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Effect of Rate or Rhythm Control on Quality of Life in Persistent Atrial Fibrillation

Results From the Rate Control Versus Electrical Cardioversion (RACE) Study

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OBJECTIVES	We studied the influence of rate control or rhythm control in patients with persistent atrial fibrillation (AF) on quality of life (QoL).
BACKGROUND	Atrial fibrillation may cause symptoms like fatigue and dyspnea. This can impair QoL. Treatment of AF with either rate or rhythm control may influence QoL.
METHODS	Quality of life was assessed in patients included in the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study (rate vs. rhythm control in persistent AF). Rate control patients (n = 175) were given negative chronotropic drugs and oral anticoagulation. Rhythm control patients (n = 177) received serial electrocardioversion, antiarrhythmic drugs, and oral anticoagulation, as needed. Quality of life was studied using the Short Form (SF)-36 health survey questionnaire at baseline, one year, and the end of the study (after 2 to 3 years of follow-up). At baseline, QoL was compared with that of healthy control subjects. Patient characteristics related to QoL changes were determined.
RESULTS	Mean follow-up was 2.3 years. At baseline, QoL was lower in patients than in age-matched healthy controls. At study end, under rate control, three subscales of the SF-36 improved. Under rhythm control, no significant changes occurred compared with baseline. At study end, QoL was comparable between both groups. The presence of complaints of AF at baseline, a short duration of AF, and the presence of sinus rhythm (SR) at the end of follow-up, rather than the assigned strategy, were associated with QoL improvement.
CONCLUSIONS	Quality of life is impaired in patients with AF compared with healthy controls. Treatment strategy does not affect QoL. Patients with complaints related to AF, however, may benefit from rhythm control if SR can be maintained. (J Am Coll Cardiol 2004;43:241-7) © 2004 by the American College of Cardiology Foundation

Atrial fibrillation (AF) causes disabling symptoms like fatigue, dyspnea, and palpitations. Additionally, patients may perceive their arrhythmia as life-threatening or disabling. As a result, quality of life (QoL) may be drastically reduced. Conceivably, normalizing the rhythm is beneficial (1). Ablation of atrioventricular conduction with implantation of an artificial pacemaker was shown to improve QoL (2-4). However, this invasive treatment is appropriate in problematic AF only. In the usual patient, amiodarone, sotalol, or propafenone may enhance QoL, especially if sinus rhythm (SR) is maintained (5). At present, it is not well known whether rhythm control is indeed superior to

rate control in terms of QoL. The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial investigators demonstrated that the type of treatment (either rhythm control using cardioversion and antiarrhythmic drug treatment or rate control, aiming at an adequate ventricular rate during accepted AF) did not affect QoL (6). Follow-up was limited to one year, and rhythm control did not include serial cardioversions and serial antiarrhythmic drug treatment. In this study, the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study, we analyzed QoL in patients randomized to rate or rhythm control (1). The aim of this study was to determine: 1) QoL in patients with persistent AF, as compared with that in age-matched healthy control subjects; 2) changes over time, and to compare rhythm and rate control with respect to these changes; and 3) to determine predictors (i.e., clinical characteristics) of improvement or a decrease in QoL.

METHODS

Patient population. This study was performed in patients with persistent AF included in the RACE study (1). The study was approved by the institutional review boards of

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Abbreviations and Acronyms

AF	= atrial fibrillation
AFFIRM	= Atrial Fibrillation Follow-up Investigation of Rhythm Management trial
CTAF	= Canadian Trial of Atrial Fibrillation trial
HF	= heart failure
NYHA	= New York Heart Association
PIAF	= Pharmacological Intervention in Atrial Fibrillation trial
QoL	= quality of life
RACE	= Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation trial
SF-36	= Short-Form 36
SR	= sinus rhythm

each participating hospital, and all patients gave written, informed consent. In the RACE study, we included 522 patients with recurrent persistent AF who were randomized to rate or rhythm control. It was shown that both strategies were associated with a comparable rate of cardiovascular

adverse events. For the present analysis, we included all 352 patients who completed the self-administered QoL questionnaire at baseline, after one year, and at the end of follow-up (end of study: at 24 months for 134 patients and at 36 months for 218 patients). Patients who died during the follow-up of RACE were not analyzed (18 patients in the rate control and 18 patients in the rhythm control group). Another 134 patients (63 rate and 71 rhythm control patients) did not complete the QoL questionnaire at either baseline, one year, or the end of the study and were excluded. All the excluded patients did not differ significantly from included patients at baseline and follow-up. Patient characteristics at baseline are shown in Table 1.

