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Women have less progression of paroxysmal atrial fibrillation: data from the RACE V study

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ABSTRACT

Background Sex differences in atrial fibrillation (AF) are observed in terms of comorbidities, symptoms, therapies received, AF progression and cardiovascular complications.

Methods We assessed the differences in prevalence and the determinants of AF progression, as well as the clinical characteristics and quality of life (QoL), between women and men with paroxysmal AF included in the RACE V (Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF) study. At baseline, extensive phenotyping was done. To assess AF progression, implantable loop recorder (ILR) monitoring was used throughout follow-up. AF progression was defined as (1) progression to persistent or permanent AF or (2) progression of paroxysmal AF (>3% burden increase).

Results 417 patients were included, 179 (43%) of whom were women. Women were older (median 67 years vs 63 years, p<0.001), less often had coronary artery disease (n=11 (6%) vs n=36 (16%), p=0.003), had more obesity (n=57 (32%) vs n=50 (21%), p=0.013), had less epicardial and pericardial fat (median 144 (interquartile range [IQR] 94–191) mL vs 199 (IQR 146–248) mL, p<0.001; and median 89 (ICQ 61–121) mL vs 105 (IQR 83–133) mL, p<0.001, respectively) and had more impaired left atrial function. The median follow-up was 2.2 (1.6–2.8) years. 51 of 417 patients (5.5% per year) showed AF progression (15/179 (8.4%) women and 36/238 (15.1%) men, p=0.032). Multivariable analysis showed tissue factor pathway inhibitor, N-terminal prohormone brain natriuretic peptide (NT-proBNP) and PR interval being associated with AF progression in women and factor XIIa:C1 esterase, NT-proBNP and proprotein convertase subtilisin/kexin type 9 in men. QoL was not different between sexes.

Conclusion Despite older age, the incidence of AF progression was lower in women. Parameters associated with AF progression varied in part between sexes, suggesting different underlying pathophysiological mechanisms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Progression of atrial fibrillation (AF) has been associated with an increased risk of cardiovascular morbidity and mortality and reduced efficacy of pharmacological and interventional rhythm control strategies.
⇒ The clinical profile of women and men with paroxysmal AF is different and may lead to differences in AF progression.

WHAT THIS STUDY ADDS

⇒ This RACE V (Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF) post-hoc analysis showed that the clinical profile is indeed different between women and men.
⇒ Furthermore, the incidence of AF progression was lower in women compared with men.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study showed that parameters associated with AF progression varied in part between sexes, suggesting different underlying pathophysiological mechanisms which could aid clinicians in a holistic approach to optimal treatment for AF.

INTRODUCTION

Evidence is growing on sex-specific differences in incidence, prevalence, risk factors and comorbidities, and outcomes of patients with atrial fibrillation (AF).[1–4] Women are generally older and have a different comorbidity profile.[1 2 5] Registry studies have reported a higher incidence of AF-related stroke and systemic thromboembolism in women than in men with AF,[6–8] and potentially a higher mortality.[7 9 10] Further, women with AF are generally more symptomatic, seek more care for symptoms and report lower quality of life (QoL).[1 8 9 11 12] Despite this higher symptom load, available data suggest that women are less likely to undergo rhythm control, including AF ablation.[2 10 13 14] Progression of

AF has been associated with an increased risk of cardiovascular morbidity and mortality and reduced efficacy of pharmacological and interventional rhythm control strategies.[15] Data on sex differences in AF progression are lacking, but probably differ since the prevalence of the most established associated risk factors and comorbidities for AF progression is not similar among sexes.[16]

The RACE V (Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF) study developed a new AF progression risk prediction model in patients with paroxysmal AF.[17 18] The aims of this prespecified subanalysis of the RACE V trial were to assess (1) whether there are sex-specific differences in clinical presentation and QoL of patients with paroxysmal AF and (2) whether the incidence and determinants of AF progression differ between sexes using extensive phenotyping at baseline and continuous rhythm monitoring during follow-up.

METHODS

The RACE V study has been previously described.[17 19] In brief, the RACE V is an investigator-initiated, prospective, Dutch multicentre registry (ClinicalTrials.gov identifier NCT02726698) which included 658 patients from multiple centres in the Netherlands. This subanalysis includes 417 patients, all having a follow-up duration of ≥1 year.[20] No patients were lost to follow-up in this first year or died before AF progression. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Trial population

A detailed overview of the inclusion and exclusion criteria has been previously described.[19] Briefly, we included patients with a history of paroxysmal AF <10 years. Eligible patients had at least two documented episodes of paroxysmal AF or one documented episode combined with two or more symptomatic episodes suspected of being AF, were willing to undergo implantation of a Medtronic (Minneapolis, USA) Reveal LINQ implantable loop recorder, and did not have a history of persistent AF, had (intention to undergo) pulmonary vein isolation (PVI) or on current amiodarone treatment. Patients with Medtronic pacemakers were also eligible if atrial high rate episodes of >190 beats per minute lasting >6 min, qualified as AF episodes, were detected. For the current analysis, we included patients who had ≥1 year of continuous rhythm monitoring as of 1 May 2020. No patients were lost to follow-up or died in the first year.

