Characterization of Different Patient Populations with Atrial Fibrillation

Kloosterman, Mariëlle

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Sex-related differences in risk factors, outcome, and quality of life in patients with permanent atrial fibrillation: results from the RACE II study

Mariëlle Kloosterman, Harry J.G.M. Crijns, Bart A. Mulder, Hessel F. Groenveld, Dirk J. Van Veldhuisen, Michiel Rienstra, Isabelle C. Van Gelder, for the RACE II investigators.

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ABSTRACT

Aims: AF risk factors translate into disease progression. Whether this affects women and men differently is unclear. We aimed to investigate sex differences in risk factors, outcome, and quality of life (QoL) in permanent AF patients.

Methods: The Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) randomized 614 patients, 211 women and 403 men, to lenient or strict rate control. In this post-hoc analysis risk factors, cardiovascular events during 3-year follow-up (cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events), outcome parameters, and QoL were compared between the sexes.

Results: Women were older (71±7 versus 66±8 years, P<0.001), had more hypertension (70 versus 57%, P=0.002), and heart failure with preserved ejection fraction (36 versus 17%, P<0.001), but less coronary artery disease (13 versus 21%, P=0.02). Women had more risk factors (3.7±1.2 versus 2.9±1.4, P<0.001) Cardiovascular events occurred in 46 (22%) women and 59 (15%) men (P=0.03). Women had a 1.52 times (95% CI:1.03-2.24) higher yearly cardiovascular event-rate (8.2% [6.0-10.9] versus 5.4% [4.1-6.9], P=0.03), but this was no longer significant after adjusting for the number of underlying risk factors. Women had reduced QoL, irrespective of age and heart rate but negatively influenced by their risk factors.

Conclusion: In this permanent AF population, women had more accumulation of AF risk factors than men. The observed higher cardiovascular event rate in women was no longer significant after adjusting for the number of risk factors. Further, QoL was negatively influenced by the higher number of risk factors in women. This suggests that sex differences may be driven by the greater risk factor burden in women.

INTRODUCTION

Atrial fibrillation (AF) is a major health burden worldwide.[1] Whilst women remain underrepresented in randomized clinical trials (RCTs) there has been an accumulation of evidence on sex-specific differences in incidence, prevalence, risk factors, presentation, and outcomes of patients with AF.[2-4] Women are generally older, more often have hypertension, but less often have coronary heart disease.[2-4] Risk factors may translate into AF development, in patients with metabolic syndrome a higher number of risk factors is associated with a stepwise increase in AF risk and poorer outcomes.[4,5] Whether this affects women and men differently is unclear. Registry studies have reported a higher incidence of AF-related stroke and systemic thromboembolism specifically in older women[6,7]. Increased mortality risk in women has also been described, but results are inconsistent.[8,9] Furthermore, women with AF are generally more symptomatic, seek more care for symptoms, and report a lower quality of life (QoL).[10] Questions on sex-specific differences in AF remain, and data on predictors of outcome is scarce to non-existent.

Gaps in knowledge on sex differences are undesirable since recognition of sex-based differences may offer an opportunity to improve personalized treatments. The aim of this Rate Control Efficacy in Permanent AF: A Comparison between Lenient versus Strict Rate Control II (RACE II) [11] post-hoc analysis was to investigate sex-differences in risk factors, cardiovascular events and associated parameters, and QoL.

METHODS

Study population

RACE II was a randomized, multicentre study comparing long-term effects of lenient versus strict rate control in 614 patients with permanent AF performed in The Netherlands between January 2005-June 2007. Eligibility criteria were: permanent AF for up to 12 months, age ≤80 years, mean resting heart rate >80 beats per minute, and current use of oral anticoagulation therapy (Vitamin K antagonists or aspirin, if no risk factors for thromboembolic complications were present according to European Society of Cardiology (ESC) AF guidelines at the time of inclusion).[12] Previous stroke, but not TIAs, was an exclusion criteria. Study design details have been described before.[11] Patients randomized to lenient rate control had a resting heart rate target <110 beats per minute (bpm). Patients randomized to strict rate control had two heart rate targets: a resting heart rate target <80 bpm and a heart rate target during moderate exercise <110 bpm. Patients were administered one or more negative dromotropic drugs until target(s) were reached. After achievement of rest and activity heart rate targets in the strict

group, 24-hour Holter monitoring was performed to check for bradycardia. Follow-up outpatient visits occurred every 2 weeks until heart rate target(s) were achieved (dose adjustment phase), and in all patients after 1, 2, and 3 years. Follow-up was terminated after 3 years or on 30 June 2009, whichever came first. The institutional review board of each participating hospital approved the study, and all patients provided written informed consent. For the present analysis sex-differences in risk factors, cardiovascular events and associated parameters, as well as QoL were assessed.

AF risk factors

Many risk factors are known to be associated with AF.[2-4,12] In RACE II extensive patient characteristics were collected and for each individual patient the number of AF risk factors was determined. Risk factors included: hypertension [1 point]; heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) [1 point]; advanced age: >65 years [1 point]; diabetes mellitus [1 point]; coronary artery disease [1 point]; overweight or obesity: body mass index (BMI) >25 kg/m^2 [1 point]; kidney dysfunction: estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 [1 point]; and moderate to severe mitral valve insufficiency (grade ≥2) [1 point] (Table 2). eGFR was calculated using MDRD formula: 175 x [serum creatinine (µmol/L) x0.0113]$^{-1.154}$ x age (years)$^{-0.203}$ (x 0.742 if female).

Blood markers

After inclusion 10mL blood was collected by vein puncture. Within 1 hour the EDTA tube was centrifuged for 10min, plasma was removed, and locally stored at -80 degrees. After study completion NT-proBNP and hsTroponin-T measurements were performed using electrochemiluminisecent immunoassays (Roche Modular E170, Roche Diagnostics, Mannheim, Germany) at the core laboratory of the University Medical Center Groningen. Overall machine day-to-day variation was 2.0-2.2%.