Quality-of-life questionnaire. Quality of life was assessed using the Medical Outcomes Study Short-Form 36 (SF-36) health survey questionnaire (7). The SF-36 is a standardized, validated, generic health survey that has been frequently used in arrhythmia studies. The SF-36 has been translated and validated in the Netherlands (8). It contains items to assess physical health (e.g., general health percep-

Table 1. Baseline Characteristics

	Rate Control Group (n = 175)	Rhythm Control Group (n = 177)
Age (yrs)	68 ± 9	68 ± 8
Male gender	107 (61%)	119 (67%)
Total AF duration (days)	511 (14-14,909)	495 (1-8,513)
Duration present episode of AF (days)	33 (1-392)	36 (1-376)
Complaints of AF	129 (74%)	124 (70%)
Fatigue	75 (58%)	67 (54%)
Dyspnea	67 (52%)	59 (48%)
Palpitations	50 (39%)	43 (35%)
Heart rate at inclusion (beats/min)	91 ± 20	90 ± 20
Underlying diseases (%)		
Coronary artery disease	22	28
Old myocardial infarction	12	17
Valvular disease	19	13
Mitral valve disease	14	11
Aortic disease	5	3
Aortic and mitral valve disease	0	1
Cardiomyopathy	11	6
History of hypertension	42	53
History of chronic obstructive lung disease	21	15
Diabetes mellitus	11	10
No heart disease	22	21
NYHA class for heart failure (%)		
I	49	48
II	49	49
III	2	3
Previous ischemic thromboembolic complication	17	12
Stroke	5	4
Previous hemorrhagic complication	9	7
Echocardiographic parameters		
Left ventricular end-diastolic diameter (mm)	53 ± 7	52 ± 7
Left ventricular end-systolic diameter (mm)	37 ± 8	37 ± 8
Fractional shortening (%)	31 ± 9	30 ± 10
Left atrial diameter, parasternal long axis (mm)	45 ± 7	45 ± 7
Left atrial diameter, apical view (mm)	64 ± 8	63 ± 8
Right atrial diameter, parasternal long axis (mm)	58 ± 8	57 ± 8

Data are presented as the mean value ± SD, number (%) of subjects, median value (range), or percentage of subjects.
AF = atrial fibrillation; NYHA = New York Heart Association.

tion, physical functioning, role limitations due to physical problems and bodily pain) and mental health (social functioning, role limitations due to emotional problems, mental health, and vitality). The SF-36 scale, which measures change in health, is not considered in the analyses. The items for general health perception and vitality measure both. Each scale is composed of a number of multiple-choice questions, ranging in a stepwise fashion from impaired/low QoL to not impaired/high QoL. For each of the eight subscales, scores are transformed to a scale ranging from 0 to 100, with lower scores representing a lower QoL.

Complaints related to AF were assessed at each study visit, using a standardized questionnaire attached to the case record form. Complaints at inclusion were assessed for the current episode of AF before randomization.

Statistical analysis. At baseline, all patients were compared with a healthy, age-matched control group consisting of 172 Dutch subjects who served to validate the Dutch version of the SF-36. At baseline, at one year, and at the end of the study, the scores on all subscales of the SF-36 were compared between the rate and rhythm control groups.

