Rhythm control strategies were not better than rate control strategies for atrial fibrillation

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**:1825–33.*

QUESTION: Is a long term rate control strategy as effective as a rhythm control strategy for atrial fibrillation (AF)?

Design

Randomised {allocation concealed*}†, blinded {outcome assessors and monitoring committee}†,* controlled trial with a mean follow up of 3.5 years (Atrial Fibrillation Follow up Investigation of Rhythm Management [AFFIRM] study).

Setting

213 clinical sites in North America.

Patients

4060 patients who were ≥65 years of age (mean age 70 y, 61% men) or had other risk factors for stroke or death; had AF that was likely to be recurrent, likely to cause illness or death, and warranted long term treatment; and had no contraindications to anticoagulants. Follow up was 98%.

Source of funding: National Heart, Lung and Blood Institute.

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Abstract and commentary also appear in ACP Journal Club.

Intervention

2027 patients were allocated to rate control using the following drugs alone or in combination as selected by the treating physician: β blockers, calcium channel blockers (verapamil and diltiazem), or digoxin. Target heart rate was ≤80 beats/min at rest and ≤110 beats/minute during the 6 minute walk test. Continuous anticoagulation was required. 2033 patients were allocated to rhythm control using the following antiarrhythmic drugs alone or in combination: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, or dofetilide. Cardioversion could be used if necessary. Continuous anticoagulation was encouraged, but could be stopped if sinus rhythm was maintained for ≥4, but preferably 12, consecutive weeks with antiarrhythmic drugs.

After failure of ≥2 trials of either a rate control or rhythm control drug, patients could be considered for non-pharmacological therapy, such as radio frequency ablation, a maze procedure, and pacing techniques as appropriate to the randomised strategy. The goal for anticoagulation with warfarin was an international normalised ratio of 2.0–3.0.

Main outcome measures

The main outcome was overall mortality. A secondary outcome was a composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest.

Main results

Analysis was by intention to treat. During the course of the study, 248 patients crossed over from the rate control group to the rhythm control group, and 594 patients from the rhythm control group crossed over to the rate control group. The rate control and rhythm control groups did not differ for death (table) or the secondary composite endpoint (32.7% *v* 32.0%, p=0.33).

Conclusion

A rate control strategy and a rhythm control strategy had similar effects on mortality and cardiovascular morbidity in patients with atrial fibrillation.

Rate control v rhythm control for atrial fibrillation‡

Outcome	Rate control	Rhythm control	RRI (95% CI)	NNT
Mortality	25.9%	26.7%	12% (–0.9 to 28)	Not significant

‡Abbreviations defined in glossary; RRI, NNT, and CI calculated from control event rate and hazard ratio reported in original article.

*See glossary.

†Information provided by author.

COMMENTARY

The AFFIRM trial and the RACE trial, along with 2 other recent randomised controlled trials—Strategies of Treatment in Atrial Fibrillation[1] and Pharmacologic Intervention in Atrial Fibrillation[2]—support the current equivalence of rate control and rhythm control in most patients with AF. None of the trials found significant differences in variously measured endpoints, such as total mortality, cardiovascular related deaths, thromboembolic events, bleeding episodes, symptoms, and quality of life. These trials reflect the general demographics of patients with persistent or likely recurrent AF, with mean ages of 60–70 years and high proportions of concomitant coronary heart disease, heart failure, and hypertension.

On the basis of these results, rate control should be the first therapeutic choice for many AF patients. Rhythm control is associated with high failure rates for maintaining sinus rhythm after cardioversion, a trend toward higher hospital admission rates (presumably because of the cardioversion procedures themselves), and a higher likelihood of drug toxicity and other adverse events. Pharmacological or electrical cardioversion, surgery, catheter ablation, pacing, and internal cardioversion devices are alternatives for patients in whom rate cannot be controlled. For younger patients with a first episode of AF and those who initially choose a "curative" approach, first line treatment using rhythm control is a reasonable alternative.