Echocardiography

Two-dimensional transthoracic echocardiography was performed at baseline in left lateral decubitus position. Images were obtained from parasternal (long- and short axis) and apical (two- and four-chamber) views. Atrial and ventricular dimensions and ejection fraction (LVEF) were quantified according to standard guideline recommendations. Left atrial volume was measured using the biplane Simpson method and indexed (LAVI) to the body surface area (BSA). BSA was calculated using the formula of DuBois and DuBois: (weight(kg)$^{0.425}$ x height(cm)$^{0.725}$) x 0.007184. Presence of HFrEF and HFpEF was determined using following respective definitions: HFrEF: LVEF<40%; HFpEF: dyspnea and/or fatigue, LVEF≥40%, NT-proBNP >900pg/ml, and structural heart disease classified as LAVI ≥34 ml/m^2 and/or left ventricular mass index ≥95 g/m^2 in women and ≥115 g/m^2 in men.[13]

Cardiovascular events

Cardiovascular events included cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate-control drugs, and pacemaker or cardioverter-defibrillator implantation. Extensive definitions of individual composites have been previously described.[11] Cardiovascular events that occurred between randomization and end of study were recorded. An endpoint adjudication committee, who were unaware of assigned treatment strategy, adjudicated endpoints. Minimal follow-up was 2 years; median follow-up was 3 years (interquartile range 2.2-3.1 years).

Quality of life

Baseline and end-of-study QoL was measured using three questionnaires. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) assessed General Health. SF-36, a validated general health survey that is frequently in arrhythmia studies, contains items to assess physical- and mental health. The survey is composed of eight subscales of multiple-choice questions, ranging in a stepwise fashion from impaired/ low QoL to not impaired/ high QoL. Subscales are transformed to a score ranging from 0-100, with lower scores representing a lower QoL. Severity of AF-related symptoms was assessed using the University of Toronto AF Severity Scale (AFSS), an instrument intended to measure perception of arrhythmia-related symptom severity. This 7-item questionnaire includes common AF symptoms (e.g. palpitations, dyspnea). Items are rated on a 6-point scale. The final score ranges from 0-35, with a higher score indicating greater AF symptom severity. Severity of fatigue was measured using the Multidimensional Fatigue Inventory-20 (MFI-20). MFI-20 contains 20 statements covering 5 domains of fatigue: general-, physical- and mental fatigue, and reduced activity and motivation. Scores range from 4-20, with higher scores indicating more fatigue.

Statistical analysis

For the purpose of this post-hoc analysis, the RACE II cohort population was stratified and analysed by sex. Baseline characteristics were compared between men and women. Variables are presented as numbers (percentage) or mean (±SD), as appropriate. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Comparisons between continuous variables were performed using the Wilcoxon rank-sum test or two-sample t-test depending on normality; comparisons between nominal variables were performed using the Pearson's χ^2 test or Fisher's exact test, depending on expected cell sizes. Yearly event-rates were calculated by dividing the number of cardiovascular events by the number of follow-up years. Individual patient years were calculated as the time from randomization until the moment of censoring. Patients were censored if they withdrew

informed consent, died, were lost to follow-up, had been followed through June 30, 2009, or had been in the trial for the maximum of 3 years. Differences in yearly event-rates were calculated by MedCalc (Windows version:17.6). Cox regression analysis was performed to determine covariates associated to cardiovascular event occurrence for the total population and women and men specifically. Predefined univariate parameters with P<0.1 and randomization strategy were tested in a multivariate Cox proportional hazards model using a backward stepwise approach according to likelihood ratio. Final multivariable models included all covariates with P<0.05 and randomization strategy to adjust for the post-hoc nature of the current analysis. Final models were tested for first-line interactions. ANOVA was used to look for differences in QoL scores after adjusting for age, heart rate and risk factors (since lower heart rates may reduce exercise capacity and induce fatigue).

Because of significant imbalances in baseline characteristics between women and men, we performed sensitivity analysis using propensity-score matching in order to compare outcomes and quality of life between matched women and men. Propensity scores were calculated for each patient using multivariable logistic regression based upon the following covariates: age, systolic blood pressure, body mass index, estimated glomerular filtration rate, presence of diabetes, left ventricular ejection fraction, NT-proBNP levels and randomization strategy. Women and men were matched in a 1:1 ratio without replacement within 0.001 units of the propensity score.

All tests of significance were 2-sided, with P values of <0.05 assumed to indicate significance. All the analyses were considered to be exploratory. Analyses were generated by using SPSS version 23.0 for Windows (IBM Corp, Chicago, IL, USA).

RESULTS

Patient characteristics and AF risk factors

RACE II included 211 women and 403 men. Women were older (71±7 versus 66±8, P<0.001), 36% of women were ≥75 years compared to 20% of men. Women had more hypertension (70% versus 57%, P=0.002), HFpEF (36% versus 17%, P<0.001), and mitral valve regurgitation (27% versus 13%, P<0.001), but less coronary artery disease (CAD) (13% versus 21%, P=0.02) (Table 1, 2). Renal function was worse in women (eGFR 61±16 ml/min/1.73m^2 versus 68±16 ml/min/1.73m^2, P<0.001). This resulted in higher $CHADS_2$ scores (1.6±1.1 versus 1.3±1.0, P<0.001) and more AF risk factors (3.7±1.2 in women versus 2.9±1.4 in men, P<0.001 [Table 2, Figure 1]). Left ventricular dimensions were smaller in women but baseline LAVI did not differ (Table 1). NT-proBNP levels were higher in women (1240 pg/ml versus 879 pg/ml, P<0.001).

