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Mending the rhythm does not improve prognosis in patients with persistent atrial fibrillation: a subanalysis of the RACE study

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KEYWORDS
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Aims To compare outcome of AF patients with effective rhythm control with patients treated with rate control.
Methods and results Out of the 266 AF patients randomized to rhythm control in the RACE study, 49 patients turned to long-term sinus rhythm and were continuously treated with oral anticoagulation. The incidence of the primary endpoint in these patients was compared to that in 178 patients out of the initial 256 rate-control patients of RACE who were in AF and using oral anticoagulation continuously. Baseline characteristics of both groups were not different. After a mean follow-up of 2.3 ± 0.6 years, the primary endpoint (a composite of cardiovascular mortality, heart failure, thrombo-embolic complications (TECs), bleeding, serious adverse effects of antiarrhythmic drugs and pacemaker implants) was 22.4% in the rhythm-control group vs. 15.2% in the rate-control group. Multivariable regression analysis indicated coronary artery disease, heart failure, and digitalis as independent risk indicators of cardiovascular morbidity and mortality. Chronic sinus rhythm did not matter.
Conclusion Among patients who remained on warfarin, those who mostly were maintained in sinus rhythm under a rhythm-control strategy did not have a superior prognosis compared to those who remained in AF under a rate-control strategy.

Introduction

Atrial fibrillation (AF) is associated with an unfavourable prognosis.[1,2] Prognosis is determined by the associated cardiovascular disease as well as by arrhythmia-related events. Recent studies showed that rhythm control does not provide any benefit over rate control in terms of morbidity and mortality.[3–6] However, these studies also showed that rhythm control produces stable sinus rhythm in hardly half of the patients. In addition, anticoagulation was discontinued in many cases despite the presence of stroke risk factors. These confounders preclude an assessment of the actual benefits of chronic sinus rhythm. In addition, the relative contribution of the associated cardiovascular disease to morbidity and mortality cannot be established. In a recent AFFIRM substudy, sinus rhythm was associated with survival, as was warfarin use.[7] However, it was unclear from that study whether sinus rhythm was causal or just a marker of survival.

The Rate Control versus Electrical Cardioversion (RACE) study was a randomized comparison of rate vs. rhythm control in patients with persistent AF.[4] Our hypothesis is that the underlying cardiovascular disease determines the risk rather than the arrhythmia itself. In this subanalysis of the RACE study, we addressed the above issues by comparing patients maintaining sinus rhythm in the rhythm-control arm with patients in permanent AF from the rate-control arm.

Methods

Study design

The RACE study was a randomized study comparing long-term effects of rate and rhythm control on morbidity and mortality in patients with persistent AF. The methods and primary outcome of this study have been described before.[4] In short, 522 patients with recurrent persistent AF were randomized to rate or rhythm control, 256 vs. 266 patients, respectively. Patients were seen in the outpatient department at 1, 3, 6, 12, and 24 months after randomization and at the end of the study (30 or 36 months). After documentation of one (non-fatal) endpoint, follow-up was continued to document additional endpoints, with a minimum follow-up of 2 years and a maximum follow-up of 3 years. Rate control was achieved with digitalis, a non-dihydropyridine calcium-channel blocker, or a beta-blocker, alone or in combination. The target

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was a resting heart rate of <100 b.p.m. Patients assigned to the rhythm-control group underwent electrical cardioversions and received antiarrhythmic drugs serially. The primary antiarrhythmic drug was sotalol, thereafter class IC antiarrhythmic drugs and amiodarone were used. The RACE study showed that rate and rhythm-control therapy in patients with persistent AF was equally effective regarding morbidity and mortality.[4] The primary endpoint occurred in 17.2% (44/256) of the patients randomized to rate control vs. 22.6% (60/266) of the patients treated according to the rhythm-control strategy, after a mean follow-up of 2.3 ± 0.6 years.

