points.** The primary end point was overall mortality. Secondary end points included a composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest. Measurements of quality of life and functional status were performed in a subset of patients.

The mean follow up was 3.5 years, with a maximum of 6 years.

**Results.** At 5 years, 35% of the patients in the rate control group were in sinus rhythm, compared with 63% in the rhythm control group.

Many patients crossed over from one treatment group to the other: 37.5% in the rhythm control group and 14.9% in the rate control group. There were also frequent crossovers back to the original treatment.

More than 85% of patients in the rate control group were taking warfarin at each assessment during the study. However, after the first 4 months of the trial, warfarin use declined to approximately 70% in the rhythm control group.

Overall mortality was not significantly different between the rate control and rhythm control groups. However, there was a trend toward more deaths in the rhythm control group than in the rate control group ($P$ = .08, adjusted $P$ = .07). The only prespecified subgroups that showed hazard ratios with trends toward a benefit with the rhythm control strategy were those younger than 65 years, and patients with congestive heart failure. The rate control strategy was associated with a statistically significant lower risk of death in patients with coronary artery disease, no congestive heart failure, or aged 65 years or older. The rest of the subgroups analyzed had either no difference or trends toward a benefit with rate control (**FIGURE 1**).

**AFFIRM data:**
**Rate control is at least as good as rhythm control for most subgroups**

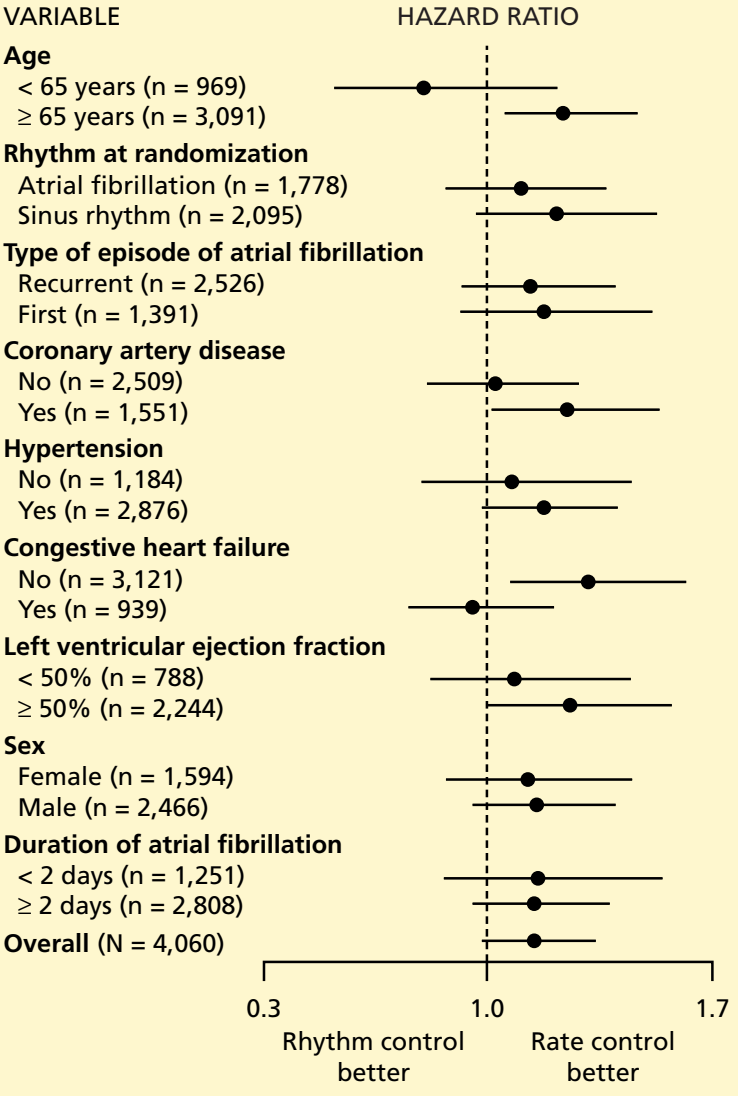


**FIGURE 1.** Hazard ratios for death in prespecified subgroups in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. The numbers in the groups do not total 4,060 for all variables because of incomplete reporting. The ratios shown are for the rhythm control group as compared with the rate control group.

FROM WYSE DG, WALDO AL, DIMARCO JP, ET AL. A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION. N ENGL J MED 2002; 347:1825–1833.