Clinical assessment

At baseline, clinical history, symptomatology, current medication, physical examination and 12-lead ECG were assessed. Additionally, echocardiography, vascular assessment and cardiac CT were done and processed and analysed in a central core lab, as described previously.[19] Cardiac CT was performed to assess coronary calcium

scores (Agatston) and epicardial and pericardial fat. Vascular assessment of the carotid arteries included measurements of intima media thickness, pulse wave velocity and plaques.

Quality of life

At baseline, 1 year and 2.5 years of follow-up, the severity of AF-related symptoms was evaluated through self-reporting by each patient, using Part C of the University of Toronto Atrial Fibrillation Severity Scale (AFSS). The AFSS is a disease-specific tool designed to assess the severity of symptoms associated with AF. This seven-item questionnaire encompasses prevalent AF symptoms experienced at rest (such as palpitations, dyspnoea, fatigue, dizziness and chest pain) as well as during physical exertion (specifically dyspnoea and fatigue). Each symptom severity is assessed on a 6-point scale, ranging from 0 to 5 points. The total score, ranging from 0 to 35 points, reflects the overall severity of AF symptoms, with higher scores indicating greater symptom severity.

Furthermore, health-related QoL was evaluated at baseline, 1 year and 2.5 years of follow-up using the EQ-5D-5L questionnaire. This instrument incorporates a visual analogue scale that requires patients to rate their current health state on a scale from 0 (representing the worst imaginable health state) to 100 (representing the best imaginable health state). One of the items assessed is the level of anxiety.

Blood biomarkers

At baseline, peripheral blood samples were collected. Patients needed to be in sinus rhythm during blood sampling and oral anticoagulation temporarily interrupted. All blood samples were processed and stored at −80°C. With multiplex immunoassays, 92 cardiovascular biomarkers from the Olink Cardiovascular III panel were assessed by Olink Bioscience (Uppsala, Sweden) on EDTA plasma baseline samples (online supplemental table S1). Complexes of activated coagulation enzymes (FXIIa, FXIa, FIXa, FXa and thrombin) with their corresponding natural inhibitor (antithrombin, alpha1-antitrypsin or C1 esterase inhibitor) ELISAs were performed to assess the degree of coagulation activity on EDTA plasma and citrated plasma samples at baseline (online supplemental table S2).

Follow-up

All patients were treated according to the European Society of Cardiology AF guidelines.[3] Follow-up visits were performed at 1 and 2.5 years. Patients could consent for 2.5 years of continuous rhythm monitoring until the end of battery of the Reveal LINQ or for 4 years in case patients had a pacemaker. In order to collect continuous data on arrhythmias, all patients received a home monitoring device (Medtronic Carelink). Both the Reveal LINQ and the pacemaker were set to atrial tachycardie (AT)/AF detection settings.

Table 1 Baseline characteristics, categorised by sex

Characteristics	Women (n=179)	Men (n=238)	P value
Age (years)	67.4 (59.3–73.3)	63.5 (57.0–69.0)	<0.001
Total history of AF (years)	2.6 (0.8–5.3)	2.7 (0.7–5.0)	0.838
Heart failure	47 (26.2)	78 (32.8)	0.161
HFrEF	3 (1.8)	7 (2.9)	0.526
HFpEF	44 (24.6)	70 (29.4)	0.318
Hypertension	145 (81.0)	193 (81.1)	1.000
Diabetes mellitus	19 (10.7)	15 (6.3)	0.147
Coronary artery disease	11 (6.1)	37 (15.5)	0.003
Atherosclerosis*	78 (43.6)	126 (52.9)	0.061
Number of comorbidities†	2 (2–4)	2 (2–3)	0.951
CHA$_2$DS$_2$-VASc score‡			
<2	67 (37.4)	162 (68.1)	<0.001
≥2	112 (62.6)	76 (31.9)	<0.001
Median	3 (2–4)	2 (1–3)	<0.001
EHRA class			0.002
I	14 (7.8)	29 (12.2)	
IIa	43 (24.0)	92 (38.7)	
IIb	86 (48.0)	81 (34.0)	
III	34 (19.0)	36 (15.1)	
IV	2 (1.2)	0 (0)	
Physical examination			
Height (cm)	168 (163–172)	183 (178–187)	<0.001
Weight (kg)	77 (68–89)	90 (80–101)	<0.001
BMI (kg/m^2)	27 (24–31)	27 (24–30)	0.391
Obesity (BMI >30)	57 (32.2)	50 (21.1)	0.013
Waist circumference (cm)	97 (86–105)	102 (97–111)	<0.001
Systolic blood pressure (mm Hg)	135 (127–145)	131 (124–143)	0.089
Diastolic blood pressure (mm Hg)	80 (73–85)	80 (74–85)	0.474
Laboratory results			
eGFR (mL/min/1.73 m^2)	80 (67–89)	81 (70–90)	0.199
ECG			
PR interval	162 (147–179)	172 (153–188)	0.002
Medications			
Beta-blocker	87 (48.9)	126 (52.9)	0.429
Verapamil/diltiazem	40 (22.5)	33 (13.9)	0.027
Digoxin	4 (2.2)	2 (0.8)	0.409
Antiarrhythmic drugs class I	43 (24.1)	51 (21.4)	0.555
Antiarrhythmic drugs class III	8 (4.5)	11 (4.6)	1.000
ACE inhibitor	31 (17.4)	51 (21.4)	0.321
Angiotensin receptor blocker	37 (20.7)	43 (18.1)	0.531
Statin	57 (32.0)	88 (37.0)	0.300
Diuretic	33 (18.5)	31 (13.0)	0.134
Anticoagulant	139 (78.1)	150 (63.0)	0.001
Vitamin K antagonist	31 (17.4)	24 (10.1)	0.040
NOAC	108 (60.8)	126 (53.0)	0.136