Table 1. Patient characteristics

	Overall (N=614)	Women (N=211)	Men (N=403)	P-value
Demographics				
Age - year	68±8	71±7	66±8	<0.001
Total AF duration* - months - median (IQR)	18 (6-60)	18 (3-59)	18 (5-60)	0.90
Duration AF episode at inclusion - months - median (IQR)	3 (1-6)	3 (1-7)	3 (1-5)	0.20
Medical history				
Cardiomyopathy	41 (7)	7 (3)	34 (8)	0.02
Respiratory disease	104 (17)	31 (15)	73 (18)	0.31
Previous hospitalization for heart failure	60 (10)	22 (10)	38 (9)	0.78
Thromboembolic complication	72 (12)	29 (14)	43 (11)	0.29
Physical examination				
Length - cm	174±9	166±7	178±7	<0.001
Weight - kg	87±17	79±15	91±16	<0.001
Body mass index - kg/m^2	28.6±4.6	28.7±4.8	28.6±4.4	0.94
Blood pressure - mmHg				
Systolic	136±18	138±18	135±18	0.02
Diastolic	83±11	84±11	83±11	0.18
Heart rate in rest - bpm	96±12	96±13	96±12	0.97
Clinical status				
Treatment				
Strict rate control	303 (49)	105 (50)	198 (49)	0.93
Lenient rate control	311 (51)	106 (50)	205 (51)	
$CHADS_2$ score				
Mean±SD	1.4±1.1	1.6±1.1	1.3±1.0	<0.001
0 or 1	373 (61)	107 (51)	266 (66)	<0.001
2	159 (26)	67 (32)	92 (23)	0.02
3-6	82 (13)	37 (18)	45 (11)	0.03
Symptoms	348 (57)	147 (70)	201 (50)	<0.001
Palpitations	145 (24)	77 (37)	68 (17)	0.001
Dyspnea	215 (35)	94 (45)	122 (30)	0.54
Fatigue	183 (30)	81 (38)	102 (25)	0.42
Functional class (NYHA) - I/II/III - (%)	65/30/5	56/37/7	70/27/3	0.003
eGFR - ml/min/1.73m^2 - mean±SD	65±16	61±16	68±16	<0.001
Treatments				
Previous ECV - number - median (IQR)	1 (0-22)	1 (0-8)	1 (0-22)	0.57
Rate control medication				
No rate control drugs	63 (10)	10 (5)	53 (13)	0.001
Beta-blocker	408 (66)	154 (73)	254 (63)	0.02
Verapamil or diltiazem	90 (15)	30 (14)	60 (15)	0.91

Table 1. Patient characteristics (continued)

	Overall (N=614)	Women (N=211)	Men (N=403)	P-value
Digoxin	198 (32)	94 (45)	104 (26)	<0.001
Other medication at baseline				
ACE-inhibitors	203 (33)	68 (32)	135 (34)	0.79
ARB	114 (19)	48 (23)	66 (16)	0.06
ACE-inhibitors and/or ARB	306 (50)	114 (54)	192 (48)	0.15
Diuretics	247 (40)	104 (49)	143 (36)	0.001
Statin	177 (29)	57 (27)	120 (30)	0.51
Vitamin K antagonists	606 (99)	209 (99)	397 (99)	0.72
Laboratory values (IQR)				
NT-proBNP - pg/ml	1003 (634-1632)	1240 (889-1907)	879 (544-1408)	<0.001
hsTroponin-T - pg/ml	9 (7-14)	9 (6-13)	9 (7-14)	0.22
Echocardiographic parameters				
Left atrial end systolic volume - ml	73±26	69±23	75±27	0.02
Left atrial volume index - ml/m^2	36±12	37±12	36±12	0.30
Right atrial length, apical view - mm	58±8	57±8	59±8	0.01
Left ventricular end diastolic dimension - ml	51±7	48±7	53±7	<0.001
Left ventricular end systolic dimension - ml	36±8	33±8	38±8	<0.001
Left ventricular mass index - g/m^2	135±44	123±39	142±45	<0.001
Left ventricular ejection fraction - %	52±12	54±12	51±12	0.002

Data are depicted as number (%) or mean±SD unless stated otherwise.
* Total AF duration denotes the time from diagnosis of AF to start of study.
ACE denotes angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ECV, electrical cardioversion; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation.

Rate control

Baseline heart rates were similar (Table 1). At baseline women more frequently used rate control drugs (often digoxin, or digoxin in combination with a beta-blocker). This persisted through follow-up (Table 1, Supplementary Table 1). After dose-adjustment, women in the lenient group used a higher dose of beta-blockers (all doses were normalised to metoprolol equivalent doses) compared to men (135±84mg versus 112±73mg, P=0.04). Women with both lenient and strict rate control used lower doses of digoxin compared to men (for lenient 169±66µg versus 201±81µg, P=0.034; for strict 189±82µg versus 211±83µg, P=0.04). This persisted till the end of follow-up. There were no sex differences in heart rate in the lenient and strict rate groups (Supplementary Figure 1).

Table 2. AF risk factors

AF risk factors - number (%)	Overall	Women	Men	P-value
Hypertension	375 (61)	147 (70)	228 (57)	0.002
Heart failure				
HFrEF	93 (15)	25 (12)	68 (17)	0.10
HFpEF*	100 (23)	52 (36)	48 (17)	<0.001
Advanced age				<0.001
65-74 years	258 (42)	101 (48)	157 (39)	
≥75 years	155 (25)	76 (36)	79 (20)	
Diabetes mellitus	70 (11)	30 (14)	38 (9)	0.08
Coronary artery disease	111 (18)	28 (13)	83 (21)	0.02
Obesity				0.34
BMI >25-30 kg/m^2	289 (47)	91 (43)	198 (49)	
BMI >30 kg/m^2	189 (31)	68 (32)	121 (30)	
Kidney dysfunction	229 (37)	110 (52)	119 (30)	<0.001
eGFR <60 ml/min/1.73m^2				
Mitral regurgitation	110 (18)	56 (27)	54 (13)	<0.001
Number of AF risk factors†	3.2±1.4	3.7±1.2	2.9±1.4	<0.001

* N=436 had data on all variables that compose HFpEF (146 women and 290 men).
† For description see methods section: AF risk factors.
BMI denotes body mass index; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SD, standard deviation.