Patient selection

The rhythm-control strategy resulted in sinus rhythm in only ~40% of cases at the end of follow-up. To study the isolated effect of long-term sinus rhythm, 'intention-to-treat' or 'on treatment' analyses within randomized groups are inappropriate because the rhythm-control group eventually would contain too many AF patients to obtain meaningful results. Therefore, we enriched the sinus rhythm group by only selecting those patients from the rhythm-control arm of RACE who maintained sinus rhythm during the study, and compared them with permanent AF patients from the rate-control group. Considering the objective of this study, we felt justified to use the current selection procedure. Because 100% sinus rhythm is an impossible goal of drug-therapy-based rhythm control of patients with persistent AF, we selected long-term sinus rhythm patients based on the presence of sinus rhythm >75% of the follow-up time, with a maximum of one electrical cardioversion per year. Because thrombo-embolism is a major confounder with respect to our primary study aim, we selected patients who used oral anticoagulation (acenocoumarol or fenprocoumon) throughout the complete follow-up [target international normalized ratio (INR) 2.5–3.5]. In the RACE study, from 4 weeks before until 4 weeks after electrical cardioversion, all patients received acenocoumarol or fenprocoumon (target INR 2.5–3.5). If sinus rhythm was present at 1 month, the oral anticoagulant could be stopped or changed to aspirin (80–100 mg daily). Aspirin was also allowed in patients in the rate-control group who were <65 years old if they had AF without underlying cardiac disease. All other patients received oral anticoagulant therapy. By selecting patients on continuous anticoagulation, a negative selection might be introduced. However, there were no differences in patient characteristics and stroke risk factors, i.e. previous TECs, hypertension, diabetes, older age, impaired left ventricular (LV) function between patients with continuous anticoagulation and interrupted anticoagulation in the chronic sinus group. So, the decision of discontinuation in the chronic sinus rhythm group was made randomly. For the present study, we selected 49 patients with long-term sinus rhythm in the rhythm-control arm and 178 patients with continuous AF in the rate-control arm.

Endpoint definition

The primary endpoint was the composite of death from cardiovascular cause, heart failure, TECs, bleeding, severe adverse effects of antiarrhythmic drugs, and the need for a pacemaker implantation. All events that occurred between randomization and the end of study were recorded. Definitions of the composites of the primary endpoint have been described before.[4] A committee of experts who were unaware of the treatment assignments adjudicated all reported endpoints.

Quality of life questionnaire

Quality of life (QoL) was determined using the Dutch version of the Medical Outcomes Study Short-form health survey (SF-36) questionnaire.[8] In short, the SF-36 contains items to assess physical health (general health perception, physical functioning, role limitations due to physical problems, and bodily pain), as well as mental health (social functioning, role limitations due to emotional problems, mental health, and vitality). QoL was assessed at baseline, after 1 year, and at the end of the study in 36 patients (74%) with chronic sinus rhythm and in 122 patients (69%) with permanent AF.

Statistical analysis

Baseline descriptive statistics are the mean ± standard deviation (SD) or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups, at baseline, follow-up, and end of study, were evaluated by Student's *t*-test or Mann–Whitney *U* test, depending on normality of the data, for continuous data and by Fisher's exact test or χ^2 test for categorical data. Bonferroni adjustment for multiple testing was performed for the drug treatment at the end of the study, echocardiographic measurements and QoL. Kaplan–Meier estimates and Cox proportional hazard regression analysis were performed to study the influence of chronic sinus rhythm on the occurrence of cardiovascular morbidity and mortality over time in the study population. By multivariable regression analysis, the influence of chronic sinus rhythm on the occurrence of cardiovascular morbidity and mortality was adjusted for age, gender, hypertension, diabetes, coronary artery disease, previous bleeding, previous TECs, limited exercise tolerance [New York Heart Association (NYHA) class II/III], and digoxin use. Linearity of the continuous variables with respect to the response variable was assessed by determining the quartiles of their distribution. Thereafter, hazard ratios for each quartile were calculated. In case of a linear trend in the estimated hazard ratios, the variable was introduced in the model as continuous. If no linearity was demonstrated, the variable was further categorized by taking together the quartiles with hazard ratios similar in magnitude, primarily the median value or otherwise based on clinical relevance. Log–log survival curves and time-dependent covariates were used to evaluate adherence of the Cox proportional hazard assumptions. In all analyses, a value of $P < 0.05$ (two-sided) was considered statistically significant.