Continued

Table 1 Continued

Characteristics	Women (n=179)	Men (n=238)	P value
Echocardiographic variables			
Left atrial volume index (mL/m^2)	29 (23–36)	30 (24–36)	0.709
Left atrial reservoir function (%)	35 (27–41)	38 (30–46)	0.007
Left atrial contractile function (%)	16 (12–20)	17 (13–23)	0.021
Left atrial conduction function (%)	18 (13–24)	20 (15–25)	0.090
Right atrial volume indexed (mL/m^2)	22 (17–28)	27 (21–33)	<0.001
Left ventricular ejection fraction (%)	50±8	51±8	0.225
CT			
Calcium score (Agatston)	18 (0–146)	52 (0–370)	0.002
Agatston >400	24 (13.4)	62 (26.0)	0.001
Pericardial fat	144 (94–191)	199 (146–248)	<0.001
Epicardial fat	89 (61–121)	105 (83–133)	<0.001
Vascular assessment			
IMT max: CCA >1 mm	50 (30.9)	78 (39.0)	0.122
IMT max: all segments >1 mm	67 (41.6)	107 (53.5)	0.026
Plaques	58 (50.0)	82 (52.6)	0.714

Data are presented as mean±SD, number of patients (%) or median (IQR).

*Atherosclerosis is the presence of history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, ischaemic cerebral infarction, peripheral vascular disease, Agatston score >400 or plaque.

†The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus, coronary artery disease, BMI >25 kg/m^2, moderate or severe mitral valve regurgitation, and kidney dysfunction (eGFR <60).

‡The CHA$_2$DS$_2$-VASc score assesses thromboembolic risk. This includes congestive heart failure/left ventricular dysfunction (C); hypertension (H); age ≥75 years (A$_2$); diabetes (D); stroke/transient ischaemic attack/systemic embolism (S$_2$); vascular disease (V); age 65–74 years (A); and sex category (female sex) (Sc).

AF, atrial fibrillation; BMI, body mass index; CCA, common carotid artery; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association class for symptoms; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IMT, intima media thickness; NOAC, novel oral anticoagulation; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

AF progression

As described previously, AF progression was defined as (1) the development of persistent or permanent AF during follow-up or (2) an increase of >3% AF burden over the first 6 months or total follow-up.[18] The 3% cut-off has been published previously, and details concerning the 3% cut-off for AF burden can be found in the paper by Nguyen *et al*.[19–21] The duration of monitoring for the current analysis lasted until 1 May 2020, until the last available rhythm monitoring for patients who died after >1 year of continuous rhythm monitoring or until the date of PVI in case of a successful PVI.

Statistical analysis

Baseline characteristics are presented as mean±SD for normally distributed data, and median and interquartile range (IQR) for non-normally distributed continuous data. Categorical data are presented as numbers with percentages. Fisher's exact test was used for binary variables, and t-test or Wilcoxon rank-sum test was used for continuous variables. Variables with a p value smaller than 0.10 in the age-adjusted and sex-adjusted analyses were included in a bidirectional stepwise variable selection, leading to a final multivariable logistic regression model.

Bidirectional stepping was done for model building and reduction, with a p value ≥0.05 as a criterion for removing a variable from the model. Imputation was implemented for missing values using the R package mice. For each logistic regression, 'massive imputation' was performed, which means that all variables in a model were at the same time also used for the imputation needed for the fit of that model. Interactions between variables were tested and no significant interactions were found, taking into account multiple testing using Bonferroni correction. P value <0.05 was considered statistically significant, except where Sidak or Bonferroni correction for multiple testing was applied to the significance level. The occurrence of AF progression between sexes was assessed by Kaplan-Meier curves and compared using a log-rank test. Analyses were conducted with R V.3.3.3.

