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Gender-Related Differences in Rhythm Control Treatment in Persistent Atrial Fibrillation

Data of the Rate Control Versus Electrical Cardioversion (RACE) Study

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OBJECTIVES This study sought to compare whether gender affects the outcome of rate versus rhythm control treatment in patients with persistent atrial fibrillation (AF).

BACKGROUND Large trials have shown that rate control is an acceptable alternative to rhythm control. However, the effects of treatment may differ between male and female patients.

METHODS In the Rate Control versus Electrical Cardioversion (RACE) study, 522 patients (192 female) were included and randomized to rate or rhythm control. The occurrence of cardiovascular end points and quality of life (QoL) were compared between female and male patients.

RESULTS At baseline, female patients differed from male patients with regard to age, underlying heart disease, diabetes mellitus, and left ventricular function. Female patients had more AF-related complaints, and QoL was significantly lower. After a mean follow-up of 2.3 ± 0.6 years, cardiovascular morbidity and mortality was equally distributed between female (21%) and male patients (19%). However, in contrast to male patients, female patients randomized to rhythm control developed more end points (adjusted hazard ratio was 3.1 [95% confidence interval 1.5 to 6.3], $p = 0.002$), mainly heart failure, thromboembolic complications, and adverse effects of antiarrhythmic drugs, compared with rate control randomized female patients. During follow-up, QoL in female patients remained worse compared with that for male patients. Randomized strategy did not influence QoL in female patients.

CONCLUSIONS In female patients with persistent AF, a rhythm control approach leads to more cardiovascular morbidity and mortality. Because treatment strategy did not influence QoL in female patients, a rate control approach may be considered in these patients. (J Am Coll Cardiol 2005;46:1298–306) © 2005 by the American College of Cardiology Foundation

Several studies have addressed the issue of gender differences in the outcome of cardiovascular diseases (1–3). Few studies have dealt with gender differences and arrhythmias (4,5). The incidence and prevalence of atrial fibrillation (AF) increases with advancing age and is higher in men than

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in women (4). Because there are almost twice as many women as men over the age of 75 years, the absolute number of men and women with AF is equal (5,6). Although AF is not fatal, thromboembolic complications, bleeding, and heart failure are important complications associated with AF. Women in particular (especially those over the age of 75 years) are at increased risk for thromboembolic complications (7). Bleeding as a complication of oral anticoagulation has also been reported to be more prevalent in women (8). In addition, gender may affect the selection of antiarrhythmic drugs for rhythm control of AF because women are more likely to develop proarrhythmia on QT prolonging antiarrhythmic drugs (9). This may reduce the success of rhythm control therapy in female patients (10).

Mortality and morbidity were comparable under long-term rate and rhythm control treatment in patients with persistent AF (11–14). It remains uncertain, however, whether this holds both for female patients and for male patients. The goals of the present substudy of Rate Control versus Electrical Cardioversion (RACE) study were: 1) to investigate the long-term outcome, i.e., cardiovascular morbidity, mortality, and quality of life (QoL) in female patients and male patients; and 2) to evaluate the outcome of rate and rhythm control treatment of persistent AF in female patients and male patients.

METHODS

Study design of the RACE study. The study design, patient characteristics, and results of the RACE study have been published previously (12). In short, 522 patients (192 females) with recurrent persistent AF were included and randomized to rate or rhythm control. Patients were followed up for at least two years, with a maximum of three years. Administration of digitalis, a nondihydropyridine calcium-channel blocker, and a beta-blocker achieved rate

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Abbreviations and Acronyms

AF = atrial fibrillation
AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management
CI = confidence interval
HR = hazard ratio
INR = international normalized ratio
NYHA = New York Heart Association
QoL = quality of life
RACE = Rate Control versus Electrical Cardioversion study
SF-36 = Medical Outcomes Study Short-Form Health Survey
SPAF = Stroke Prevention in Atrial Fibrillation

control, alone or in combination. The target was a resting heart rate of <100 beats/min. Patients assigned to the rhythm control group underwent serial electrocardioversions and institution of serial antiarrhythmic drugs, i.e., sotalol, class IC antiarrhythmic drugs, and amiodarone. Cardioversion was performed under adequate anticoagulation (target international normalized ratio [INR], 2.5 to 3.5). All patients received acenocoumarol or fenprocoumon, unless long-term sinus rhythm was achieved or when rate control treated patients were <65 years old and had lone AF. In these instances, aspirin (80 to 100 mg daily) was allowed.