The composite end point likewise was not significantly different between groups, although in the rhythm control group there were higher incidences of torsade des pointes and cardiac arrest due to pulseless electrical activity, bradycardia, or nonventricular fibrillation or tachycardia rhythm, as well as more hospitalizations after baseline. Ischemic strokes occurred equally frequently in both groups, mostly in patients in whom warfarin was stopped or was subtherapeutic.

Overall quality of life, studied in a subset of patients recruited from 25% of the study sites, improved with time in both groups although measures were similar between groups. Results of functional status testing are pending, including 6-minute walk testing and Mini-Mental State Examinations.

## CONCLUSIONS FROM THE FOUR STUDIES

None of the four randomized trials showed any significant differences between the rate and rhythm control strategies in any primary end point (TABLE 2).

The overall mortality rate was similar with both strategies, although the AFFIRM study demonstrated a trend toward a lower mortality rate with the rate control strategy.

There was no significant difference in symptom improvement between strategies in PIAF or in the composite end points in the STAF pilot trial and RACE. Quality of life and symptoms improved with time but, overall, appeared similar. Exercise tolerance appeared better in the rhythm control arm of PIAF.

The rhythm control strategy was associated with more hospitalizations and higher risk of other arrhythmias.

Of note: sinus rhythm was difficult to maintain in the long term in all four studies, and crossover rates were high with both strategies.

Also of note: a rhythm control strategy did not reduce the risk of stroke. AFFIRM showed no reduction in thromboembolism with rhythm control, and in RACE the incidence of thromboembolism was higher in the rhythm control group. In both of these studies most events occurred either off anticoagulation therapy or with subtherapeutic anticoagulation.

**Warfarin is the only therapy reported to improve survival in atrial fibrillation**

## IMPLICATIONS FOR MANAGEMENT

### Anticoagulation is important, even with rhythm control

One of the main implications of the RACE and AFFIRM studies is that anticoagulation remains important in patients with risk factors for stroke, even with a rhythm control strategy and apparent maintenance of sinus rhythm. Both studies enrolled patients who were older and who had risk factors for stroke. Thus, despite maintenance of sinus rhythm for 4 weeks after cardioversion, the continued risk for stroke confirms that anticoagulation should be continued in these patients with risk factors.

Current guidelines recommend continued anticoagulation with warfarin in these patients whether they have chronic persistent or paroxysmal atrial fibrillation.[8,9]

In fact, warfarin is the only intervention or pharmacologic therapy that has been reported to improve survival in patients with atrial fibrillation. In a combined analysis of five randomized studies of warfarin, the Atrial Fibrillation Investigators[10] reported that warfarin reduced the risk of death by 33%.

### An individualized approach is needed

All four studies confirm that rate control is acceptable as a primary approach or if attempts at rhythm control yield unsatisfactory results. However, these trials enrolled patients with persistent or recurring atrial fibrillation expected to require long-term management. An attempt at cardioversion for new-onset, first-episode, or persistent atrial fibrillation was permitted or even encouraged prior to randomization in AFFIRM.

Thus, patients with new-onset atrial fibrillation may warrant at least an initial rhythm control approach with cardioversion or antiarrhythmic drug therapy, at least in the short term. In addition, atrial fibrillation that remains symptomatic despite adequate rate control may still justify a rhythm control approach, particularly as fewer patients with significant symptoms in atrial fibrillation may have been enrolled in these trials.

Finally, results of these studies may not apply as powerfully to younger patients, who have a longer risk for developing the potential

complications of structural remodeling or who may have more symptoms. The mean age was 68 years in the RACE study and 70 years in AFFIRM. In AFFIRM, there was a trend toward a benefit in favor of rhythm control for patients younger than 65 years. In PIAF, where the mean age was slightly younger (60–61 years), exercise tolerance was better with a rhythm control strategy.

In addition, many younger patients may be candidates now or in the future for nonpharmacologic approaches, such as curative ablation, which were used only rarely in these studies.

Thus, an individualized approach to patients with atrial fibrillation remains important. While rate control can be rationalized as primary therapy, particularly in patients at high risk for arrhythmias, who are elderly, or who have minimal symptoms, rhythm control may still be justified in younger patients or patients who still have symptoms despite adequate rate control. In addition, patients with new or first-episode atrial fibrillation often warrant at least an initial trial of rhythm control.

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**Rhythm control may still be justified in young patients and new-onset or symptomatic disease**