What are the potential and proven advantages for rate or rhythm control of atrial fibrillation?

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Atrial fibrillation is not benign: all patients, even without underlying heart disease, ultimately develop left ventricular dysfunction. Despite theoretical advantages for rhythm control over rate control, of the four recent randomized trials, one showed a trend for lower mortality with rate control while the other three found no difference. However the trials excluded the highly symptomatic arrhythmic patients who are typically younger and, in half the cases, have no associated cardiovascular condition. The trials also omitted to show how sinus rhythm would have influenced morbidity and mortality had it been maintained in more patients. Restoration of sinus rhythm with cardioversion and antiarrhythmic prophylaxis or other nonpharmacologic interventions remains mandatory in such patients. Safer and more effective rhythm control methods would cover an important unmet need.

Keywords: atrial fibrillation; treatment; clinical study; cardioversion; antiarrhythmic drug; nonpharmacological intervention

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Atrial fibrillation (AF) is not a benign condition.[1,2] It causes symptoms like palpitations, chest pain, dyspnea, and fatigue. Some patients experience presyncope at arrhythmia onset or termination. All patients with longer-lasting AF develop left ventricular dysfunction, even those without underlying heart disease, and some incur a tachycardiomyopathy. Apart from the above, AF is associated with excess thromboembolic complications. Finally, due to treatment of AF with oral anticoagulation and antiarrhythmic drugs, bleeding and severe adverse effects, respectively, may occur.

The optimal treatment regimen remains unclear. For years, maintenance of sinus rhythm has been the main therapeutic goal, using repeated electrical cardioversion (ECV) and prophylactic antiarrhythmic drugs (rhythm-control strategy).[3] The rationale for this approach was that it was expected to reduce symptoms, reduce the incidence of heart failure, improve exercise tolerance, reduce the risk of thromboembolic complications and bleeding (after eventual discontinuation of oral anticoagulation), improve quality of life, and improve survival.[4] However, frequent recurrences of AF and (life-threatening) side effects of antiarrhythmic drugs decrease the potential benefits of ECV.[5-7] An alternative approach is acceptance of AF, with therapy aimed at adequate control of the ventricular rate during AF using negative chronotropic drugs and prevention of thromboembolic complications with oral anticoagulation (rate-control strategy). Recently, four studies, the North American AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the European PIAF (Pharmacological Intervention in Atrial Fibrillation), RACE (RAte Control versus Electrical cardioversion for persistent atrial fibrillation), and STAF (Strategies of Treatment of Atrial Fibrillation) studies,[8-11] investigated whether rate control was equivalent, or not inferior, respectively, to rhythm con-

SELECTED ABBREVIATIONS AND ACRONYMS

AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
CTAF	Canadian Trial of Atrial Fibrillation
ECV	electrical cardioversion
PIAF	Pharmacological Intervention in Atrial Fibrillation
RACE	RAte Control versus Electrical cardioversion for persistent atrial fibrillation
STAF	Strategies of Treatment of Atrial Fibrillation

trol. The primary end point was mortality in AFFIRM, improvement in AF-related symptoms in PIAF, a composite of morbidity (heart failure, thromboembolic complications, bleeding, adverse events related to antiarrhythmic drugs, and pacemaker implantation) and mortality in RACE, and a composite of death, ischemic stroke, and major embolism in STAF.

In this article, we discuss the beneficial effects of both rate control and rhythm control in terms of prevention of morbidity and mortality due to (treatment of) AF.

REDUCTION OF SYMPTOMS AND IMPROVEMENT IN QUALITY OF LIFE

Symptoms during AF differ from patient to patient. The clinical basis of AF-related symptoms is not completely established. It is believed that they are related to the severity of the underlying heart disease and the hemodynamic deterioration associated with the high and irregular ventricular rate and loss of atrial contribution to cardiac output. Younger patients with paroxysmal AF often report more complaints. Depending on the patient groups investigated, different data on symptoms and impairment of quality of life are reported. Savelieva and Camm showed that, in at least one third of AF patients, no obvious symptoms were observed,[12] which is in accordance with our RACE data in patients with persistent AF.[10] Hamer,[13] in contrast, reported that symptoms related to *paroxysmal* supraventricular tachycardia without underlying heart disease (38% of the patients had AF) were troublesome in 68% of patients.