Results

Characteristics of the patients

Table 1 shows the baseline characteristics of the study population. Patients with long-term sinus rhythm had slightly more often hypertension paralleled by more frequent Angiotensin-converting enzyme-inhibitor (ACE-I) use. *Table 2* shows the baseline echocardiographic measurements.

Follow-up

During a mean follow-up of 2.3 ± 0.6 years, the average heart rate in the rate-control arm was 83 ± 15 b.p.m. Patients in the rhythm-control arm had a slightly lower average rate (78 ± 17; $P = 0.11$). At consecutive visits, the rate was stable in both groups. At the end of follow-up, most rate-control patients were on digitalis, mostly in combination with a beta-blocker (*Table 3*). In the rhythm-control patients, a median of one electrical cardioversion was needed to obtain long-term sinus rhythm. The median duration of sinus rhythm in this group was 93% of the follow-up time (range 75–100%). At the end of follow-up, 15 patients used sotalol, 11 had amiodarone, and 13 patients were on flecainide. NYHA class for heart failure did not change significantly over time and was not different between the two groups (*Figure 1*). During long-term follow-up, left and right atrial sizes were smaller in the

Table 1 Characteristics of the study patients at entry divided by long-term rhythm

Patient characteristics	Sinus rhythm ($n = 49$)	AF ($n = 178$)	*P*-value
Age (years)	70 ± 9	69 ± 9	0.6
Male sex	31 (63%)	108 (61%)	0.9
Total AF duration (days)	482 (27–8513)	517 (14–14 909)	0.5
Duration present episode of AF (days)	31 (1–172)	36 (1–399)	0.2
Complaints of AF	38 (78%)	124 (70%)	0.4
Palpitations	13 (27%)	45 (25%)	0.9
Dyspnea	21 (43%)	60 (34%)	0.2
Fatigue	20 (41%)	63 (35%)	0.5
NYHA class for heart failure			0.4
I	20 (41%)	91 (51%)	
II	28 (57%)	82 (46%)	
III	1 (2%)	5 (3%)	
Coronary artery disease	17 (35%)	45 (25%)	0.2
Valvular disease	9 (18%)	31 (17%)	0.8
Cardiomyopathy	3 (6%)	19 (11%)	0.6
History of hypertension	28 (57%)	77 (43%)	0.1
No heart disease	10 (20%)	37 (21%)	1.0
History of chronic obstructive pulmonary disease	5 (10%)	29 (16%)	0.1
Diabetes mellitus	2 (4%)	22 (12%)	0.1
Previous TEC	8 (16%)	27 (15%)	0.8
Previous bleeding	3 (6%)	13 (7%)	1.0
Drug treatment			
Digitalis alone	15 (31%)	39 (22%)	0.3
Beta-blocker alone	14 (29%)	42 (24%)	0.5
Verapamil or diltiazem alone	1 (2%)	13 (7%)	0.3
Digitalis and beta-blocker	14 (29%)	43 (24%)	0.6
Digitalis and verapamil or diltiazem	3 (6%)	26 (15%)	0.2
Beta-blocker and verapamil or diltiazem	1 (2%)	5 (3%)	1.0
Digitalis, beta-blocker, and verapamil or diltiazem	—	1 (0.6%)	1.0
ACE-I	24 (49%)	46 (26%)	0.003
Angiotensin II receptor antagonist	7 (14%)	12 (7%)	0.1
Diuretics	25 (51%)	74 (42%)	0.3
Cholesterol lowering drug	10 (20%)	20 (11%)	0.1
Resting heart rate (b.p.m.)	92 ± 21	90 ± 20	0.6
Blood pressure (mmHg)			
Systolic	147 ± 22	144 ± 22	0.4
Diastolic	87 ± 10	85 ± 11	0.4

patients maintaining sinus rhythm compared with those with permanent AF (*Table 2*).