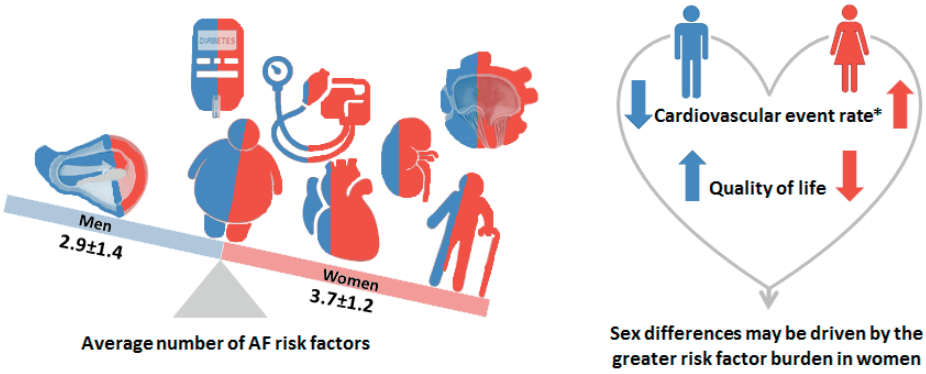

Figure 1. Sex differences in risk factors
In the RACE II population, consisting of patients with permanent AF, women had more accumulation of AF risk factors than men. Colors in the left panel [men blue, women red] represent the distribution of risk factors in the RACE II population.
*The observed higher cardiovascular event rate in women was no longer significant after adjusting for the number of risk factors. Further, QoL was negatively influenced by the higher number of risk factors in women. This suggests that sex differences may be driven by the greater risk factor burden in women.

Cardiovascular events

During 3-year follow-up (interquartile range 2.2-3.1 years) 105 (17%) cardiovascular events occurred, 46 (22%) in women and 59 (15%) in men (Table 3). Yearly cardiovascular event-rate was 6.3%/year (95% CI;5.2-7.7). Women had a 1.52 (1.03-2.24) times higher yearly event-rate: 8.2%/year (95% CI;6.0-10.9) in women versus 5.4 %/year (95% CI;4.1-6.9) in men, P=0.03. After adjusting for age it remained significant, P=0.04. It was no longer significant after adjusting for the number of risk factors (P=0.16). Additionally, in women and men no significant difference in primary outcome between lenient and strict rate control was observed, respectively P=0.31 and P=0.89. In the propensity score matched cohort also no differences in outcome between women and men were observed. (Supplementary Table 2 and 3)

Table 3. Cardiovascular events during follow-up

	Overall	Women	Men	P-value
Yearly cardiovascular event - rate - % (95% CI)	6.3 (5.2-7.7)	8.2 (6.0-10.9)	5.4 (4.1-6.9)	0.03
Total cardiovascular events* - number (%)	105 (17.1)	46 (21.8)	59 (14.6)	0.03
Death from cardiovascular cause	20 (3.3)	9 (4.3)	11 (2.7)	0.34
Cardiac arrhythmic death	7 (1.1)	4 (1.9)	3 (0.7)	0.24
Cardiac non-arrhythmic death	3 (0.5)	1 (0.5)	2 (0.5)	0.99
Non-cardiac vascular death	10 (1.6)	4 (1.9)	6 (1.5)	0.74
Heart failure hospitalisation	22 (3.6)	9 (4.3)	13 (3.2)	0.50
Stroke	15 (2.4)	5 (2.4)	10 (2.5)	0.99
Ischemic stroke	11 (1.8)	4 (1.9)	7 (1.7)	0.99
Haemorrhagic stroke	5 (0.8)	1 (0.5)	4 (1.0)	0.67
Systemic embolism	1 (0.2)	-	1 (0.2)	0.99
Bleeding	28 (4.6)	14 (6.6)	14 (3.5)	0.10
Intracranial bleeding	3 (0.5)	1 (0.5)	2 (0.5)	0.99
Extracranial bleeding†	25 (4.1)	13 (6.2)	12 (3.0)	0.08
Syncope	6 (1.0)	4 (1.9)	2 (0.5)	0.19
Life threatening adverse effects of rate control drugs	5 (0.8)	3 (1.4)	2 (0.5)	0.35
Sustained ventricular tachycardia or ventricular fibrillation	1 (0.2)	-	1 (0.2)	0.99
Implantable cardioverter defibrillation implantation	1 (0.2)	-	1 (0.2)	0.99
Pacemaker implantation	6 (1.0)	2 (0.9)	4 (1.0)	0.99

*Includes the total number of cardiovascular events that occurred during follow-up.
† Extracranial bleeding events in women included: gastrointestinal (N=4), post-surgery/intervention (N=3), knee hematoma (N=2), large hematoma upper leg after trauma (N=3), retroperitoneal (N=1). Extracranial bleeding events in men included: gastrointestinal (N=5), post-surgery/intervention (N=4), retroperitoneal bleeding (N=1), urinary tract (N=1), pulmonary related to bronchus carcinoma (N=1).