End points. The primary end point was the composite of death from cardiovascular cause, heart failure, thromboembolic complications, bleeding, severe adverse effects of antiarrhythmic drugs, and the need for a pacemaker implantation. All events that occurred between randomization and the end of the study were recorded. Definitions of the composites of the primary end point have been described previously (12). A committee of experts, who were unaware of the treatment assignments, adjudicated all reported end points.

QoL. The QoL was determined using the Dutch version of the Medical Outcomes Study Short-Form Health Survey (SF-36) questionnaire as has been described before (15). In short, the SF-36 contains items for assessing physical health (general health perception, physical functioning, role limitations attributable to physical problems and bodily pain) as well as mental health (social functioning, role limitations attributable to emotional problems, mental health, and vitality). The QoL was assessed at baseline, after one year, and at the end of the study in 126 female patients (66%) and in 226 male patients (68%). In addition, a healthy age-matched control group was selected from Dutch subjects, and served to validate the Dutch version of the SF-36 (64 healthy age-matched control female patients and 113 healthy age-matched control male patients).

Statistical analysis. Baseline descriptive statistics are the mean ± standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups, in terms of patient characteristics and QoL at baseline, different follow-up times, and end of study were evaluated by student *t* test or Mann-Whitney *U* test, depending on normality of the data, for continuous data. We determined whether the data were normally distributed by using the Shapiro-Wilk test for normality. For categorical data, predominantly the Fisher exact test (in case of binomial proportions) was used; in case of more than two-response categories, the chi-square test was used. Kaplan-Meier estimates and Cox proportional hazard regression analyses were performed to study the influence of gender and randomized treatment on the occurrence of cardiovascular morbidity and mortality over time in the study population. Linearity of the continuous variables with respect to the response variable was assessed by determining the quartiles of their distribution. Thereafter, hazard ratios (HRs) for each quartile were calculated. In case of a linear trend in the estimated HRs, the variable was introduced in the model as continuous. If no linearity was shown, the variable was further categorized by taking together the quartiles with HRs similar in magnitude, primarily the median value or otherwise based on clinical relevance. All patient characteristics, medication use, and changes in stroke risk factors during follow-up were included. All univariate predictors with $p < 0.1$ were tested in a multivariate model, including interaction terms. In the multivariate model, a variable was excluded when $p \geq 0.05$. In all analyses, a value of $p < 0.05$ was considered statistically significant. All analyses were performed according to the intention-to-treat principle.

RESULTS

Patient characteristics. In the RACE study, 192 female patients and 330 male patients were included (Table 1). At baseline, female patients were significantly older than male patients. Coronary artery disease was less frequently present, whereas hypertension and diabetes mellitus occurred more often in female patients compared with male patients. At baseline, the systolic blood pressure was higher in female patients compared with male patients. Atrial sizes were comparable, but fractional shortening was higher in female patients.

There were more female patients with hypertension in the rhythm control randomized group, in comparison with female patients randomized to rate control (72% vs. 53%, $p = 0.005$). No other differences between rate and rhythm control randomized female patients were observed. The use of drugs in these two groups at baseline and at the end of the study is shown in Table 2. No important differences between female patients and male patients were observed.

Follow-up. Patients were followed up for a mean duration of 2.3 ± 0.6 years; 49% of the female patients and 51% of the male patients were randomized to rhythm control. In the rhythm control strategy, 34 female patients (35%) versus 66 male patients (39%) were in sinus rhythm at the end of the study (p = NS) after a median of 2 (0 to 11) versus 2 (0 to 6) electrical cardioversions (p = NS), respectively. Continuous oral anticoagulation was used in 74% of the female