Cardiovascular morbidity and mortality

Eleven (22%) and 25 (15%) patients in the sinus rhythm and AF group, respectively, developed at least one endpoint (*Table 4*). Endpoint events were most frequent in the sinus rhythm patients. In particular, TECs and pacemaker implantations were frequent. At the time of their TEC, INR in the four sinus rhythm patients was inadequate (<2.0) in three patients and adequate in one. All four patients had their last cardioversion >7 weeks before. The INR in the rate-control patients at the time of their stroke was <2.0 in eight of nine patients. Bleeding was a significant problem in the rate-control group. INR was >3 at the time of bleeding in all eight patients with a major bleeding. Restoration of sinus rhythm led to pacemaker implants in 6% of patients, whereas pacemakers were only needed in 1% of rate-control patients. The distribution of the components of the endpoint events was similar in the two groups. Kaplan–Meier estimates of the first occurrence of the primary endpoint over time are shown in *Figure 2*. Events were evenly distributed over time in both groups.

Influence of chronic sinus rhythm on cardiovascular morbidity and mortality

By multivariable analysis, long-term sinus rhythm was not associated with event-free survival, rather the reverse, although not statistically significant [adjusted hazard ratio 1.8 (0.8–3.7), $P = 0.1$]. The multivariable regression analysis did show coronary artery disease, limited exercise tolerance (NYHA class II/III), and digitalis use as significant risk indicators of cardiovascular morbidity and mortality (*Table 5*).

Although no difference in the primary outcome was observed, it may be argued that pacemaker implantations, that were more frequently observed in the rhythm-control treated group, are of a lower weight in the primary endpoint

Table 2 Echocardiographic measurements and changes over time according to long-term rhythm

Echocardiographic measurements treatment	Baseline	*P*-value	1 year	*P*-value	2 years	*P*-value	Change from baseline to 2 years	*P*-value
Left atrial size, long-axis view (mm)								
AF	45 ± 7		46 ± 6		46 ± 7		+1.2 ± 6	
Sinus rhythm	45 ± 9	1.0	43 ± 6	0.02	45 ± 8	1.0	+0.7 ± 7	1.0
Left atrial size, apical view (mm)								
AF	65 ± 9		67 ± 9		68 ± 8		+4.2 ± 7	
Sinus rhythm	62 ± 8	0.7	61 ± 9	0.01	63 ± 8	0.01	+0.6 ± 7	0.2
Right atrial size, apical view (mm)								
AF	58 ± 9		61 ± 8		63 ± 7		+4.7 ± 9	
Sinus rhythm	58 ± 8	1.0	54 ± 8	0.01	57 ± 8	0.01	−2.6 ± 7	0.01
LV end-diastolic diameter (mm)								
AF	52 ± 7		52 ± 7		53 ± 7		+0.3 ± 6	
Sinus rhythm	51 ± 7	1.0	53 ± 5	1.0	53 ± 6	1.0	+3.3 ± 5	0.08
LV end-systolic diameter (mm)								
AF	36 ± 8		36 ± 9		36 ± 8		−0.7 ± 8	
Sinus rhythm	36 ± 8	1.0	35 ± 7	1.0	35 ± 6	1.0	−0.6 ± 6	1.0
Fractional shortening (%)								
AF	31 ± 9		32 ± 11		33 ± 9		+1.9 ± 11	
Sinus rhythm	29 ± 11	1.0	34 ± 12	1.0	34 ± 8	1.0	+4.8 ± 11	1.0
Septal wall thickness (mm)								
AF	10 ± 2		10 ± 2		10 ± 2		−0.1 ± 2	
Sinus rhythm	10 ± 2	1.0	10 ± 2	1.0	10 ± 2	1.0	−0.6 ± 3	1.0
Posterior wall thickness (mm)								
AF	10 ± 2		10 ± 2		10 ± 2		+0.1 ± 2	
Sinus rhythm	10 ± 2	1.0	10 ± 2	0.3	10 ± 2	1.0	−0.1 ± 3	1.0

P-value between AF and sinus rhythm patients.