Parameters associated with cardiovascular event occurrence

In multivariable analysis, AF duration (Hazard Ratio [HR] 1.01 per month [95% CI 1.00-1.01], P=0.004), female sex (HR 1.87 [95% CI 1.15-3.03], P=0.011), NT-proBNP (HR 1.03 per 100 [95% CI 1.01-1.04], P=0.001), and hsTroponin-T (HR 1.02 per 1 [95% CI 1.01-1.04), P=0.003) were associated with the occurrence of cardiovascular events in the total population (Table 4). In women LAVI (HR 1.09 per 1 ml/m^2 [95% CI 1.05-1.14], P<0.001) and AF duration (HR 1.03 per month [95% CI 1.01-1.04], P<0.001) were associated with outcome, in men NT-proBNP (HR 1.08 per 100 [95% CI 1.03-1.13], P<0.001) and hsTroponin-T (HR 1.09 per 1 [95% CI 1.04-1.13], P<0.001). There were interactions between LAVI and AF duration (P=0.03) and NT-proBNP and hsTroponin-T (P=0.02) in women and men, respectively.

Table 4. Multivariable Cox regression analyses

	Overall		Women		Men	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Lenient rate control	0.84 (0.52-1.36)	0.47	0.57 (0.26-1.25)	0.16	1.00 (0.50-2.00)	0.99
Duration of AF per month	1.01 (1.00-1.01)	0.004	1.03 (1.01-1.04)	<0.001		
Female sex	1.87 (1.15-3.03)	0.011				
NT-proBNP per 100	1.03 (1.01-1.04)	0.001			1.08 (1.03-1.13)	<0.001
hsTroponin-T	1.02 (1.01-1.04)	0.003			1.09 (1.04-1.13)	<0.001
LAVI (ml/m^2)			1.09 (1.05-1.14)	<0.001		
Duration AF · LAVI			1.00 (0.99-1.00)	0.031		
NT-pro · hsTroponin-T					0.99 (0.99-1.00)	0.016

AF denotes atrial fibrillation; CI, confidence interval; HR, hazard ratio; LAVI, left atrial volume index.

Symptoms and quality of life

Women had more symptoms (70% versus 50%, P<0.001), Table 1). At the end of follow-up, 42% of men and 53% of women had symptoms (P=0.004): dyspnoea (25% versus 38%, P=0.03), fatigue (20% versus 31%, P=0.15), and palpitations (5% versus 20%, P<0.001) were more frequent in women. QoL, as assessed with SF-36, MFI-20 and AFSS was significantly lower in women, also after correcting for heart rate, age, and number of risk factors (Figure 2). This remained unchanged during follow-up. Differences in physical functioning and fatigue scales were most pronounced. Emotional limitations (SF-36) and mental fatigue (MFI-20) did not differ between the sexes. Similar results were observed in the matched cohort (Supplementary Table 4) The number of AF risk factors was associated with a reduced QoL, more clearly in women than in men, this suggests that women are more negatively affected, in terms of QoL, by permanent AF; per risk factor baseline SF-36 physical score decreased by 1.40 in women (95% CI -2.68 to -0.46) and by 1.21 in men (95% CI -1.90 to -0.54), both P<0.05. This was also true for

MFI-20 scales with the exception of mental fatigue. The number of risk factors was not a predictor for SF-36 mental scores or AFSS in both sexes.(11)

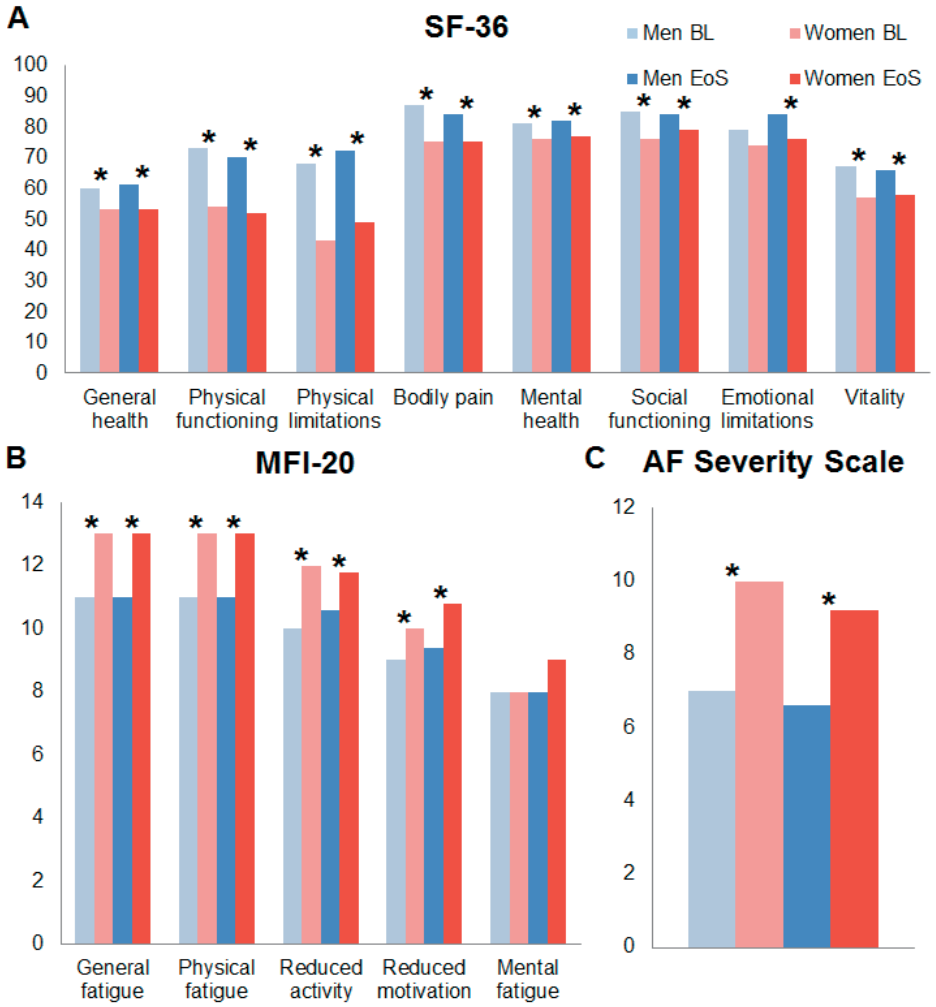

Figure 2. Quality of life

Three quality of life (QoL) scores at baseline (BL) and end of study (EoS):

A) The Medical Outcomes Study Short-Form questionnaire (SF-36). SF-36 scores range from 0-100, with lower scores representing a lower QoL.