RESULTS

A total of 179 women and 238 men were included in the RACE V study (table 1). At baseline, women were significantly older (67 years vs 63 years, p<0.001), less often had coronary artery disease (n=11 (6%) vs n=36 (16%), p=0.003), had more obesity (n=57 (32%) vs n=50
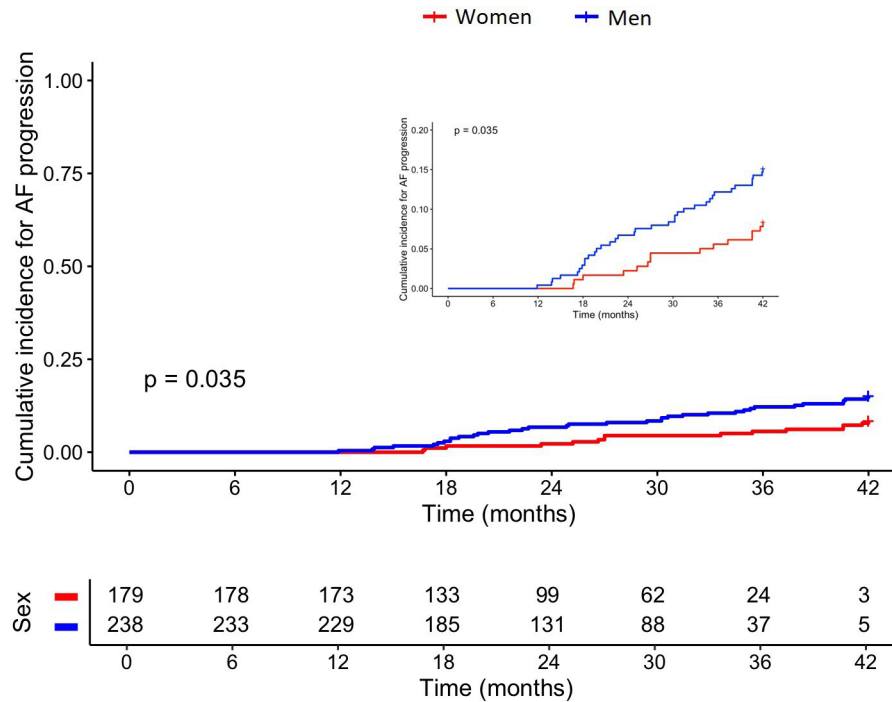
Figure 1 Differences in the incidence of atrial fibrillation (AF) progression between women and men.

(21%), p=0.013), had less epicardial and pericardial fat (median 144 (IQR 94–191) mL vs 199 (IQR 146–248) mL, p<0.001; and median 89 (IQR 61–121) mL vs 105 (IQR 83–133) mL, p<0.001, respectively) and had more impaired left atrial function. The median CHA_2DS_2-VASc score was higher in women (3 vs 2, p<0.001) and they experience more symptoms as measured by the European Heart Rhythm Association (EHRA) score.

The median follow-up was 2.2 (1.6–2.8) years. In terms of AF progression, a total of 51 out of 417 patients (5.5% per year) showed progression. Figure 1 shows that progression differed between women and men; 15 of 179 (8.4%) women and 36 of 238 (15.1%) men progressed (p=0.032). Progression to persistent or permanent AF occurred in 10 (5.6%) women vs 25 (10.5%) men; progression of self-terminating paroxysmal AF to >3% burden increase was seen in 5 (2.8%) women vs 11 (4.6%) men, respectively. Sex-related differences in the clinical characteristics of women and men with or without AF progression are shown in table 2.

Symptoms and QoL at baseline and during follow-up
The EHRA class was higher in women (p=0.002 for group comparison) (table 1). Figure 2 shows the differences in QoL as assessed by the AFSS. Women more often experienced palpitations throughout follow-up (baseline: 1.3±0.10 vs 0.8±0.07, p=0.002; 1-year follow-up 1.1±0.10 vs 0.7±0.07, p=0.005). They also experienced more shortness of breath during exercise at 1 year (1.4±0.11 vs 1.1±0.09, p=0.033). At that time, women experienced more often tiredness both at rest and during little exercise (p value for both comparison <0.001). No differences between the total AFSS score and the EQ-5D-5L questionnaire were observed (figure 3). Both women and men who suffered

from anxiety as assessed by the EQ-5D-5L questionnaire had lower AFSS and EQ-5D-5L health scores as compared with those who did not. The AFSS score at baseline for women with anxiety was 10.8±1.0 vs 5.9±0.5 (p<0.001) and the health score was 69.8±2.3 with anxiety vs 78.0±1.1 without anxiety (p<0.001). For men with anxiety, the AFSS score at baseline was 9.9±0.8 vs 4.6±0.4 (p<0.001) and the health score 69.5±2.0 for those with anxiety and 81.2±0.8 for those without anxiety (p<0.001).