Table 3 Drug treatment at the end of the study

	Sinus rhythm ($n = 29$)	AF ($n = 108$)	*P*-value
Rate control treatment			
Digitalis alone	7 (24%)	21 (19%)	1.0
Beta-blocker alone	11 (38%)	20 (19%)	0.6
Verapamil or diltiazem alone	2 (7%)	12 (11%)	1.0
Digitalis and beta-blocker	1 (3%)	29 (27%)	0.08
Digitalis and verapamil or diltiazem	–	15 (14%)	0.6
Beta-blocker and verapamil or diltiazem	–	2 (2%)	1.0
Digitalis, beta-blocker, and verapamil or diltiazem	–	6 (6%)	1.0
Rhythm control treatment			
Flecainide	8 (28%)	5 (5%)	0.02
Propafenone	1 (3%)	–	1.0
Sotalol	6 (21%)	9 (8%)	1.0
Amiodarone	10 (35%)	1 (1%)	0.02
Other drug treatments			
ACE-I	15 (52%)	39 (36%)	1.0
Angiotensin-II receptor antagonist	4 (14%)	8 (7%)	1.0
Diuretics	19 (66%)	47 (44%)	0.6
Cholesterol lowering drug	10 (34%)	16 (15%)	0.5

All patients were on oral anticoagulants during the complete study.

when compared with hospitalization for heart failure and cardiovascular death. However, after excluding pacemaker implantation as part of the primary endpoint, long-term sinus rhythm remained unrelated to event-free survival [adjusted HR 1.6 (0.7–3.6), $P = 0.29$]. It also may be disputed whether patients who continued oral anticoagulation represent a 'negative selection group' because of the presence of stroke risk factors. We observed no differences in patient characteristics and stroke risk factors between patients who were on continuous anticoagulation vs. those who had their anticoagulation interrupted, both in the chronic sinus rhythm group and in the AF group (data not shown).

Quality of life

Table 6 shows QoL data. At baseline, 1 year, and end of study, no differences in QoL were seen between patients with long-term sinus rhythm and patients with permanent AF on all SF-36 subscales. QoL did not change significantly in both groups during follow-up. Only vitality was reduced in patients with permanent AF compared with those in sinus rhythm (-3 and $+8$, $P = 0.02$).

Discussion

After the rhythm vs. rate-control studies,[3–6] the question remains whether entirely effective rhythm control, i.e. rhythm control producing sustained sinus rhythm will improve prognosis of patients or not compared with rate control. The present analysis of the RACE study strongly suggests that even under optimal conditions of continuous anticoagulation, chronic sinus rhythm does not ameliorate cardiovascular prognosis in this group of persistent AF patients.

Role of long-term sinus rhythm

The reason why maintaining sinus rhythm does not ameliorate morbidity and mortality probably relates to the major impact of the underlying heart disease on prognosis. This is in line with our finding that coronary heart disease as well as exercise intolerance significantly predicts events. In addition, the fact that the type of events was similar in the study groups also supports the notion that heart disease rather than AF determines prognosis. Furthermore, antiarrhythmic and antithrombotic drug treatment provoked a great deal of major adverse effects. In addition, despite sinus rhythm and despite continuous anticoagulation, quite some TECs occurred. Taken together, the underlying heart disease in combination with inefficacious and adverse drugs exerts such negative effect on morbidity and mortality, which long-term normal sinus rhythm cannot make up for those.