Table 1. Baseline Characteristics of the Patients According to Gender

Patient Characteristics	Female Patients (n = 192)	Male Patients (n = 330)	p Value
Age (yrs)	71 ± 8	67 ± 9	<0.001
Total AF duration (days)	444 (27–14,909)	470 (1–14,399)	NS
Duration present episode of AF (days)	33 (1–399)	32 (1–395)	NS
Atrial fibrillation	96%	91%	0.03
Atrial flutter	4%	9%	
Treatment			NS
Rate control	51%	49%	
Rhythm control	49%	51%	
Complaints of AF	77%	66%	0.007
Palpitations	33%	24%	0.03
Dyspnea	39%	33%	NS
Fatigue	47%	35%	0.006
NYHA functional class for heart failure*			NS
I	53%	49%	
II	43%	49%	
III	5%	2%	
Coronary artery disease	21%	31%	0.01
Old myocardial infarction	8%	19%	0.001
Valve disease	21%	14%	NS
Cardiomyopathy	6%	11%	NS
History of hypertension	63%	41%	<0.001
No heart disease	12%	26%	<0.001
History of chronic obstructive pulmonary disease	12%	16%	NS
Diabetes mellitus	17%	6%	<0.001
Previous ischemic thromboembolic complication	16%	13%	NS
Previous bleeding	11%	6%	0.02
Heart rate (rest) (beats/min)	91 ± 21	90 ± 21	NS
Blood pressure (mm Hg)			
Systolic	148 ± 25	141 ± 20	<0.001
Diastolic	86 ± 11	85 ± 11	NS
Echocardiographic measurements			
Size of left atrium, long-axis (mm)	44 ± 6	45 ± 7	NS
Size of left atrium, apical view (mm)	63 ± 8	64 ± 9	NS
Size of right atrium, apical view (mm)	57 ± 8	58 ± 8	NS
Left ventricular end-diastolic diameter (mm)	50 ± 6	54 ± 7	<0.001
Left ventricular end-systolic diameter (mm)	35 ± 7	38 ± 8	<0.001
Septal thickness (mm)	10 ± 2	10 ± 3	NS
Posterior wall thickness (mm)	9 ± 2	10 ± 2	NS
Fractional shortening (%)	32 ± 9	29 ± 10	0.03

*Chi-square test.
AF = atrial fibrillation; NS = nonsignificant; NYHA = New York Heart Association.

patients (84% rate control, 64% rhythm control, $p = 0.001$) and in 72% of the male patients (83% rate control, 62% rhythm control, $p < 0.001$). All other patients had their oral anticoagulation treatment interrupted or stopped. After two years of follow-up, the New York Heart Association (NYHA) functional class of heart failure was comparable between female patients (75% class I, 25% class II and III) and male patients (67% class I, 33% class II and III; p = ns). In both female patients and male patients, a significant improvement in NYHA functional class for heart failure was observed from baseline to end of study (1.5 ± 0.6 vs. 1.3 ± 0.5, $p < 0.001$; and 1.5 ± 0.5 vs. 1.4 ± 0.5, $p < 0.001$, in female patients and male patients, respectively). There were no major differences in heart rate during follow-up between female patients and male patients treated with rate or rhythm control. However, the higher systolic blood pressure in female patients compared with male patients remained constantly present during follow-up. During follow-up, fractional shortening remained significantly higher in female patients and improvement was significantly more pronounced (Table 3).

Cardiovascular morbidity and mortality. The primary end point occurred in 41 female patients (21%) and 63 male patients (19%) (Table 4). The rate of death was similar in both groups, 7%. Causes of death were comparable given the small number. Fatal bleeding occurred only in male patients. Hospitalization for heart failure and thromboembolic complications occurred in similar proportions in female patients and male patients. All female patients and male patients with a thromboembolic complication had at least one stroke risk factor. The rhythm at the moment of the thromboembolic complication was mostly AF (10 female patients with AF, 3 female patients in sinus rhythm; 17 male patients with AF and 5 in sinus rhythm), and

Table 2. Treatment at Baseline and End of Study in Both Female and Male Patients Stratified According to Randomized Strategy