Quality of life using the Short Form–36 (SF-36) health survey questionnaire (which may a better method to assess symptoms) was significantly worse in patients with paroxysmal and persistent AF, compared with healthy controls.[9,11,14,15] Most information about changes in quality of life in patients with AF comes from highly symptomatic patients who are resistant to drug therapy and undergo pacemaker implantation and subsequently atrioventricular node ablation. In these patients, quality of life improved significantly after the procedure.[13,16,17] Recently, the effects of either rhythm-control or rate-control therapy (using negative chronotropic drugs and not atrioventricular node ablation) were investigated. The CTAF (Canadian Trial of Atrial Fibrillation) showed that in patients with *symptomatic* AF (40% had persistent AF), quality of life improved after 12 months of follow-up with either amiodarone, sotalol, or propafenone, especially for those who kept sinus rhythm after conversion.[14] In the AFFIRM, RACE, and STAF studies, quality of life did not change significantly during long-term follow up, neither with rate control nor with rhythm control.[8,11,15] Patients in the rhythm-control group who maintained sinus rhythm, however, showed a minor improvement in quality of life.[18] In contrast, the PIAF investigators showed a significant improvement in quality of life at 12 months' follow-up for almost all SF-36 subscales in both the rate- and rhythm-control groups.[9] Accordingly, 60% and 56% of patients in the rate- versus rhythm-control group, respectively, reported improvement in clinical symptoms (ie, primary end point of PIAF). Importantly, in that study, only symptomatic patients were included, whereas in the RACE study, 70% of patients were symptomatic. Taken together, improvement in quality of life can be expected especially in the highly symptomatic patients, irrespective of treatment regimen. Even so, some data suggest that quality of life may improve after restoration of permanent sinus rhythm. In general, however, both rate- and rhythm-control treatment strategies do not seem to affect quality of life importantly. This relates to the fact that long-term maintenance of sinus rhythm is achieved only in the minority of patients and symptoms related to the associated cardiovascular condition may be vast and may even nullify the potential beneficial effects of permanent sinus rhythm.

IMPROVEMENT OR REVERSAL OF HEART FAILURE

AF may cause heart failure by reducing cardiac output due to loss of atrial kick, excessive rate response, rhythm irregularity, progression of the underlying heart disease, and development of tachycardia-related cardiomyopathy. Small-scale studies have demonstrated that, in case of an inadequate control of the ventricular rate during AF (>100 bpm), a tachycardia-related cardiomyopathy may develop,[16,19-21] which is reversible after adequate rate control or rhythm control (ie, restoration of sinus rhythm). Heart failure has, however, also been reported to occur in patients with AF and a normal heart rate.[22] After regularization of the rhythm by His bundle ablation, a significant improvement in the left ventricular ejection fraction could be demonstrated, which suggests that the irregularity per se may contribute to the development of left ventricular dysfunction.[23,24] Thus, either with rate or rhythm control, improvement or reversal of heart failure may be obtained, but data come from individual patients. RACE revealed that admittance for heart failure was similar in patients treated by rate control versus rhythm control, 3.5% (9/256) versus 4.5% (12/266), respectively, during a fol-

low up of 2.3 years. The latter data are probably not an adequate representation of rhythm control since only 39% of patients were in sinus rhythm at the end of follow-up. Also, data on the occurrence of heart failure during rate control may depend on the degree of rate control. In RACE, acceptable rate control was defined as a resting heart rate <100 bpm. The question remains whether rigid rate control (resting heart rate, eg, <80 bpm) may be associated with an improved prognosis, especially in terms of prevention of deterioration of heart failure, compared with the approach used in RACE. The data available now indicate that, during both rate and rhythm control, heart failure may develop or deteriorate either due to progression of the underlying disease or an inadequate control of the ventricular rate, eg, during a recurrent episode of AF, or adverse effects of (antiarrhythmic) drugs.

IMPROVEMENT IN EXERCISE TOLERANCE

Exercise capacity varies considerably in patients with AF and also depends on the severity of the underlying heart disease and patients' age.[25,26] Nevertheless, patients with lone AF may have a reduced maximal oxygen consumption compared with age-matched controls without AF.[26] Several small-scale studies investigated exercise tolerance measured as maximal oxygen consumption before and after restoration of sinus rhythm or long-term acceptance of AF *(Table I).*[25,27-30] Gosselink et al demonstrated in a nonrandomized study that patients who maintained sinus rhythm during a follow-up of 2 years showed an improvement in exercise tolerance.[27] In contrast, patients who were in AF again at that time after an initial successful cardioversion demonstrated a small, but significant, decrease *(Table II).*[9,27] In the randomized PIAF study, patients treated by rhythm control had better exercise tolerance compared with those treated by rate control *(Table II)* though, in that study, the improved exercise tolerance did not translate into a significant improvement in quality of life.[9]

REDUCTION OF THROMBOEMBOLIC COMPLICATIONS

AF is associated with thromboembolic complications, usually stroke. Studies of secondary prevention recently demonstrated that heart rhythm is not an independent risk factor for stroke in patients with nonvalvular AF.[31] Instead, other factors, including age >65 years, history of stroke and hypertension, diabetes mellitus, congestive heart failure, impaired left ventricular function, coronary artery disease,

Study	No. Pts	HR at rest (bpm)		Peak exercise HR (bpm)		Peak VO_2 (mL/min/kg)	
		Pre-ECV	1 mo	Pre-ECV	1 mo	Pre-ECV	1 mo
Lipkin et al,[28] 1988	14	62	70	164*	132	23	26*
Atwood et al,[25] 1988	11	113	76	192*	144	21	23
Lundström et al,[29] 1992	16	75	64	174*	145	23	25*
Van Gelder et al,[30] 1993	8	123	81	184*	147	20	25*
Gosselink et al,[27] 1994	63	96	75	175*	140	21	24*

* $P<0.05$ compared with baseline.