B) The multidimensional fatigue inventory (MFI-20). MFI-20 scores range from 0-35, with higher scores indicating greater AF symptom severity.

C) The Toronto AF severity scale (AFSS). AFSS score ranges from 4-20, with higher scores indicating more fatigue.

*P-values <0.05 between the sexes.

DISCUSSION

We show that men and women with permanent AF are not the same. Women were older, had more AF risk factors, and more frequently used rate control drugs. In women and men, different parameters were associated with events. The observed higher cardiovascular event rate in women was no longer significant after adjusting for the number of risk factors. Further, QoL was negatively influenced by the higher number of risk factors in women. These results suggest that sex differences are mainly driven by the presence of more risk factors in women.

Patient characteristics and AF risk factors

In line with published data we describe different patient characteristics in women and men.[2-4] Women were older and more likely to have hypertension, HFpEF, poorer kidney function, and more mitral regurgitation. This may partially reflect the epidemiologically later age at AF onset in women and the fact that ageing allows the acquirement of more risk factors. [2-4] Men had more often coronary artery disease.[4]

Risk factors play a prominent role in AF pathophysiology and sex may modulate how various risk factors contribute to AF.[4,14] The prevalence of major risk factors have changed in both men and women during the years, and the population attributable risk of AF risk factors changed too.[1-2] AF risk factors translate into disease progression; a higher number of risk factors is associated with a stepwise increase in AF risk and AF progression including poorer outcomes in patients with metabolic syndrome.[4,5] The specific pathophysiological mechanisms, however, remain incompletely studied. The presence of more risk factors in women, as demonstrated by our data, may explain the worse outcome and worse quality of life observed.

Women more frequently used rate control drugs, specifically digoxin, or digoxin in combination with a beta-blocker. The Euro Observation Research Programme on Atrial Fibrillation (EORP-AF) survey also reported more digoxin use in women.[2] Prescribed dosages of beta-blockade were higher in women receiving lenient rate control. Reasons are speculative, but greater symptom burden in women may prompt treating physicians to prescribe a higher dose. The higher rates of digoxin use may also reflect poorer tolerability and/or effect to commonly used rate-control medications. Additionally, women more often used a diuretic drug. To what extent sex differences in clinical profile and outcome reflect treatment disparities remains unknown.

Cardiovascular events

Women in RACE II experienced a higher cardiovascular event-rate. This was caused by a slightly higher, non-significant, occurrence of nearly all primary endpoint components. After adjustment for the number of underlying risk factors, however, the difference was no longer significant. In our cohort matched on sex and risk factors, we also observed no difference in outcome between women and men, further supporting the unmatched results. There have been longitudinal studies that reported higher mortality rates[8,9], and higher risk of stroke and thromboembolism in mostly older women, but results vary.[6,7] Women in RACE II were on average 5 years younger than in the Framingham Original cohort, and follow-up was shorter.[8] Additionally, RACE II patients were treated according to prevailing European Society of Cardiology AF guidelines at the time of inclusion,[12] including oral anticoagulation in nearly all patients. This is contrary to studies that describe higher stroke and systemic embolisms rates in women.[7] We observed a trend towards more extracranial bleeding events in women, conceivably explained by the fact that women had multiple risk factors associated with increased bleeding risk, including advanced age and kidney dysfunction.[15]

Parameters associated with cardiovascular event occurrence

We describe sex-specific parameters associated with cardiovascular event occurrence. In women, LAVI and duration of AF were associated with primary endpoint occurrence. This supports findings of AFFIRM that described female sex and mitral valve regurgitation being independently associated with LA enlargement,[14] and LA enlargement being associated with a higher risk of cardiovascular death only in women.[14] LA enlargement is often an expression of risk factor and age-related degeneration due to hemodynamic changes in pressure- and volume load.[16] Similarly, longer AF durations are associated with more severe remodelling, larger atria and worse outcome.[4] Women included in RACE II had more AF risk factors, possibly partially explaining the link between LAVI and outcome. However, we cannot exclude a sex difference in atrial structural remodelling resulting in a more pronounced abnormal atrial milieu. Our findings confirm LA size as a marker in prognosis assessment of AF patients and underscore the clinical relevance of LA measurements.[16] However, it should be noted that in AF patients visualization of the left atrium may be suboptimal and complicated by irregular contractions of the LA wall, limiting the reproducibility of LA parameters measures.

In men NT-proBNP and hsTroponin-T were associated with primary endpoint occurrence, despite NT-proBNP levels being higher in women. It is known that women have higher NT-proBNP levels, regardless of menopause status or hormone therapy, and require higher cut-offs for optimal sensitivity and specificity in systolic dysfunction detection.[17] The independent predictive value of hsTroponin-T and NT-proBNP for car-

diovascular death and thromboembolic events in anticoagulated AF patients has been described in a substudy of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial.[18] NT-proBNP is a marker of atrial- and ventricular dysfunction.[19] Origin of elevated hsTroponin-T in AF patients is not completely known, but may be due to mechanisms such as increased and irregular ventricular rate causing oxygen supply-demand mismatch and subsequent ischemia, oxidative stress, and volume and pressure overload.[19] The specific role of these blood biomarkers, which may reflect sex differences in cardiovascular pathophysiology, should be investigated further.