	Female Patients (%)		Male Patients (%)	
	Rate Control	Rhythm Control	Rate Control	Rhythm Control
Baseline				
Beta-blocker	22	18	24	17
Diltiazem or verapamil	26	12	27	21
Digoxin	66	59	60	52
Class Ic antiarrhythmics	7	13	9	12
Sotalol	26	39	27	37
ACE and AR inhibitors	39	47	32	36
Cholesterol-lowering drugs	12	13	14	14
End of study				
Beta-blocker	35	24	36	25
Diltiazem or verapamil	42	11	32	17
Digoxin	67	36	57	34
Class Ic antiarrhythmics	7	18	4	18
Amiodarone	1	20	4	19
Sotalol	12	31	13	24
ACE and AR inhibitors	49	57	41	43*
Cholesterol-lowering drugs	12	17	18	20

*$p < 0.05$ female compared with male patients, randomized to rhythm control.
ACE = angiotensin-converting enzyme; AR = angiotensin receptor.

predominantly occurred while receiving inadequate anticoagulant therapy (INR <2). The incidence of bleeding was lower in female patients compared with male patients. Almost all bleeding in both the female patients and the male patients occurred while the INR was >3. Severe adverse effects of antiarrhythmics and pacemaker implantations occurred mainly in female patients. Adverse effects of antiarrhythmic drugs in female patients included sick sinus syndrome (n = 7; 4 on flecainide, 1 on sotalol, 2 on amiodarone) necessitating pacemaker implantation in 2, torsades des pointes (n = 1; on sotalol), and rapid, hemodynamically significant atrioventricular conduction during atrial flutter (n = 1; on flecainide). In male patients, torsades des pointes occurred in one while being treated with amiodarone and haloperidol, one developed ventricular tachycardia under flecainide, two had digoxin intoxication

Table 3. Echocardiographic Measurements and Changes Over Time According to Gender

	Baseline	1 Year	2 Years
Left atrial size, long-axis view (mm)			
Female	44 ± 6	45 ± 7	45 ± 6
Male	45 ± 7	46 ± 7	46 ± 8
Left atrial size, apical view (mm)			
Female	63 ± 8	65 ± 8	66 ± 9
Male	64 ± 9	65 ± 9	67 ± 10
Right atrial size, apical view (mm)			
Female	57 ± 8	60 ± 8	61 ± 10
Male	58 ± 8	60 ± 8	62 ± 8
Left ventricular end-diastolic diameter (mm)			
Female	50 ± 6	51 ± 6	49 ± 6
Male	54 ± 7*	54 ± 6*	54 ± 7*
Left ventricular end-systolic diameter (mm)			
Female	35 ± 7	33 ± 7	32 ± 6
Male	38 ± 8*	36 ± 8*	38 ± 9*
Fractional shortening (%)			
Female	32 ± 9	34 ± 8	35 ± 9
Male	29 ± 10*	33 ± 9	30 ± 11*
Septal wall thickness (mm)			
Female	10 ± 2	10 ± 2	10 ± 2
Male	10 ± 3	11 ± 2	11 ± 3
Posterior wall thickness (mm)			
Female	10 ± 2	9 ± 2	10 ± 2
Male	10 ± 2	10 ± 2*	10 ± 2

*$p < 0.05$, female compared with male patients.

Table 4. Incidence of the Primary End Point and Its Components According to Gender*

End Point, % (n)	Female Patients (n = 192)	Male Patients (n = 330)	Absolute Difference (90% CI)
End point	21.4 (41)	19.1 (63)	2.3 (−4.5 to 9.0)
Death from cardiovascular causes	6.8 (13)	7.0 (23)	−0.2 (−4.1 to 3.7)
Sudden death	4.2 (8)	2.4 (8)	
Heart failure	0.5 (1)	1.2 (4)	
TEC	2.1 (4)	0.6 (2)	
Bleeding	—	2.7 (9)	
Heart failure	3.6 (7)	4.2 (14)	−0.6 (−3.5 to 2.3)
Thromboembolic complications	6.8 (13)	6.7 (22)	0.1 (−3.8 to 4.0)
Bleeding	1.6 (3)	5.5 (18)	−3.9 (−6.5 to 1.3)
Severe adverse effects of AAD	4.7 (9)	1.5 (5)	3.2 (0.4 to 6.0)
Pacemaker implantation	3.6 (7)	1.2 (4)	2.4 (−0.04 to 4.9)

*Some patients had more than one end point.
AAD = antiarrhythmic drugs; CI = confidence interval; TEC = thromboembolic complications.