An additional advantage to rate control is the understood need to use aspirin, or more typically warfarin, indefinitely to prevent thromboembolic events. The AFFIRM and RACE trials allowed clinicians to stop antithrombotic therapy in rhythm controlled patients if they so desired, but most patients continued receiving antithrombotic preventive therapy. Guidelines support discontinuation of antithrombotic therapy in rhythm controlled patients after a period of stability.[3] This, however, seems imprudent because rhythm is assessed infrequently in day to day clinical practice, AF recurrence is probable for most patients, and data show that patients with AF are more likely to have embolic events as a result of thrombi from other sources.[4–6].

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Rate control was not inferior to rhythm control for recurrent persistent atrial fibrillation

Van Gelder IC, Hagens VE, Bosker HA, 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.*

QUESTION: Is rate control inferior to rhythm control for persistent atrial fibrillation (AF)?

Design

Randomised {allocation concealed*}†, blinded {outcome assessors and monitoring committee}†,* controlled, non-inferiority trial with mean follow up of 2.3 years (Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation [RACE] Study).

Setting

31 centres in the Netherlands.

Patients

522 patients (mean age 68 y, 63% men) with recurrent persistent AF or flutter, 1–2 electrical cardioversions during the previous 2 years, and no contraindications to oral anticoagulation. Exclusion criteria were arrhythmia lasting >1 year, New York Heart Association class IV heart failure, current or previous treatment with amiodarone, or a pacemaker. All patients were included in the analysis.

Intervention

256 patients were allocated to rate control, which comprised digitalis, a non-dihydropyridine calcium channel blocker, and a β blocker, alone or in combination. Target resting heart rate was <100 beats/minute. 266 patients were allocated to rhythm control and had electrical cardioversion without previous treatment with antiarrhythmic drugs, after which they received sotalol, 160–320 mg/day. If AF recurred, electrical cardioversion was repeated, and sotalol was replaced by flecainide, propafenone, or amiodarone. Patients received acenocoumarol or fenprocoumon for electrical cardioversion. Oral anticoagulation could be stopped or changed to aspirin, 80–100 mg/day, if sinus rhythm was present at 1 month.

Main outcome measure

A composite endpoint of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, need for pacemaker implantation, or severe adverse effects of antiarrhythmic drugs. Criterion for non-inferiority was an upper boundary of the 90% confidence interval (CI) ≤10% for the difference between the incidence of the primary endpoint in the rate control group and the rhythm control group.

Main results

Analysis was by intention to treat. The rate control group was not inferior to the rhythm control group for the primary endpoint (table) or for the individual components of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, or pacemaker implantation. The rate control group had fewer severe adverse effects of antiarrhythmic drugs (table).

Conclusion

Rate control was not inferior to rhythm control for persistent recurrent atrial fibrillation and was associated with fewer severe adverse effects from antiarrhythmic drugs.

*See glossary.

†Information provided by author.

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Rate control v rhythm control for recurrent persistent atrial fibrillation at mean 2.3 years follow up‡

Outcomes	Rate control	Rhythm control	Absolute difference (90% CI)
Composite endpoint	17.2%	22.6%	–5.4% (–11.0 to 0.4)
Severe adverse effects	0.8%	4.5%	–3.7% (–6.0 to –1.4)

‡Abbreviations defined in glossary; composite endpoint = death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, need for pacemaker implantation, or severe adverse effects of antiarrhythmic drugs. Criterion for non-inferiority was a CI upper boundary ≤10%.

COMMENTARY—*continued from previous page*

Given that rate control is currently a mainstay of AF treatment, is there a "best drug" for rate control? Probably not. But because cardiac disease and hypertension are common in patients with AF, β blockers such as metoprolol would be an appropriate first choice for patients who can tolerate this class of drugs.[7] The literature suggests that patients may require more than one drug for good rate control.[3]

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