Determinants of AF progression in women and men
The baseline levels of the 92 Olink biomarkers and coagulation markers are presented in online supplemental tables S1 and S2. Differences in Olink and coagulation biomarkers in women and men with or without AF progression are provided in online supplemental tables S3 and S4. Table 3 shows the results of the multivariable analysis assessing the parameters associated with AF progression in women and men. In women, decreased tissue factor pathway inhibitor (TFPI) (OR 2.22, 95% CI 1.24 to 3.99, p=0.008), higher N-terminal prohormone brain natriuretic peptide (NT-proBNP) (OR 2.10, 95% CI 1.15 to 3.83, p=0.016) and longer PR interval (OR 1.72, 95% CI 1.04 to 2.84, p=0.034) were associated with AF progression. In men, multivariable factor XIIa:C1 esterase inhibitor (median) (OR 3.06, 95% CI 1.32 to 7.08, p=0.009), higher NT-proBNP (OR 2.01, 95% CI 1.33 to 3.04, p<0.001) and higher proprotein convertase subtilisin/kexin type 9 (PCKS9) (OR 1.60, 95% CI 1.12 to 2.29, p=0.011) were associated with AF progression. Interaction analysis showed no significant differences in sex, clinical parameters and AF progression.

Table 2 Differences in clinical characteristics between women and men with and without AF progression

Characteristics	AF progression Women (n=15)	No AF progression Women (n=164)	P value	AF progression Men (n=36)	No AF progression Men (n=202)	P value
Age (years)	70.5 (64.5–74.2)	67.0 (58.8–72.9)	0.165	63.4 (58.8–70.3)	63.6 (56.8–68.9)	0.451
Total history of AF (years)	3.6 (2.4–4.5)	2.4 (0.8–5.4)	0.383	2.7 (0.7–5.1)	2.7 (0.7–5.0)	0.783
Heart failure	3 (37.5)	44 (46.8)	0.723	18 (66.7)	60 (50.0)	0.138
HFrEF	0 (0.0)	3 (1.9)	1.000	4 (11.8)	3 (1.6)	0.013
HFpEF	3 (37.5)	41 (43.2)	1.000	13 (50.0)	57 (47.5)	0.832
Hypertension	14 (93.3)	131 (79.9)	0.309	32 (88.9)	161 (79.7)	0.251
Diabetes mellitus	2 (13.3)	17 (10.4)	0.665	3 (8.3)	12 (5.9)	0.707
Coronary artery disease	1 (6.7)	10 (6.1)	1.000	10 (27.8)	27 (13.4)	0.043
Atherosclerosis*	5 (33.3)	73 (44.5)	0.588	21 (58.3)	105 (52.0)	0.587
Number of comorbidities†	2 (2–3)	2 (2–4)	0.987	3 (2–4)	2 (2–3)	0.012
CHA_2DS_2-VASc score‡	3 (3–4)	3 (2–4)	0.806	2 (2–3)	2 (1–3)	0.008
<2	4 (26.7)	63 (38.4)	0.534	19 (52.8)	143 (70.8)	0.450
≥2	11 (73.3)	101 (61.6)	0.534	17 (47.2)	59 (29.1)	0.052
EHRA class			0.056			0.193
I	4 (26.7)	10 (6.1)		7 (19.4)	22 (10.9)	
IIa	4 (26.7)	39 (23.8)		17 (47.2)	75 (37.1)	
IIb	4 (26.7)	82 (50)		8 (22.2)	73 (36.1)	
III	3 (19.9)	31 (19.5)		4 (11.2)	32 (15.9)	
IV	0 (0)	2 (0.6)		0 (0)	0 (0)	
Physical examination			0.059			0.193
Height (cm)	168±8	168±7	0.873	182±8	183±7	0.331
Weight (kg)	72 (64–94)	78 (68–88)	0.780	91 (83–103)	90 (80–100)	0.669
BMI (kg/m²)	28 (22–33)	27 (24–31)	0.830	27 (25–31)	27 (24–29)	0.471
Obesity (BMI >30)	5 (33.3)	52 (31.7)	0.771	10 (27.8)	40 (19.8)	0.276
Waist circumference (cm)	102 (94–110)	96 (86–105)	0.234	105 (101–115)	102 (96–110)	0.022
Systolic blood pressure (mm Hg)	130 (130–142)	136 (127–145)	0.675	130 (120–140)	132 (125–144)	0.318
Diastolic blood pressure (mm Hg)	75 (70–86)	80 (74–84)	0.309	80 (73–84)	80 (74–86)	0.302
Laboratory results						
eGFR (mL/min/1.73 m²)	75 (63–79)	81 (68–89)	0.122	74 (68–86)	83 (71–90)	0.037
ECG						
PR interval	175 (146–209)	161 (147–178)	0.171	179 (165–194)	168 (152–188)	0.033
Medications						
Beta-blocker	10 (66.7)	77 (47.0)	0.182	22 (61.1)	104 (51.5)	0.365
Verapamil/diltiazem	2 (13.3)	38 (23.2)	0.526	5 (13.9)	28 (13.9)	1.000
Digoxin	1 (6.7)	3 (1.8)	0.299	1 (2.8)	1 (0.5)	0.280
Antiarrhythmic drugs class I	4 (26.7)	39 (23.8)	0.760	1 (2.8)	50 (24.8)	0.002
Antiarrhythmic drugs class III	0 (0)	8 (4.9)	1.000	4 (11.1)	7 (3.5)	0.067
ACE inhibitor	0 (0)	31 (18.9)	0.077	11 (30.6)	40 (19.8)	0.184
Angiotensin receptor blocker	6 (40)	31 (18.9)	0.089	8 (22.2)	35 (17.3)	0.484
Statin	6 (40)	51 (31.1)	0.565	20 (55.6)	68 (33.7)	0.015
Diuretic	3 (20)	30 (18.3)	1.000	7 (19.4)	24 (11.8)	0.279
Anticoagulant	14 (93.3)	125 (76.2)	0.196	31 (86.1)	119 (58.9)	0.001
Vitamin K antagonist	5 (33.3)	26 (15.9)	0.145	5 (13.9)	19 (9.4)	0.378