(atrioventricular block in one and ventricular tachycardia in the other), and one had atrioventricular block under amiodarone, necessitating pacemaker implantation. Of all sudden cardiac deaths in female patients, one patient used sotalol. Pacemaker implantations in female patients were performed after atrioventricular node ablation because of intolerable symptoms (three patients) and for sick sinus syndrome unmasked by cardioversion (four patients). In male patients, pacemaker implantations were performed after atrioventricular ablation because of intolerable symptoms in two patients, and for bradycardia during AF in one patient. The occurrence of bradyarrhythmias during follow-up was significantly influenced by female gender (adjusted HR, 4.8 [95% confidence interval (CI) 1.2 to 18.8]; p = 0.02), hypertension (adjusted HR, 9.0 [95% CI 1.1 to 71.6]; p = 0.04), and amiodarone use (adjusted HR, 5.8 [95% CI 1.7 to 19.5]; p = 0.004).

Gender difference in outcome rate versus rhythm control. Randomized strategy importantly influenced the occurrence of end points in female patients (Table 5, Fig. 1). The primary end point occurred in 10 female patients (11%) treated with rate control versus 31 female patients (33%) treated with rhythm control. Cardiovascular mortality, heart failure, thromboembolic complications, serious adverse effects of antiarrhythmic drugs, and pacemaker implantation predominantly occurred in female patients treated with rhythm control. In male patients, the occurrence of the primary end point was equally distributed between rate and rhythm control treatment.

Determinants of cardiovascular morbidity and mortality. By Cox regression analysis, all patient characteristics (including gender); treatment variables (including medication use and treatment strategy); and changes in blood pressure, left-ventricular hypertrophy, atrial sizes, and left ventricular dysfunction during follow-up were included. In the total population, hypertension, coronary artery disease, heart failure NYHA functional class II/III, and previous bleeding were independent predictors of the occurrence of the primary end point, but not gender or age. To investigate the influence of gender on outcome of rate or rhythm control treatment, we repeated these analyses in female patients and male patients, respectively (Table 6). All univariate variables with $p < 0.1$, including age, were added stepwise in the multivariate models. In male patients, there was no association between treatment strategy and adverse outcome. However, in female patients there was a significant relationship between rhythm control treatment and event-free survival (adjusted HR, 3.1 [95% CI 1.5 to 6.3]; p = 0.002) (Fig. 2).

Quality of life. Female patients had more AF-related complaints, especially palpitations and fatigue (Table 1). The QoL of female patients was significantly lower than in male patients, measured on six of eight scales (Fig. 3A). Compared with the healthy age-matched female control

Table 5. Incidence of the Primary End Point and Its Components According to Treatment Strategy and Gender*

	Female Patients			Male Patients		
End Point, %	Rate Control (n = 95)	Rhythm Control (n = 97)	Absolute Difference (90% CI)	Rate Control (n = 161)	Rhythm Control (n = 169)	Absolute Difference (90% CI)
End point	10.5	32.6	−21.4 (−32.3 to −10.5)	21.1	17.2	4.0 (−4.0 to 11.9)
Death from cardiovascular causes	3.2	10.3	−7.2 (−13.3 to −1.0)	9.3	4.7	4.6 (−0.2 to 9.4)
Heart failure	1.1	6.2	−5.1 (−9.6 to −0.6)	5.0	3.6	1.4 (−2.3 to 5.2)
Thromboembolic complications	2.1	11.3	−9.2 (−15.4 to −3.1)	7.5	5.9	1.5 (−3.2 to 6.2)
Bleeding	2.1	1.0	1.1 (−1.9 to 4.1)	6.2	4.7	1.5 (−2.8 to 5.7)
Severe adverse effects of AAD	—	9.3	−9.3 (−14.4 to −4.2)	1.2	1.8	−0.5 (−2.8 to 1.7)
Pacemaker implantation	2.1	5.2	−3.0 (−7.6 to 1.5)	0.6	1.8	−1.2 (−3.1 to 0.8)

*Some patients had more than one end point.
AAD = antiarrhythmic drugs; CI = confidence interval.