Table I. *Functional capacity before and after electrical cardioversion (ECV) of persistent AF. Pts, patients.*

Study	No. Pts	Peak VO_2 (mL/min/kg)			6-Min walk test (m)		
		Pre-ECV	1 mo	24 mo	Pre-ECV	1 mo	12 mo
Gosselink et al,[27†] 1994	17	21	22	24*			
Gosselink et al,[27‡] 1994	11	21	22	21*			
PIAF rate,[9] 2000	82				502	535	508
PIAF rhythm,[9] 2000	77				500	535	548**

* $P<0.05$.
** $P<0.01$ compared with baseline.
†Pts who were in sinus rhythm after 1 month and 24 months of follow-up.
‡Pts who were in AF after 1 month and 24 months of follow-up.

Table II. *Functional capacity after long-term sinus rhythm or atrial fibrillation (AF) after cardioversion of persistent AF. ECV, cardioversion; Pts, patients.*

	Rate control (N=256)	Rhythm control (N=266)
Death from cardiovascular causes	18 (7.0%)	18 (6.8%)
Cerebral/retroperitoneal bleeding	6	3
Heart failure	4	1
Thromboembolism (stroke)	0	6
Sudden cardiac death	8	8

Table III. *Incidence of cardiovascular death in the RACE study (RAte Control versus Electrical cardioversion for persistent atrial fibrillation).*

and enlarged left atrium, are important. This may relate to the fact that, in addition to the development and subsequent migration of atrial thrombi, emboli originating in the thoracic aorta and the carotid arteries also contribute to stroke.[32] Therefore, it was not surprising that, both in RACE and AFFIRM, rhythm control did not reduce the thromboembolic complication rate. In AFFIRM, all patients had risk factors for thromboembolic complications, in RACE 90% of the patients. The majority occurred either after discontinuation of oral anticoagulation after restoration of sinus rhythm or while receiving inadequate anticoagulant therapy (international normalized ratio [INR] below 2). Therefore, if risk factors are present, lifelong oral anticoagulation is necessary, independently of the chosen treatment strategy and the actual rhythm.

REDUCTION OF BLEEDING

The efficacy of warfarin for prevention of thromboembolic complications must be balanced against the risk of major bleeding. The risk of major bleeding is related to the intensity of anticoagulation. It was believed that rhythm control might reduce the risk of bleeding since, after long-term maintenance of sinus rhythm, oral anticoagulation may be eventually discontinued. However, since it has now been recognized that lifelong oral anticoagulation is necessary in patients with (a history of) AF and risk factors for thromboembolic complications independent of the actual rhythm, the risk of bleeding will not be lowered by rhythm control.

REDUCTION OF MORTALITY

Several cohort studies have demonstrated that the risk of death in subjects with AF is roughly twice that found in subjects with sinus rhythm.[33-36] However, it is a matter of debate whether AF itself results in excess mortality or whether it reflects increased mortality of associated conditions. Patients with lone paroxysmal AF (ie, without underlying heart disease) do not have an impaired prognosis.[35-37] The AFFIRM study investigated whether rhythm control therapy reduced mortality. In that study, there was a trend toward an increased overall mortality in patients treated by rhythm control (25.9% versus 26.7%, P=0.08 in the rate- versus rhythm-control group during a mean follow-up of 3.5 years). Rhythm control was associated with excess mortality among older patients, those with congestive heart failure, and those with coronary artery disease. After adjustment for these covariates, the trends towards an increased mortality in rhythm-control compared with the rate-control group persisted. Also, in this study the majority of patients (87.6%) had underlying heart disease. No data on cause of mortality and differences between both treatment strategies are yet available. In RACE, cardiovascular mortality was comparable between both groups, but the cause of death was different *(Table III).* The above indicates that mortality seems to be comparable with either treatment strategy.

CONCLUSION

As described above, theoretically, rhythm control would have advantages above rate control. Remarkably, there was a trend for a lower mortality in the rate-control treated patients in AFFIRM. Similarly, in the other studies, rhythm control did not differ from rate control. At first glance, this may seem to imply that the attempt to restore sinus rhythm is no longer justified. However, the randomized studies did not deal with the highly symptomatic arrhythmic patient. Typically, this patient is relatively young and does not have associated cardiovascular conditions in half of the cases. In these patients, restoration of sinus rhythm with cardioversion and prophylactic antiarrhythmic drugs or other nonpharmacological interventions remains essential. The development of new, safer and more effective, rhythm-control methods, would cover an unmet need. In this respect it is also important to note that the randomized studies cannot answer the question of how morbidity or mortality would have been influenced if sinus rhythm had been maintained in a significant number of patients. Indeed, long-term maintenance of sinus rhythm could be achieved in only a minority of patients: 56% maintenance of sinus rhythm after 1 year in PIAF, 63% after 5 years in AFFIRM, 39% after 2.3 years in RACE, and 40% after 1 year in STAF.[8-11]

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