Continued

Table 2 Continued

Characteristics	AF progression Women (n=15)	No AF progression Women (n=164)	P value	AF progression Men (n=36)	No AF progression Men (n=202)	P value
NOAC	9 (60)	99 (60.3)	1.000	26 (72.2)	100 (49.5)	0.018
Echocardiographic variables						
Left atrial volume index (mL/m²)	28 (23–35)	29 (24–36)	0.954	35 (29–39)	29 (23–35)	0.012
Left atrial reservoir function (%)	31 (27–35)	35 (28–41)	0.211	31 (26–47)	39 (31–46)	0.085
Left atrial contractile function (%)	13 (10–15)	16 (13–20)	0.036	13 (11–19)	18 (14–23)	0.022
Left atrial conduction function (%)	19 (14–23)	18 (13–24)	0.875	18 (13–26)	20 (15–24)	0.770
Right atrial volume indexed (mL/m²)	25 (18–29)	22 (18–27)	0.654	31 (23–38)	27 (21–33)	0.028
Left ventricular ejection fraction (%)	51±8	50±8	0.577	50±9	51±8	0.529
Moderate mitral valve regurgitation	0 (0)	3 (1.8)	1.000	3 (8.3)	1 (0.5)	0.012
CT						
Calcium score (Agatston)	21 (0–145)	18 (0–130)	0.975	197 (55–738)	26 (0–280)	<0.001
Agatston >400	2 (13.3)	22 (13.4)	1.000	13 (36.1)	49 (24.6)	0.155
Pericardial fat	153 (120–186)	143 (94–191)	0.933	214 (150–263)	195 (144–247)	0.454
Epicardial fat	92 (63–114)	89 (61–122)	0.536	109 (85–144)	103 (83–132)	0.262
Vascular assessment						
IMT max: CCA >1 mm	5 (41.7)	45 (30.0)	0.517	14 (48.3)	64 (37.4)	0.306
IMT max: all segments >1 mm	5 (41.7)	62 (41.6)	1.000	15 (51.7)	92 (53.9)	0.843
Plaques	4 (80)	54 (48.7)	0.364	11 (55.0)	71 (52.2)	1.000

Data are presented as mean±SD, number of patients (%) or median (IQR).

*Atherosclerosis is the presence of history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, ischaemic cerebral infarction, peripheral vascular disease, Agatston score >400 or plaque.

†The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus, coronary artery disease, BMI >25 kg/m², moderate or severe mitral valve regurgitation, and kidney dysfunction (eGFR <60).

‡The CHA_2DS_2-VASc score assesses thromboembolic risk. This includes congestive heart failure/left ventricular dysfunction (C); hypertension (H); age ≥75 years (A_2); diabetes (D); stroke/transient ischaemic attack/systemic embolism (S_2); vascular disease (V); age 65–74 years (A); and sex category (female sex) (Sc).

AF, atrial fibrillation; BMI, body mass index; CCA, common carotid artery; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association class of symptoms; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IMT, intima media thickness; NOAC, novel oral anticoagulation.

DISCUSSION

In this predefined analysis of the RACE V registry, we found important data on sex differences in patients with paroxysmal AF. First, the clinical profile is importantly different between women and men, and women more often had symptoms. In addition, the rate of AF progression was lower in women. The determinants of AF progression were also not similar between sexes, suggesting distinct underlying pathophysiological mechanisms playing a role in AF progression.

Differences in clinical, echocardiographic and blood biomarker characteristics between sexes

In line with published data, we describe the differences in clinical profile of women and men with PAF.[12] Women included in the RACE V study were significantly older and less often had coronary artery disease, which was further supported by the observed lower calcium score on CT scan (as a derivate risk factor for coronary artery disease). In addition, the amount of epicardial and