To analyze patient characteristics associated with low QoL at baseline, patients with low scores (scores lower than the mean value - 1 SD) were identified. To assess the relevance of changes in the different subscales over time, changes in the scores from baseline to the end of the study were divided into relevant and irrelevant. For each of the eight subscales, the relevance of a change in QoL was defined according to the number of steps by which the patient improved or worsened on the multiple-choice questions that comprised each SF-36 subscale. The following changes in QoL for the individual patient were regarded as relevant and relied on the number of questions that comprised each SF-36 subscale: 1 step for role limitations due to physical problems and for role limitations due to emotional problems; 2 steps for social functioning and bodily pain; and 3 steps for general health perception, physical functioning, mental health, and vitality. The effect sizes were calculated according to Cohen (9) by dividing the differences in the mean QoL score by the pooled standard deviation to assess the change in QoL for each subscale within the randomized arm. Clinical correlates of a change in QoL, including clinical baseline and follow-up characteristics, were determined. Subanalysis was performed to determine whether relevant QoL changes were correlated with randomized strategy. To examine changes over time for each SF-36 scale, the method of repeated measures was performed. For a comparison of scores between groups and with the control group, the Student *t* test for independent variables was used. The univariate chi-square test and Student *t* test for independent variables, followed by multivariate stepwise regression analyses, were performed to determine indicators of relevant QoL changes over follow-up. All analyses were performed on an intention-to-treat basis.

RESULTS

QoL at baseline. Quality of life at baseline did not differ between the 352 analyzed patients and the patients for whom the baseline questionnaire was available but who had to be excluded for missing follow-up questionnaires. Also, their baseline characteristics were comparable (data not shown). At baseline, there were no significant differences in QoL between the rate and rhythm control groups (Table 2).

At study entry, QoL was lower for our patients compared with a healthy, age-matched control group. Differences in physical and emotional role limitations were highest (Fig. 1).

Low QoL scores for physical health at baseline (scores on the subscales under the mean value - 1 SD) were more frequent among: 1) females ($p < 0.01$; physical functioning and physical role limitations); 2) patients whose age was under the median value of 69 years ($p < 0.05$; physical functioning); 3) patients with a duration of AF above the median of 32 days ($p < 0.05$; physical functioning); and 4) patients with reduced exercise tolerance (New York Heart Association [NYHA] functional class II/III) ($p < 0.05$; general health, physical functioning, role physical, and bodily pain). Low QoL scores for mental health were more frequent among patients >69 years old ($p < 0.05$; mental health and social functioning). Patients with complaints of AF, especially fatigue ($p < 0.05$; general health, physical functioning, physical role limitations, bodily pain, social functioning, and vitality), and those with reduced fractional shortening ($p < 0.05$; role physical, social functioning, and vitality) had a reduced score for both physical and mental health parameters.

Quality of life from baseline to study end. At 12-month follow-up in the rate control group, four subscales of the SF-36 had improved (Table 2). At study end, three subscales had significantly improved: role limitations due to physical problems, social functioning, and mental health. Physical functioning worsened over time.

After one year of rhythm control therapy, QoL improved on three subscales, including two scales measuring physical health. However, at the end of the study, no significant changes were present compared with baseline scores.

When the scores on the SF-36 subscales at 12-month follow-up and study end were compared between the rate and rhythm control groups, no significant differences were found in any of the eight subscales (Table 2). The absolute differences between the scores at baseline and study end were not statistically different between rate and rhythm control. The percentage of patients with a relevant increase in follow-up was generally higher than that of patients with a relevant decrease in QoL over time; however, the effect sizes within each randomized strategy were small and always below 0.25 (i.e., one-fourth of SD) (Table 2).

The occurrence of complaints related to AF was comparable between the rate and rhythm control groups over follow-up. Fatigue and dyspnea were most common.