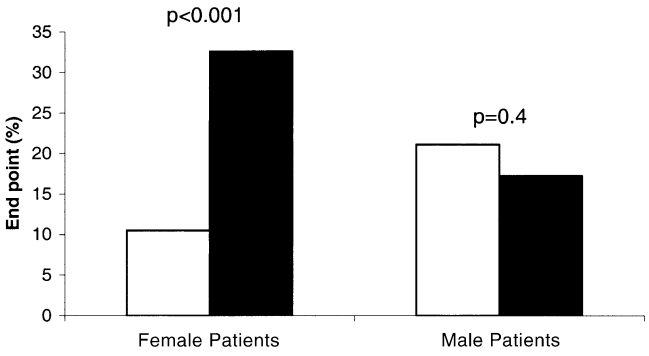

Figure 1. Occurrence of the primary end point according to gender and randomized strategy. **Open bars** = rate control; **solid bars** = rhythm control.

group, QoL in female patients with persistent AF was significantly lower on the general health, physical role limitations, pain, and vitality SF-36 subscales, thus predominantly on physical health scales (Fig. 3B). Both healthy women and women with persistent AF had a worse QoL than healthy men (data not shown). After 12 months and at the end of the study, QoL differences between female patients and male patients remained present. At 12 months, female patients scored lower on five of eight SF-36 scales and at the end of the study on seven of eight SF-36 scales. The QoL did not largely change in both groups during follow up (data not shown). Additional analysis of QoL in female patients was performed to determine the effects of treatment strategy on QoL. No significant differences between rate and rhythm control treated patients was found.

DISCUSSION

Large studies have indicated that rate and rhythm control treatment were comparable with regard to morbidity and mortality (11–14). The present subanalysis of the RACE study suggests that this may not automatically apply to both female patients and male patients. The present data show that rhythm control in female patients with recurrent persistent AF enhances cardiovascular morbidity and mortality, largely because of more thromboembolic complications, heart failure, and severe adverse effects of antiarrhythmic drugs.

Table 6. Predictors of the Occurrence of the Primary End Point Over Time of the Female and Male Patients

Baseline Characteristics	Hazard Ratio (95% CI)	p Value
Female patients		
Rhythm control treatment	3.1 (1.5–6.3)	0.002
Male patients		
Rhythm control treatment	0.5 (0.2–1.0)	0.058
Rhythm control × hypertension*	3.2 (1.1–9.5)	0.03
Hypertension	1.0 (0.5–2.1)	0.95
Coronary artery disease	2.1 (1.3–3.6)	0.005
Valve disease	2.1 (1.2–3.8)	0.01

*Significant interaction between rhythm control and hypertension.
CI = confidence interval.

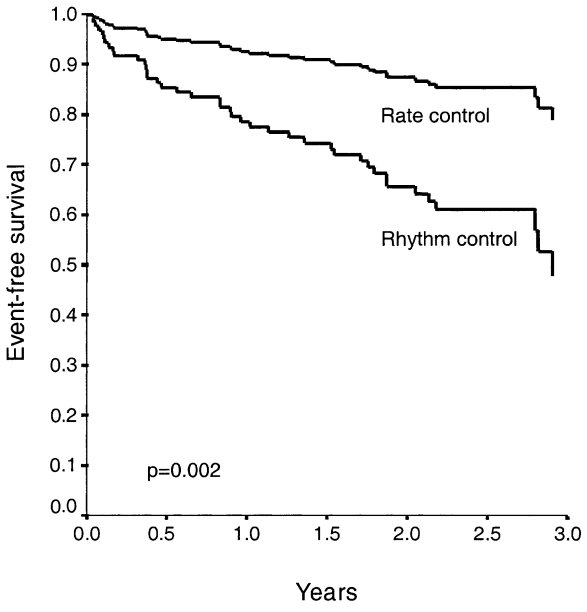

Figure 2. Event-free survival of female patients stratified to rate or rhythm control treatment.