pericardial fat was lower. The pivotal role of risk factors and comorbidities in the AF pathophysiology, incident AF and AF progression is well known.[18] Our most important finding is that, in patients with paroxysmal AF, AF progression is significantly lower in women as compared with men. Looking at differences between women with and without AF progression and men with and without AF progression, we observed another remarkable difference between sexes. In women, we did not find any clinical difference between those who progressed and those who did not, whereas men with AF progression more often had a history of coronary artery disease (as also illustrated by a higher calcium score), heart failure with reduced ejection fraction, more comorbidities, a wider waist circumference and slightly lower estimated glomerular filtration rate. One might argue that an underlying heart disease is of importance in the AF progression for men only; however, we must acknowledge that our data are limited by the small proportion of women who
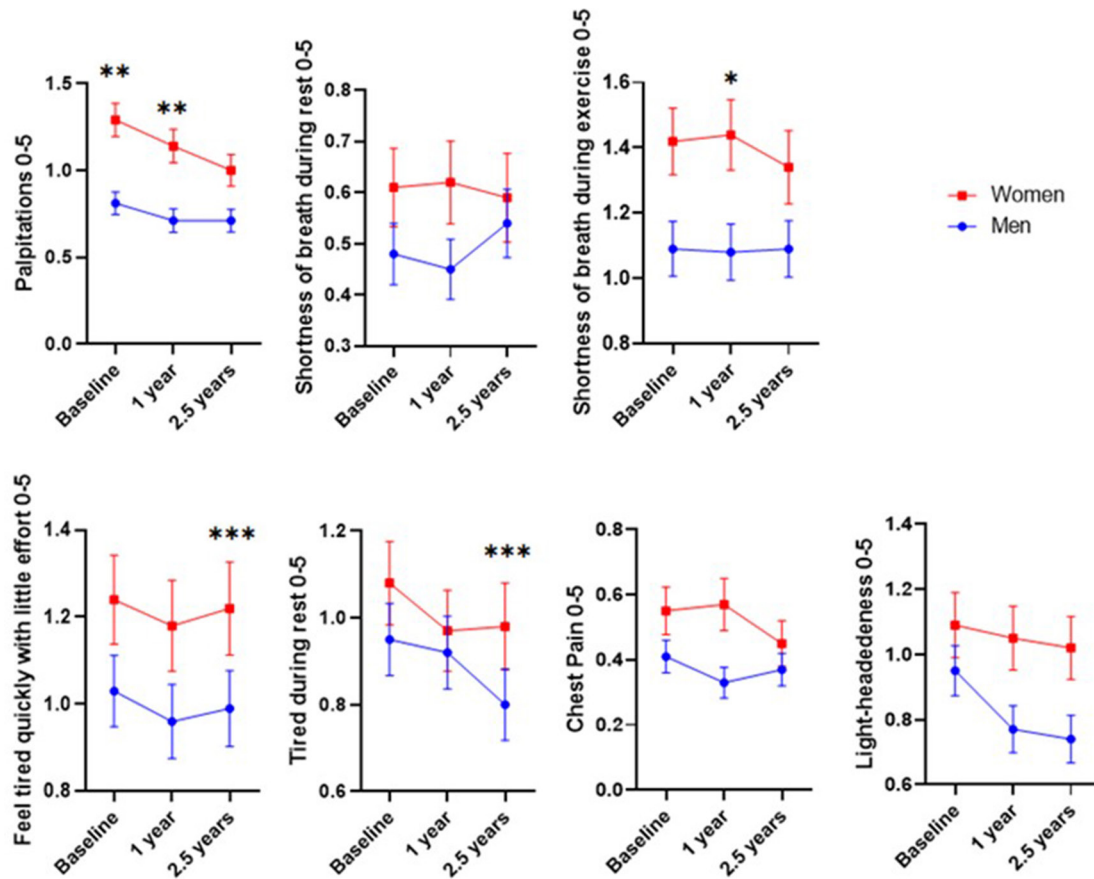
Figure 2 Sex differences in atrial fibrillation symptom severity (as assessed by the Atrial Fibrillation Severity Scale components); 0 signifies the absence of occurrence, while 5 indicates a significant level of distress or impact experienced. *P<0.05, **P<0.01, ***P<0.001.

experienced AF progression. The observation that women with paroxysmal AF showed a lower progression rate was unexpected but is in line with more recent data showing that women do not necessarily have worse outcomes.[8 22 23]

We also explored whether there were differences in the underlying pathophysiological mechanisms for AF progression between women and men, assessing the role of 101 blood biomarkers including coagulation markers. For women and men, different blood biomarkers were in part found to be associated with AF progression, suggesting distinct underlying pathophysiological factors contributing to AF progression. In women, TFPI, prolonged PR interval and NT-proBNP were associated

with AF progression, and in men NT-proBNP, PCKS9 and factor XIIa:C1 esterase inhibitor. Differences in blood biomarkers associated with AF progression between sexes have not been studied before. Both in women and men, hypercoagulability seemed to play a role, as suggested by lower levels of TFPI and increased activity of factor XIIa:C1 esterase inhibitor, respectively, suggesting a role of hypercoagulability in driving AF progression as previously shown in preclinical studies.[24] In addition, both in women and men, NT-proBNP was an independent marker of risk of AF progression. Although it is well known that NT-proBNP is increased during AF, even without overt heart failure,[16] the association with AF progression again
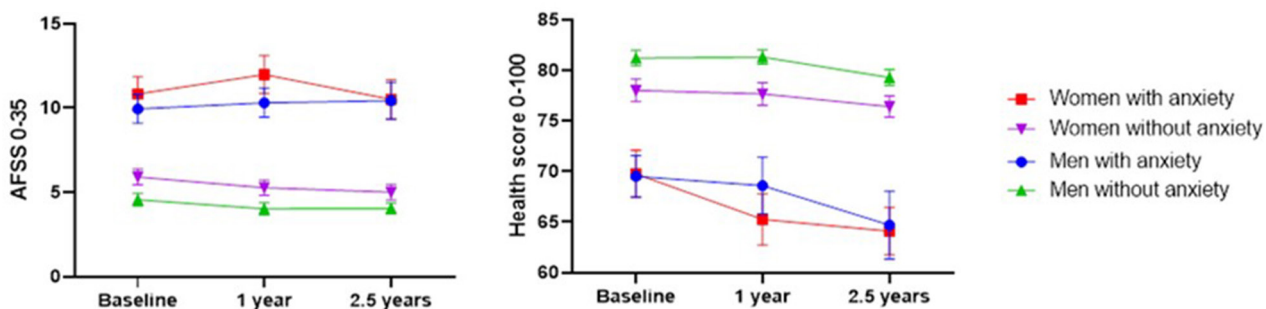