Table 2. Short-Form 36 Quality-of-Life Scores

SF-36 Subscale Strategy	Baseline	12 Months	Study End	Change From Baseline to Study End‡	Effect Size (Baseline to Study End)	Relevant Increase From Baseline to Study End (%)	Relevant Decrease From Baseline to Study End (%)
General health							
Rate	54 (19)	58 (18)*	57 (18)	+3	0.16	23	14
Rhythm	54 (18)	58 (20)*	54 (20)	0	0	19	16
Physical functioning							
Rate	62 (24)	62 (23)	59 (25)*†	-3	-0.12	14	22
Rhythm	64 (24)	67 (24)*	64 (27)	0	0	18	21
Role physical							
Rate	45 (46)	59 (42)*	53 (44)*	+8	0.18	26	18
Rhythm	50 (44)	61 (43)*	55 (45)	+5	0.11	23	17
Bodily pain							
Rate	80 (22)	81 (21)	79 (23)	-1	-0.04	14	20
Rhythm	81 (21)	82 (22)	80 (22)	-1	-0.05	16	15
Mental health							
Rate	73 (18)	77 (18)*	76 (17)*	+3	0.17	25	14
Rhythm	74 (18)	76 (19)	76 (18)	+2	0.11	25	18
Social functioning							
Rate	76 (24)	81 (21)*	81 (21)*	+5	0.22	26	13
Rhythm	78 (22)	79 (25)	80 (23)	+2	0.09	16	11
Role emotional							
Rate	73 (41)	76 (38)	73 (39)	0	0	19	18
Rhythm	70 (42)	74 (39)	74 (38)	+4	0.10	24	17
Vitality							
Rate	60 (22)	59 (20)	59 (21)	-1	-0.05	16	19
Rhythm	60 (21)	62 (21)	62 (21)	+2	0.10	25	17

*p < 0.05 compared with baseline score. †p < 0.05 compared with 12-month score. ‡No significant differences between groups. SF-36 = Medical Outcomes Study Short-Form 36.

Determinants of QoL changes. For the total study group, we investigated which baseline (Table 1) and follow-up parameters were related to a relevant change in each subscale of the SF-36 at study end. The follow-up parameters were randomized strategy, underlying disease, NYHA class for heart failure (HF), improvement or worsening of echocardiographic parameters (left ventricular and atrial diameters, fractional shortening), presence of SR at study end, and occurrence of a severe adverse cardiovascular event, including HF, thromboembolic complication, bleeding, implantation of a pacemaker, or severe adverse effects of medication.

Stepwise regression analyses revealed that age <69 years, complaints of AF (especially fatigue and dyspnea) at inclusion, a short duration of AF, and SR at the end of follow-up were determinants of relevant QoL improvement during follow-up (Table 3; only determinants that were significant with use of multivariate analysis are shown). The type of randomized strategy (rate or rhythm control) was not associated with relevant changes.

A total of 35 patients (10%) showed a major improvement in QoL, defined as relevant improvements on five or more subscales of the SF-36. Characteristics (baseline and follow-up parameters) associated with improved QoL on five or more subscales were the same as those identified using the stepwise regression analysis: younger age (<69 years, p = 0.020), shorter duration of AF (<32 days, p = 0.005), presence of dyspnea (p = 0.048) or fatigue (p =

0.005) at inclusion, and SR at the end of the study (p = 0.003). In 23 patients (6.5%), QoL on five or more subscales deteriorated. No parameters were related to a significant decrease in QoL on five or more subscales.

For the rate control group alone, the presence of SR at study end resulted in a relevant improvement in QoL on five or more subscales (p = 0.002). However, the number of patients who improved was small (5 of 17 patients with SR at study end in the rate control group). For the rhythm control group, younger age (p = 0.041), shorter duration of AF (p = 0.026), and presence of SR at end of the study led to a relevant QoL improvement (11 of 65 patients with SR at study end, p = 0.022). The number of electrical cardioversions needed in these patients with SR at study end did not have any association with QoL.

There were no interactions between the determinants of QoL and the randomized strategy, indicating that there were no subgroups of patients in whom either rate or rhythm control is preferable.

DISCUSSION

This study shows that patients with persistent AF have a lower QoL than their healthy age-matched controls. Furthermore, QoL did not change significantly during long-term rhythm control treatment, whereas during rate control treatment, minor changes occurred. However, there were no differences in QoL between the rate control and rhythm