Gender differences in cardiovascular morbidity and mortality. Although we observed, in line with previous findings, gender differences in baseline characteristics (8,16,17), most remarkably hypertension and diabetes, there were no major differences in the occurrence rate of the primary end point between female patients and male patients in the RACE population. In contrast, in the Framingham Heart study, mortality was higher in female patients compared with male patients (18), whereas in the Renfrew/Paisley study, not only mortality but also stroke and heart failure took place more frequently in female patients (19). On the other hand, the Western Australia Survey found no differences in the cardiovascular and all-cause mortality rates between female patients and male patients (20). In all of these studies, no data on actual treatment strategy were provided.

We noticed, however, important differences in the distribution of the components of the primary end point between female patients and male patients. First, in contrast to previous data, bleeding occurred predominantly in male patients (8,21). Our total annual bleeding rate was 1.7% (male patients, 2.3%; female patients, 0.7%), which compares favorably with the annual bleeding rate during oral anticoagulation therapy in the Stroke Prevention in Atrial Fibrillation (SPAF)-I, -II, and -III studies (1.5%, 1.7%, and 2.1%, respectively) (22–24). As mentioned before, bleeding occurred predominantly at the moment of a too high INR. Therefore, the lower bleeding rate in female patients may have been related to the fact that female patients may have been less likely to receive adequate anticoagulant therapy, as has been described before (8,25), or did not take their anticoagulant therapy.

Secondly, severe adverse effects of antiarrhythmic drugs occurred most frequently in female patients. Although

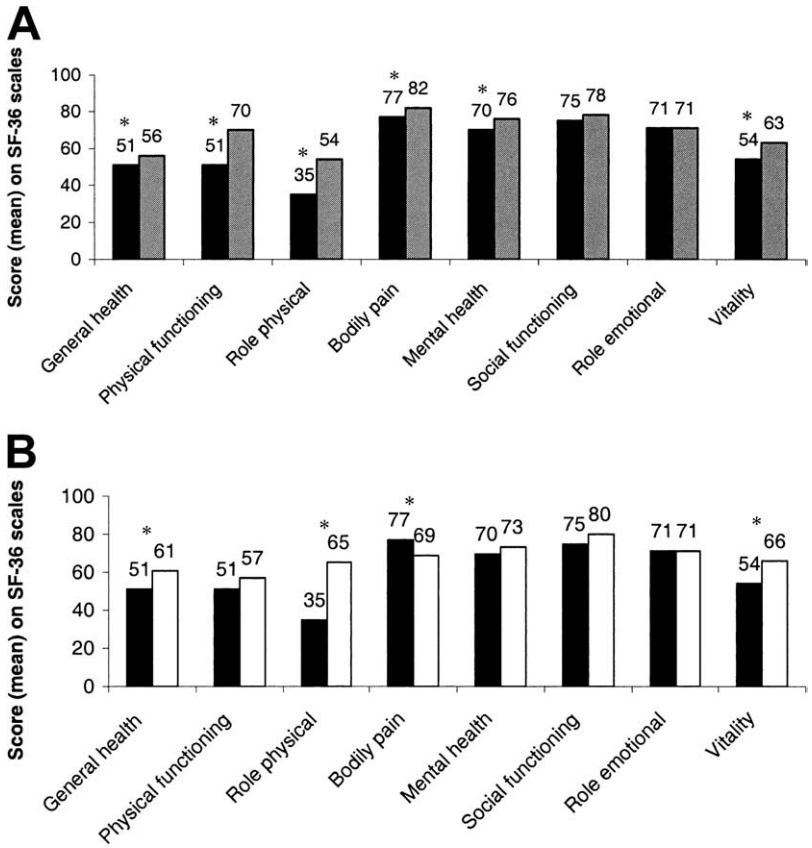

Figure 3. Quality of life scores of female patients versus male patients **(A)** and female patients versus female control subjects (matched for age) **(B)**. *$p < 0.05$. **Solid bars** = female patients (n = 128); **shaded bars** = male patients (n = 330); **open bars** = female control subjects (n = 64).

female patients are more prone compared with male patients to develop torsades des pointes during administration of class IA or III antiarrhythmic drugs (9), this gender difference was previously not observed (26). Also the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators did not describe any difference in prevalence of torsades des pointes between female patients and male patients (27). In our study, most adverse effects of antiarrhythmic drugs, however, were not related to the occurrence of tachycardias, but instead to bradyarrhythmias, i.e., unmasking of the sick sinus syndrome and symptomatic bradycardia. This could be a chance finding because the numbers are small. It also may have been caused by the use of negative chronotropic drugs, but this was not significantly different between rhythm control treated female patients and male patients.