Quality of life

Studies indicate that women are more likely to experience symptoms and a worse QoL.[10,20] We report that women experienced mainly physical limitations during follow up; no differences in mental status were observed. Observed differences remained after correcting for age, heart rate and risk factors. Additionally, in our matched cohort similar results were observed. Women continued to experience more severe physical limitations and reduced activity than men. Women more often used dual therapy (digoxin and beta-blocker) and higher dosages of beta-blocker. Higher dosages of beta blockade may result in more pronounced adverse effects, including fatigue, negatively affecting women's physical ability.[2] The number of AF risk factors was associated with a reduced QoL, more clearly in women than in men, this suggests that women are more negatively affected, in terms of QoL, by permanent AF.

Limitations and strengths

Present study is a post hoc analysis of RACE II and thus not specifically designed to study sex differences. Our data is restricted to observations and cannot reveal (causal) mechanisms. Therefore the current study should be interpreted as hypothesis generating since the (pathophysiological)processes that underlie the observed sex differences remain elusive. Furthermore, there is an inherent baseline risk (factor) difference between men and women which is intertwined with the outcome difference observed. This may be bias in enrolment in the RACE II trial, actual population differences, or both. Therefore current population may not be representative of a population based sample. Additionally, we adjusted for randomization strategy in our analyses, but not for the high number of possible combinations of negative dromotropic drugs and dosages, as this would inappropriately complicate the analyses. The performed propensity score matching, albeit balancing covariates on average, also has it disadvantages. The matched cohort is smaller, the relative importance of covariates in their effects on outcome and quality of life may differ, and unmeasured characteristics and confounders remain unbalanced. Nevertheless, these additional data support our main results.

Data on time in therapeutic range in patients receiving a vitamin K antagonist is missing, and the RACE II study was performed in the pre-NOAC era. Additionally, follow up for cardiovascular events was limited to a relatively short follow up of three years. These factors should be kept in mind when interpreting the results. Echocardiographic measurements were performed during AF, which may have influenced measurements, but this was the same for all patients. Blood markers represent one single-time point, but all patients were in stable condition and permanent AF at time of blood withdrawal. Studied risk factors were limited to those pre-specified, and therefore collected, in RACE II. Women were underrepresented in RACE II, as in many RCTs. Increasing female participation in RCTs will improve generalizability of trials and allow for effect modification by sex, which is essential to generate adequate evidence in women. Strengths include our well-characterized cohort, frequent follow-up, and data collection of events. An independent endpoint committee who were unaware of assigned treatment strategy adjudicated all endpoints.

CONCLUSION

Important sex differences exist in patients with permanent AF. Women were older, had more AF risk factors, and more frequently used rate control drugs. In women and men, different parameters were associated with events. The observed higher cardiovascular event rate in women was no longer significant after adjusting for the number of risk factors. Further, QoL was negatively influenced by the higher number of risk factors in women. These findings highlight AF complexity and heterogeneity. More knowledge about sex-specific differences in AF risk and risk factors is essential to optimize cardiovascular care for both men and women.

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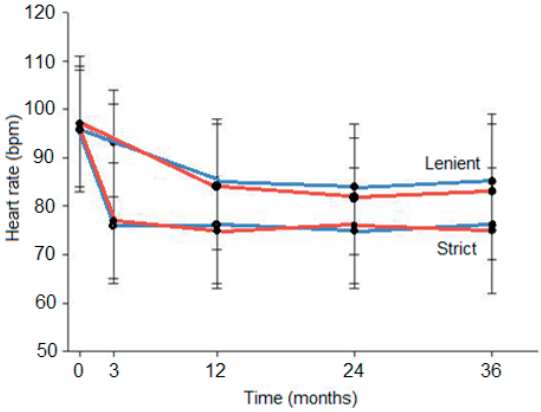
SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Heart rate
Heart rate in beats per minute (bpm) during RACE II for women (red) and men (blue) in the lenient and strict rate control arm.

Supplementary Table 1. Rate-control medication in the lenient versus strict group during follow-up in women and men

	Women		Men	
	Lenient (N=106)	Strict (N=105)	Lenient (N=205)	Strict (N=198)
Baseline				
No rate control drugs	6 (6)	4 (4)	30 (15)†	23 (12)†
Beta-blocker alone	42 (40)	42 (40)	98 (48)	94 (47)
Verapamil/diltiazem alone	2 (2)	5 (5)	16 (8)†	14 (7)
Digoxin alone	11 (10)	12 (11)	9 (4)†	12 (6)
Beta-blocker + verapamil/diltiazem	4 (4)	6 (6)	3 (1)	5 (3)
Beta-blocker + digoxin	29 (27)	25 (24)	24 (12)†	24 (12)†
Verapamil/diltiazem + digoxin	4 (4)	4 (4)	10 (5)	10 (5)
Beta-blocker + verapamil/diltiazem + digoxin	2 (2)	3 (3)	0 (-)	2 (1)
End of dose-adjustment phase				
No rate control drugs	6 (6)	1 (1)	26 (13)	2 (1)*
Beta-blocker alone	38 (36)	20 (19)*	94 (46)	41 (21)*
Verapamil/diltiazem alone	2 (2)	4 (4)	16 (8) †	12 (6)
Digoxin alone	11 (10)	1 (1)*	10 (5)	4 (2)
Beta-blocker + verapamil/diltiazem	6 (6)	16 (15)*	6 (3)	22 (11)*
Beta-blocker + digoxin	30 (28)	42 (40)	30 (15) †	71 (36)*
Verapamil/diltiazem + digoxin	6 (6)	8 (8)	12 (6)	21 (11)
Beta-blocker + verapamil/diltiazem + digoxin	3 (3)	11 (10)*	0 (-)†	16 (8)*
End of study visit				
No rate control drugs	3 (3)	0 (-)	21 (10) †	5 (3)*
Beta-blocker alone	29 (27)	15 (14)*	82 (40)†	36 (18)*
Verapamil/diltiazem alone	2 (2)	2 (2)	12 (6)	6 (3)
Digoxin alone	6 (6)	3 (3)	11 (5)	3 (2)*
Beta-blocker + verapamil/diltiazem	7 (7)	12 (11)	5 (2)	21 (11)*
Beta-blocker + digoxin	61 (58)	39 (37)	38 (19) †	59 (30)*
Verapamil/diltiazem + digoxin	6 (6)	7 (7)	11 (5)	20 (10)
Beta-blocker + verapamil/diltiazem + digoxin	3 (3)	10 (10)*	1 (0.5)	21(11)*

All values depicted as number (%).