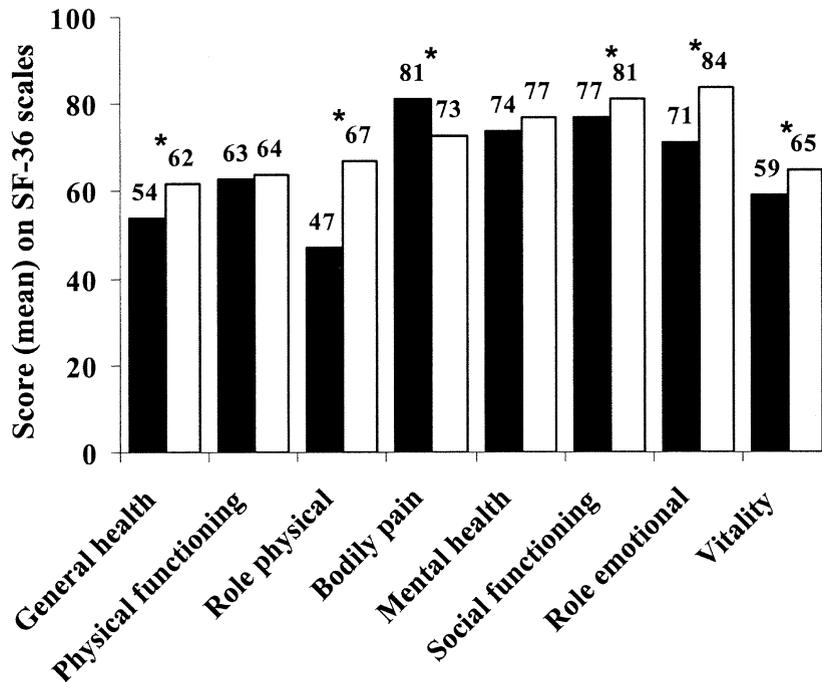


Figure 1. Quality-of-life comparison between study patients at baseline and control subjects.*p < 0.05. **Solid bars** = RACE subjects (n = 352); **open bars** = control subjects (n = 172).

control groups at the end of follow-up. Finally, maintenance of SR rather than the assigned treatment strategy was an important parameter for improvement of QoL.

QoL in persistent AF. Compared with healthy volunteers, QoL was significantly reduced in our patients. This is in accordance with Dorian *et al.* (10), who showed that patients with heart disease (either AF or HF or ischemic heart disease) had lower scores on the SF-36 subscales than did healthy controls. However, this is in contrast to another study in which a cohort of older ambulatory patients with chronic AF (mean age 76 years) was compared with an age-matched control group of patients in SR. In the latter

study, exercise tolerance and QoL were comparable between both groups, even though a higher level of comorbidity was found in the AF group (11).

In the present study, impaired QoL at baseline predominantly occurred in patients with complaints related to AF (especially fatigue), patients with more severe underlying heart disease (NYHA class II/III HF and/or reduced fractional shortening), and females. About 80% of our patients had, apart from AF, underlying heart disease, which may have contributed significantly to their complaints and impaired QoL (10,12,13). Complaints were an important determinant of reduced physical and mental

Table 3. Determinants of Relevant Changes per SF-36 Subscale From Baseline to End of Study

SF-36 Subscale	Determinants of Relevant QoL Changes	Standardized Regression Coefficient (95% CI)	p Value
Relevant Improvement			
Physical functioning	Sinus rhythm at study end	0.15 (0.04 to 0.27)	0.007
	Role physical	0.12 (0.00 to 0.24)	0.047
Bodily pain	Complaints of AF at baseline	0.12 (0.01 to 0.24)	0.041
	Duration of present AF <32 days*	-0.13 (-0.24 to -0.02)	0.024
Social functioning	Duration of present AF <32 days*	-0.12 (-0.23 to -0.10)	0.032
	Age <69 years*	-0.18 (-0.29 to -0.07)	0.001
Vitality	Sinus rhythm at study end	0.23 (0.11 to 0.33)	< 0.001
Relevant Decrease			
Role emotional	Coronary artery disease at baseline	-0.20 (-0.32 to -0.08)	0.001
Vitality	Diabetes at baseline	-0.14 (-0.26 to -0.03)	0.011

*Median value. No significance was reached on multivariate analysis in the subscales of general health and mental health.

AF = atrial fibrillation; CI = confidence interval; QoL = quality of life; SF-36 = Medical Outcomes Study Short-Form 36.

health scores of QoL. It may be speculated that these complaints were (predominantly) caused by the presence of underlying heart disease, and not by AF, especially since fatigue and dyspnea, and not palpitations, were the most frequent complaints in patients with reduced QoL. However, complaints such as fatigue are also a common finding in patients with AF without underlying heart disease (14).