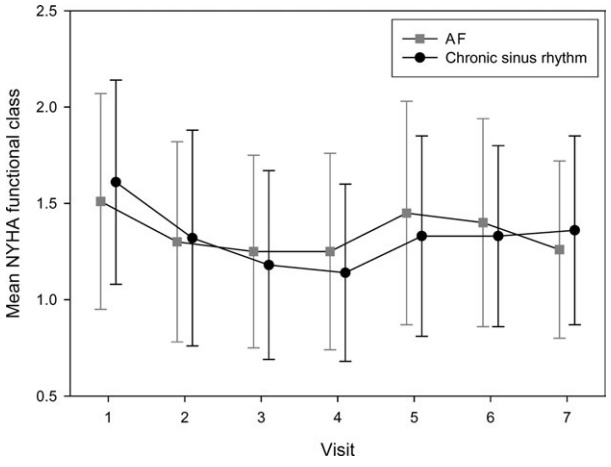

Figure 1 Mean (±SD) NYHA functional class of heart failure at each study visit in patients maintaining chronic sinus rhythm (rhythm control) and patients with permanent AF (rate control).

The importance of underlying heart disease was also observed in a recent substudy reported from the AFFIRM study[7] which showed that increasing age, coronary artery disease, heart failure, diabetes previous stroke or TIA, recent history of smoking, LV dysfunction, and mitral regurgitation were significantly associated with an increased risk of death. Thus, both presence and severity of associated cardiac disease seem important determinants of morbidity and mortality and should receive ample attention when managing AF patients.

In contrast with our findings, the AFFIRM substudy suggested that sinus rhythm is associated with improved survival.[7] However, patients included in this analysis were considered to have maintained sinus rhythm during follow-up if it was present at the moment of a follow-up visit. It may, however, be possible that patients considered to be continuously in sinus rhythm during follow-up may have been in AF in between the follow-up visits. This is even more likely because many paroxysmal AF patients were included in the AFFIRM study.[3] The authors also concluded that because of the retrospective nature of the analysis, they could not exclude that sinus rhythm is just a marker rather than a determinant of survival. The AFFIRM substudy also suggested that the beneficial effects of antiarrhythmic drugs (permanent sinus rhythm) may have been offset by their deleterious effects (pro-arrhythmia, non-cardiac adverse effects). Considering the type of adverse events among the sinus rhythm patients, we do not feel that deleterious antiarrhythmic drugs prevented us from finding beneficial effects of long-term sinus rhythm.

Table 4 Incidence of the primary endpoint and its components according to long-term rhythm[a]

Endpoint	Sinus rhythm ($n = 49$)	AF ($n = 178$)	Absolute difference (95% CI)
Endpoint	11 (22%)	25 (15%)	7.3 (−6.0 to 22.8)
Death from cardiovascular causes	2 (4%)	11 (6%)	−2.1 (−4.2 to 7.9)
Sudden death	—	3 (2%)	
Heart failure	—	3 (2%)	
TEC	2 (4%)	—	
Bleeding	—	5 (3%)	
Heart failure	2 (4%)	6 (3%)	0.7 (−5.6 to 7.0)
TEC	4 (8%)	9 (5%)	3.1 (−5.5 to 11.8)
Bleeding	1 (2%)	8 (5%)	−2.5 (−7.5 to 2.6)
Severe adverse effects of antiarrhythmic drugs	1 (2%)	1 (0.6%)	1.5 (−2.7 to 5.6)
Pacemaker implantation	3 (6%)	2 (1%)	5.0 (−2.1 to 12.1)

[a]Some patients had more than one endpoint.

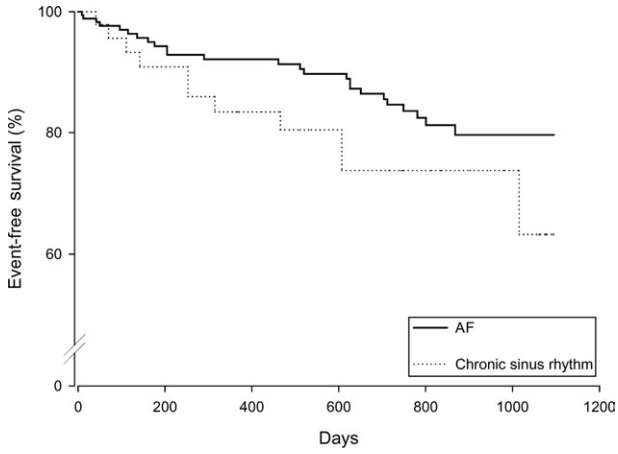

Figure 2 Kaplan–Meier curves for event-free survival of patients maintaining chronic sinus rhythm and patients with permanent AF.