* P<0.05 between lenient and strict rate control in women and men.

† P<0.05 between women and men within randomization strategy.

Supplementary Table 2. Patients characteristics after propensity score matching

	Women (N=70)	Men (N=70)	P-value
Demographics			
Age - year	68±7	68±9	0.65
Total AF duration* - months - median (IQR)	22 (6-62)	15(5-50)	0.39
Current AF episode duration - months - median (IQR)	3 (1-7)	2 (1-5)	0.13
Medical history			
Hypertension	48 (69)	39 (56)	0.16
Coronary artery disease	5 (7)	10 (14)	0.27
Diabetes	6 (9)	10 (14)	0.43
Previous hospitalization for heart failure	8 (11)	2 (3)	0.10
Ischemic thromboembolic complication	12 (17)	9 (13)	0.64
Physical examination			
Body mass index - kg/m^2	28.5±4.8	27.5±4.3	0.25
Blood pressure - mmHg Systolic	135±16	137±15	0.65
Clinical status			
Randomization strategy - strict / lenient (%)	56 / 44	53 / 47	0.87
$CHADS_2$ score	1.5±1.2	1.4±1.1	0.57
Symptoms	49 (70)	33 (47)	0.01
Palpitations	31 (44)	9 (13)	0.002
Dyspnea	33 (47)	20 (29)	0.04
Fatigue	25 (36)	17 (24)	0.20
NYHA class III (%)	7	6	0.99
eGFR - ml/min/1.73m^2	80±26	76±21	0.34
Treatments			
Beta-blocker	57 (81)	45 (64)	0.04
Verapamil or diltiazem	11 (16)	14 (20)	0.66
Digoxin	23 (32)	15 (21)	0.18
ACE-inhibitor and/or ARB	38 (54)	36 (51)	0.87
Diuretics	30 (43)	26 (37)	0.61
Statin	17 (24)	17 (24)	0.99
Vitamin K antagonists	70 (100)	70 (100)	-
Laboratory values (IQR)			
NT-proBNP - pg/ml	1074 (713-1806)	828 (473-1506)	0.01
Echocardiographic parameters			
Left ventricular ejection fraction - %	51±11	52±12	0.49

Data are depicted as number (%) or mean±SD unless stated otherwise.
* Total AF duration denotes the time from diagnosis of AF to start of study.
ACE denotes angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation.

Supplementary Table 3. Cardiovascular events during follow-up in propensity score matched women and men

	Women (N=70)	Men (N=70)	P-value
Primary endpoint occurrence*	12 (17)	8 (11)	0.27
Total cardiovascular events†- number (%)	16 (23)	10 (14)	0.19
Death from cardiovascular cause	4 (6)	3 (4)	
Cardiac arrhythmic death	1 (1)	1 (1)	
Cardiac non-arrhythmic death	1 (1)	1 (1)	
Non-cardiac vascular death	2 (3)	1 (1)	
Heart failure hospitalisation	3 (4)	4 (6)	
Stroke	-	1 (1)	
Ischemic stroke	-	-	
Haemorrhagic stroke	-	1 (1)	
Systemic embolism	-	-	
Bleeding	7 (10)	1 (1)	
Intracranial bleeding	-	1 (1)	
Extracranial bleeding	7 (10)	-	
Syncope	1 (1)	1 (1)	
Life threatening adverse effects of rate control drugs	-	-	
Sustained ventricular tachycardia or - fibrillation	-	-	
Implantable cardioverter defibrillation implantation	-	-	
Pacemaker implantation	1 (1)	-	

*Primary endpoint includes the first event for each patient.
†The total cardiovascular events include all events during follow up. The tabulations show which events occurred.

Supplementary Table 4. Baseline quality of life in propensity score matched women and men

	Women (N=70)	Men (N=70)	P-value
SF-36			
- General health	53±18	58±18	0.11
- Physical functioning	56±25	72±21	<0.001
- Physical limitations	46±44	72±36	<0.001
- Bodily pain	77±25	88±16	0.004
- Mental health	79±15	79±16	0.76
- Social functioning	78±22	87±18	0.01
- Emotional limitations	77±39	78±36	0.87
- Vitality	58±22	65±19	0.05
- Summary score physical	39±10	46±8	<0.001
- Summary score emotional	54±9	53±9	0.62
MFI-20			
- General fatigue	12±5	11±4	0.56
- Physical fatigue	12±5	11±4	0.10
- Reduced activity	12±5	10±4	0.04
- Reduced motivation	10±4	9±4	0.24
- Mental fatigue	7±4	8±4	0.43
AFSS			
	9±7	6±5	0.003

All values depicted as mean±SD.
SF-36: The Medical Outcomes Study Short-Form questionnaire. Scores range from 0-100, with lower scores representing a lower QoL.
MFI-20: The multidimensional fatigue inventory. Scores range from 0-35, with higher scores indicating greater AF symptom severity.
AFSS: The Toronto AF severity scale. The score ranges from 4-20, with higher scores indicating more fatigue.