Figure 3 Role of anxiety in symptom severity and quality of life in men and women. Anxiety was defined according to the EQ-5D-5L questionnaire. AFSS, Atrial Fibrillation Severity Scale.

Table 3 Multivariable logistic regression analysis assessing parameters associated with atrial fibrillation progression in women and men

	OR (95% CI)	P value
Women		
TFPI decrease (per SD)	2.22 (1.24 to 3.99)	0.008
PR interval increase (per SD)	1.72 (1.04 to 2.84)	0.034
NT-proBNP increase (per SD)	2.10 (1.15 to 3.83)	0.016
Men		
NT-proBNP increase (per SD)	2.01 (1.33 to 3.04)	<0.001
PCSK9 increase (per SD)	1.60 (1.12 to 2.29)	0.011
Factor XIIa:C1 esterase inhibitor (below median)	3.06 (1.32 to 7.08)	0.009

NT-proBNP, N-terminal prohormone brain natriuretic peptide; PCSK9, proprotein convertase subtilisin/kexin type 9; TFPI, tissue factor pathway inhibitor.

stresses the intertwined relationship between AF and heart failure and calls for more improvement in diagnostic methods assessing heart failure during AF.[25 26] A longer PR interval and/or an enlarged left atrium as signs of more severe atrial electroanatomical remodelling (atrial cardiomyopathy) promoting AF progression were observed in women but not in men and this is in line with previous studies showing that PR interval is associated with incident AF.[27] The fact that it was only observed in women may relate to different associated comorbidities between sexes.[1 2 4] In contrast, higher levels of PCSK9 were associated with AF progression in men. Higher levels of PCKS9 are suggested to be associated with cardiovascular events in patients with AF, possibly through atherosclerosis and inflammation,[28] and are in agreement with the fact that men more often suffer from coronary artery disease as an associated comorbidity.

Symptoms and QoL
Although women included in our study reported more symptoms, the QoL as assessed by the AFSS and the EQ-5D-5L questionnaire was not different between women and men, which is in contrast to previous studies.[1 11] This might be because only patients with paroxysmal AF were selected for the present study, whereas Kloosterman et al[12] assessed the symptoms and quality of life in patients with PAF and persistent AF undergoing ablation and Lip et al investigated all patterns of AF.[1] However, it may also relate to the fact that we included patients with paroxysmal AF and relatively low AF burden. It is likely that these questionnaires do not capture AF symptoms, but more likely symptoms related to the associated comorbidities; therefore, symptoms may not be related to the AF itself but to the associated comorbidities as well.[29] Of interest is our observation that those patients who experienced anxiety had worse QoL in both sexes. Future research is warranted whether there is a relationship between AF and stress, initiated by modulation of the immune and autonomic nervous systems by stress.[30]

Strengths and limitations
Strengths include the well-phenotyped cohort and availability of continuous rhythm monitoring for the total follow-up duration. Limitations include the modest sample size (specifically women), the limited follow-up duration and the observational nature. Although the subanalysis was prespecified, the limitations of the current study are the same as those of other multicentre observational studies, such as potential bias in patient selection, referral and treatment. In patients with PAF and relatively low AF burden, questionnaires were used to assess AF symptoms and QoL. It is likely that these questionnaires did not only capture AF symptoms. Also, there may be bias in patient selection. For example, referral of patients with paroxysmal AF from the general practitioner to the hospital may be different (later) for women and men. Also, the willingness of patients to be included in the trial may vary among women and men at different ages. Furthermore, for women, an insight into the association of hormones and biomarker expression in women in residual confounding may have impacted the multivariable analyses. Longer follow-up would furthermore lead to more robust analyses, considering the relatively short follow-up. Also, we did not take death into account as a competing event. Furthermore, whether PVI may have led to slower rate of progression is unknown.

CONCLUSIONS
The clinical profile of women and men with paroxysmal AF is different. Despite older age, the prevalence of AF progression was lower in women than in men. Determinants associated with AF progression varied between sexes, suggesting different pathophysiological mechanisms in women and men. Interestingly, in both women and men, hypercoagulation seems to play a role in AF progression.

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