Table 5 Multivariable Cox proportional hazard regression analysis of the occurrence of the primary endpoint over time

Baseline characteristics	Hazard ratio (95% CI)	*P*-value
Effective rhythm control	1.8 (0.8–3.7)	0.1
Age >70 years	1.6 (0.7–3.4)	0.2
Male gender	1.7 (0.7–4.1)	0.2
Hypertension	1.7 (0.8–3.6)	0.2
Diabetes	1.1 (0.2–1.3)	0.9
Coronary artery disease	2.5 (1.2–5.4)	0.02
Previous bleeding	3.0 (1.0–9.4)	0.06
Previous TEC	1.0 (0.3–2.9)	1.0
Heart failure NYHA class II/III	2.5 (1.2–5.5)	0.02
Digitalis use	4.5 (1.7–12.0)	0.003

In line with the above mentioned AFFIRM findings,[7] Pappone *et al.*[9] showed in a retrospective analysis that restoration of sinus rhythm by pulmonary vein ablation reduced mortality and morbidity. In addition, Hsu *et al.*[10] very recently showed that restoration and maintenance of sinus rhythm by radiofrequency ablation, and thus not by drugs, significantly improved cardiac function and symptoms in AF patients with heart failure. Whether it also reduces morbidity and mortality was not investigated. Both ablation studies were not randomized and did not compare rate control with effective rhythm control.

Oral anticoagulation and INR

The INR was too low in almost all patients at the time of their TEC. It is widely known that adequate institution of oral anticoagulation is difficult to achieve. The SPORTIF II trial showed that after 12 weeks of treatment with warfarin, only 57% of the AF patients were within the target range between 2.0–3.0, whereas in 43% of the patients, the actual INR was out of the target range.[11] Thus, in agreement with the previous data, our results also indicate that achieving an adequate INR with the current available oral anticoagulant therapy is difficult but extremely important. Furthermore, it should be noted that despite chronic sinus rhythm thrombi may form and lead to embolization. In the present study, all stroke patients had stroke risk factors. Our results therefore stress again the notion that chronic sinus rhythm does not obviate anticoagulation, especially not if stroke risk factors are present.

Selection of patients

Because current views support the use of oral anticoagulation irrespective of the rhythm, we evaluated only patients who were on oral anticoagulation during the complete follow-up. By selecting patients on continuous anticoagulation, a negative selection might have been introduced. However, we observed no differences in patient characteristics and stroke risk factors between patients who were on continuous anticoagulation vs. those who had their anticoagulation interrupted, both in the chronic sinus rhythm group and in the AF group. The latter makes it unlikely that selection of patients has played a role in the present analysis. Obviously, continuous anticoagulation precluded finding a positive effect of oral anticoagulation as was seen in the recent AFFIRM substudy.[7]

Quality of life

Comparing QoL in both groups, no clinically significant differences were found. In the PIAF study, patients in the rhythm-control group had better exercise tolerance.[5] Unfortunately, exercise tolerance was not tested in the RACE study. In a previous study, we showed that in the subgroup of lone AF, restoration and long-term maintenance of sinus rhythm provides far better QoL than that seen in the rate-control counterparts.[8] Altogether, these data support the notion that QoL is controlled by the underlying heart disease rather than by the arrhythmia. These findings parallel the absence of beneficial effect of sinus rhythm concerning morbidity and mortality.