Why females had an impaired QoL is difficult to explain. However, in the Canadian Trial of Atrial Fibrillation (CTAF), QoL was also significantly impaired in women compared with men, despite comparable severity of underlying heart disease (15).

Rate versus rhythm control. At the end of the study, no differences between the rate and rhythm control groups were present. For the rate control group, improvements in physical and mental scales of the SF-36 were present at 12-month follow-up and at the end of the study. Because almost all patients had persistent AF, and no spontaneous improvements might be expected given the age of the patients, these may be regarded as a general treatment effect of both the arrhythmia and underlying disease. The latter includes adjustments of rate control therapy and therapy for the underlying heart disease, as needed, and careful and close monitoring by the treating physician and study nurses. At study end, physical functioning was significantly reduced. This is likely related to an impaired physical capacity as a consequence of progression of chronic underlying heart disease and noncardiac illness in this elderly study population. After 12-month of follow-up, QoL in patients treated according to the rhythm control protocol improved on three SF-36 subscales but returned to baseline scores at study end. This also may relate to the aforementioned issues, but also to the fact that after 12 months, 55% of patients were still in SR (vs. 39% at study end).

These trends in both groups indicate that treatment of AF in a study like this, with relatively frequent visits, may improve QoL in the short term, possibly due to treatment effects, irrespective of the kind of therapy. However, during long-term follow-up, these improvements largely vanish.

No significant changes in QoL could be demonstrated between the two treatment groups. This may relate to the fact that SR could be maintained only in a minority of patients during long-term follow-up.

The CTAF, PIAF, and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators recently performed comparable QoL assessments with follow-up studies at one year (5,6,16). In AFFIRM, no significant differences between the two groups at any point during follow-up could be demonstrated (16). The PIAF investigators showed a significant improvement in QoL at 12-month follow-up for almost all SF-36 subscales in both the rate and rhythm control groups. In contrast, our study showed only a few changes after 12-month follow-up. The CTAF study, which randomized patients after successful cardioversion to amiodarone, sotalol, or propafenone,

showed that after three months of rhythm control therapy, QoL improved independent of the drug used, compared with baseline QoL. At 12-month follow-up, QoL remained unchanged.

Predictors of changes of QoL. As in CTAF, we also found that SR at the end of the study was the most important determinant of QoL improvement. In CTAF and in the present study, improvements were present for both physical and mental health scales, indicating that SR may improve exercise tolerance and a sense of vitality. Thus, rhythm control may be beneficial in improving QoL if effective. Therefore, better means of maintaining SR may have a major general impact on QoL in patients with persistent AF.

In the present study, 10% of the patients showed a major QoL improvement, defined as a relevant increase on five or more SF-36 subscales. Improvements may be expected in younger patients, patients with a short duration of AF, and subjects in whom SR was restored. In general, if SR can be restored and maintained during long-term follow-up, an improvement of QoL can be expected. Therefore, these patients remain candidates for the rhythm control strategy, notwithstanding the results of PIAF, AFFIRM, and RACE (1,6,16).

Study limitations. It is important to state that QoL covers a wide range of patients' sense of well-being, complaints in daily living, complaints of cardiac and noncardiac diseases, and social functioning. Although the SF-36 is a validated questionnaire for QoL research, it is possible that some aspects of QoL or changes in QoL in patients with AF are not measured. In further research, additional QoL measurements, using, for example, AF-specific questionnaires, as previously used by Dorian et al. (5,10), are warranted.

Conclusions. Patients with persistent AF have a lower QoL than do healthy, age-matched controls. This holds true especially for patients with complaints of AF, those with symptoms of HF, and females. Treatment strategy (rate or rhythm control) does not greatly influence QoL, as only minor changes occurred on the SF-36 scores. This predominantly relates to the fact that more than half of the patients in the rhythm control strategy had permanent AF during the last period of follow-up. Improvement of QoL is most likely to occur in patients in whom SR can be maintained during long-term follow-up.

Although rate control is not inferior to rhythm control, with regard to morbidity and mortality (AFFIRM and RACE), long-term SR by a rhythm control approach may be preferable for improvement of subjective general well-being.

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