Thirdly, in accordance with the previous text, more pacemaker implantations were observed in female patients, which was largely because more female patients had sick sinus syndrome.

Female gender and outcome of rate and rhythm control treatment. One of the major findings of the present analysis was an important difference in event-free survival between rhythm control randomized and rate control randomized female patients. The latter difference was not observed in male patients. Female patients randomized to rhythm control had a three times greater risk of developing cardiovascular morbidity and mortality, which was mainly because of the higher occurrence rate of heart failure, thromboembolic complications, and severe adverse effects of antiarrhythmic drugs.

There are several explanations for why there were more hospitalizations for heart failure and thromboembolic complications in female patients treated with rhythm control. Female patients in both treatment strategies were comparable with regard to patient characteristics, except for hypertension, which was more common in female patients than in male patients and predominantly in female patients randomized to rhythm control treatment. No other important differences were observed. Use of antiarrhythmic drugs, number of recurrences of AF and re-electrical cardioversions, NYHA functional class for heart failure, and atrial sizes and left ventricular function were very comparable during follow-up. If anything, left ventricular function was better preserved in female patients at inclusion and remained significantly improved during follow-up without any difference between rate and rhythm control randomized female patients. Also, with regard to thromboembolic complications, the use of oral anticoagulation and the presence of any thromboembolic risk factor was not different between the respective groups. Clearly, oral anticoagulation was more often discontinued in the rhythm control group, but

that was the case in both female patients and male patients. Our annual thromboembolic complication rate was slightly higher than observed in the SPAF studies (2.9% vs. 2.3%, 1.3%, and 1.9% in the SPAF-I, -II, and -III studies, respectively). Whereas the yearly rate was comparable in the rate and rhythm control randomized male patients (3.2% vs. 2.5%), thromboembolic complications almost only occurred in female patients randomized to rhythm control (0.9% vs. 4.9%, respectively). Although after correcting for the observed differences in hypertension history and blood pressure, rhythm control remained associated with a worse prognosis in female patients and not in male patients, we cannot definitely exclude that hypertension has influenced outcome in the female rhythm control strategy.

Gender differences in QoL. The QoL in female patients was impaired in comparison with that of healthy female controls. In agreement with this finding, female patients experienced more complaints of AF, especially palpitations and fatigue. This is in accordance with previous reports showing that patients with heart disease have lower QoL scores than healthy controls (13,28). In comparison with male patients, female patients had lower QoL scores on almost all SF-36 subscales. It is difficult to explain these gender differences. However, in the Canadian Trial of Atrial Fibrillation, QoL was also impaired in female patients compared with male patients, despite comparable severity of underlying heart disease (29). This reduced QoL in female patients may have been caused by the presence of more complaints, which are known to be important determinants of reduced physical and mental health scores (15). This can be partly attributable to a heightened sensitivity to the disease and symptoms, a difference in perception of illness, or a lower threshold of women for experiencing illness burden (29), but also to a lower chest volume or less chest thickness. Another possibility can be that more women are more likely to seek medical care when they experience symptoms (30). In addition, it may be possible that female patients are more prone to depression and anxiety than male patients (31,32), which may be reflected by the more impaired mental health in female patients compared with male patients in our study.

Study limitations. The present study is a post-hoc analysis, and therefore is not designed to determine gender differences in outcome after treatment. Another important limitation is the relatively small number of female patients and the disproportionate number of female patients with hypertension assigned to the rhythm control strategy. However, after correcting for these differences in hypertension history, blood pressure at baseline, and the change of the blood pressure during follow-up, rhythm control remained associated with a worse prognosis in female patients.

CONCLUSIONS

In female patients with recurrent persistent AF, a rhythm control treatment enhances cardiovascular morbidity and mortality, largely because of the occurrence of heart failure, thromboembolic complications, and severe adverse effects of antiarrhythmic drugs. Because treatment strategy does not have any influence on QoL in female patients, a rate control approach may be preferable.

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