Heart failure

Moderate heart failure, as represented by reduced exercise tolerance NYHA class II, was seen in half of the patients in both our study groups. The impact of AF on survival in heart failure patients has been reported variably.[2,12–14] Apparently, if heart failure is not very advanced, AF can be deleterious, whereas there is no impact of AF on survival in severe heart failure.[15] Despite the fact that our patients had only a moderate form of heart failure, those with permanent AF did not worse than those in chronic sinus rhythm. Apart from small numbers, this may relate to the fact that all patients in RACE had AF to start with, whereas in the heart failure studies, AF patients were compared with sinus rhythm patients who had not suffered from AF before. Above all, it may simply mean that wiping of the arrhythmia from the electrocardiogram does not mean that prognosis always improves. In this respect, the results of the AF–CHF study are eagerly awaited.[16]

Limitations

This present analysis is both retrospective and non-randomized. For that reason, we cannot adjust for variables that were not measured or collected. Selection of patients was performed on the basis of >75% presence of sinus rhythm

Table 6 SF-36 QoL scores over time according to long-term rhythm

SF-36 Subscale treatment	Baseline	*P*-value	12 months	*P*-value	Study end	*P*-value	Change from baseline to study end	*P*-value
General health								
AF	56 ± 19		59 ± 18		56 ± 18		+1	
Sinus rhythm	54 ± 15	1.0	58 ± 18	1.0	55 ± 19	1.0	+1	1.0
Physical functioning								
AF	63 ± 25		62 ± 23		59 ± 24		−4	
Sinus rhythm	59 ± 24	1.0	63 ± 22	1.0	60 ± 27	1.0	+3	0.5
Role physical								
AF	48 ± 46		62 ± 42		54 ± 44		+6	
Sinus rhythm	38 ± 42	1.0	53 ± 40	1.0	43 ± 47	1.0	+11	1.0
Bodily pain								
AF	81 ± 21		81 ± 22		80 ± 22		−1	
Sinus rhythm	77 ± 20	1.0	77 ± 19	1.0	78 ± 23	1.0	+2	1.0
Mental health								
AF	75 ± 18		77 ± 18		76 ± 17		+2	
Sinus rhythm	73 ± 17	1.0	80 ± 16	1.0	77 ± 15	1.0	+6	1.0
Social functioning								
AF	78 ± 23		83 ± 21		80 ± 22		+2	
Sinus rhythm	78 ± 20	1.0	81 ± 21	1.0	79 ± 20	1.0	+3	1.0
Role emotional								
AF	71 ± 41		78 ± 37		74 ± 38		+4	
Sinus rhythm	71 ± 40	1.0	71 ± 37	1.0	61 ± 44	1.0	−4	1.0
Vitality								
AF	62 ± 21		59 ± 20		59 ± 21		−3	
Sinus rhythm	55 ± 20	1.0	63 ± 20	1.0	63 ± 20	1.0	+8	0.02

P-value between AF and sinus rhythm patients.

during follow-up. However, as neither Holter recordings nor rhythm strips were recorded routinely during follow-up, we cannot be sure that patients have suffered from asymptomatic AF in between. In addition, the number of patients with long-term sinus rhythm was relatively small, which may have precluded finding a strong beneficial effect of the 'right' rhythm on prognosis. By selecting fit patients who kept sinus rhythm, we expected to find such a result, but unfortunately, their event rate was relatively high when compared with permanent AF patients. Although firm conclusions cannot be drawn at this stage, our results are nonetheless useful for guiding patient management while awaiting results of further studies, which may, e.g. show beneficial effects of maintaining sinus rhythm in heart failure patients.

Implications

This study suggests that the rhythm is far less important than the associated cardiovascular disease in causing major cardiovascular events. Apparently, in the present patient population, the associated disease is so influential that effective rhythm control cannot make a difference. Therefore, diagnosis and treatment of AF patients should first of all focus on the conditions linked to AF. Only in the patients symptomatic with AF, rhythm control may be pursued. Definitely, the search for safer and more effective methods to cure AF and protect patients from thromboembolic events will and must continue.

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