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# Prospective Assessment of Sex-Related Differences in Symptom Status and Health Perception Among Patients With Atrial Fibrillation

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***Background*—**We prospectively assessed sex-specific differences in health perception, overall symptom status, and specific symptoms in a large cohort of patients with atrial fibrillation.

***Methods and Results*—**We performed a prospective multicenter observational cohort study of 1553 patients with atrial fibrillation. Patients completed questionnaires about personal characteristics, comorbidities, and symptoms on a yearly basis. Mean age was 70±11 years among women and 67±12 years among men. Health perception on a visual analogue scale ranging from 0 to 100 (with higher scores indicating better health perception) was significantly lower in women than in men (70 [interquartile range: 50–80] versus 75 [interquartile range: 60–85]; $P<0.0001$). More women than men had any symptoms (85.0% versus 68.3%; $P<0.0001$), palpitations (65.2% versus 44.4%; $P<0.0001$), dizziness (25.6% versus 13.5%; $P<0.0001$), dyspnea (35.7% versus 21.8%; $P<0.0001$), and fatigue (25.3% versus 19.1%; $P=0.006$). At 1-year follow-up, symptoms decreased in both sexes but remained more frequent in women (49.1% versus 32.6%, $P<0.0001$). In multivariable adjusted longitudinal regression models, female sex remained an independent predictor for lower health perception (ß=−4.8; 95% CI, −6.5 to −3.1; $P<0.0001$), any symptoms (odds ratio [OR]: 2.6; 95% CI, 2.1–3.4; $P<0.0001$), palpitations (OR: 2.6; 95% CI, 2.1–3.2; $P<0.0001$), dizziness (OR: 2.9; 95% CI, 2.1–3.9; $P<0.0001$), dyspnea (OR: 2.1; 95% CI, 1.6–2.8; $P<0.0001$), fatigue (OR: 1.6; 95% CI, 1.2–2.2; $P=0.0008$), and chest pain (OR: 1.8; 95% CI, 1.3–2.6; $P=0.001$).

***Conclusions*—**Women with atrial fibrillation have a substantially higher symptom burden and lower health perception than men. These relationships persisted after multivariable adjustment and during prospective follow-up. **(*J Am Heart Assoc*. 2017;6: e005401. DOI: 10.1161/JAHA.116.005401.)**

**Key Words:** atrial fibrillation • epidemiology • health perception • sex-related differences • symptoms

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the population,[1] and the number of affected individuals is expected to double until 2060.[2] Patients with AF have an increased risk of developing stroke, heart failure, cognitive dysfunction, and death, further underscoring the public health importance of the arrhythmia.[3–6] A recent meta-analysis highlighted a higher risk of adverse outcomes in women compared with men.[7]

In addition to an increased risk of cardiovascular events and death, patients with AF also have poor quality of life and high prevalence of symptoms related to either the arrhythmia or the underlying structural heart disease.[8–10] Less evidence

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## Clinical Perspective

### What Is New?

- Women with atrial fibrillation report more symptoms than men, including a higher burden of palpitations, dyspnea, fatigue, and dizziness.
- These findings persist after comprehensive adjustment and during longitudinal follow-up.

### What Are the Clinical Implications?

- Women with atrial fibrillation have a substantially higher symptom burden and lower health perception than men.
- Whether women should be considered more often for interventions to reduce their symptom burden should be studied in a randomized trial.

is available about sex-specific differences in symptom status or overall health perception in AF patients. Symptoms related to AF include palpitations, dyspnea, chest pain, dizziness, and, less commonly, syncope, fatigue, and anxiety.[9] Some studies reported that women were more symptomatic than men.[10,11] A recent meta-analysis pointed out that asymptomatic AF is more often associated with male sex, regardless of age.[12] However, none of these studies performed multivariable adjustment to correct for potential confounders. Consequently, it is currently unclear whether sex is an independent predictor of symptom status or whether the increased symptom burden among women is due to their older age[11,13] or an increased prevalence of risk factors and/or comorbidities. Finally, it is also relatively unknown whether these potential sex-related differences persist during prospective follow-up.

To address some of these issues, we evaluated sex-related differences in overall health perception and various symptom categories at baseline and during prospective follow-up in a large and unselected cohort of patients with AF.

## Methods

BEAT-AF (Basel Atrial Fibrillation Cohort) is an ongoing prospective, observational, multicenter cohort study. Between 2010 and 2014, 1553 patients with documented AF were enrolled across 7 centers in Switzerland. All patients were required to have AF that was previously documented by ECG, rhythm strip, or device interrogation. Exclusion criteria were the inability to sign informed consent and the exclusive presence of short transient episodes of AF (eg, AF after cardiac surgery). For the purpose of this study, we excluded 11 (0.7%) patients because of missing symptom data at baseline, such that 1542 (99.5%) patients remained in the analysis. The study protocol was approved by the local ethics committees, and informed written consent was obtained from each participant.

### Assessments

Patients completed detailed questionnaires about personal, medical, nutritional, and lifestyle factors. Symptoms potentially related to AF included palpitations, dyspnea, fatigue, dizziness, chest pain, effort intolerance, and syncope. Overall symptoms included the presence of at least 1 of these symptoms. Overall health perception was self-assessed by the participants using a visual analogue scale (VAS) ranging from 0 (worst) to 100 (best). The VAS used in this study is very similar to the Euro-Quol VAS, which has been validated extensively, including in patients with AF.[14–16] Body mass index was calculated as weight in kilograms divided by height in meters squared. All participants underwent recording of a resting 12-lead ECG.

Echocardiography was not mandatory in BEAT-AF; however, information on left ventricular ejection fraction from a transthoracic echocardiogram obtained not more than 3 months before enrollment was available for 567 (36.8%) patients.

### Follow-up Examinations

Yearly follow-up examinations were performed in all patients by mail and phone interviews. Patients completed information about personal, nutritional, and lifestyle factors and health perception on paper-based, mailed questionnaires. Trained study personnel subsequently completed questionnaires on symptoms potentially related to AF, updated comorbidities, medication use, and intercurrent adverse events by phone. For the present analysis, we used all data up to the 3-year follow-up examination, as available in August 2015. At that time, 1-year follow-up was available for 90.1% of the participants, 2-year follow-up was available for 64.9%, and 3-year follow-up was available for 38.1%.

### Statistical Analysis

Baseline and symptom characteristics were stratified by sex. Data distribution of continuous variables was checked using skewness, kurtosis, and visual inspection of the histogram. Continuous variables were presented as mean±SD and compared using Student *t* tests or medians (interquartile range [IQR]) and compared using the Wilcoxon rank sum test, as appropriate. Categorical variables were presented as numbers (percentages) and compared using $\chi^2$ or Fisher exact tests.

To assess the covariate-adjusted odds ratio (OR) with 95% confidence interval (CI) for the predictor female sex and to take advantage of the longitudinal follow-up available in this cohort, longitudinal mixed logistic regression analysis was performed

using binary symptom-related variables as the outcome. To account for the fact that observations from the same patients are not independent of each other, we included patient identifier as a random effect into the model. Longitudinal mixed linear regression with patient identifier as a random effect was performed to calculate ß coefficients (95% CI) for continuous outcome variables. All regression models were adjusted for a predefined set of covariates including baseline body mass index, systolic blood pressure, heart rate, and updated information on history of coronary heart disease, diabetes mellitus, hypertension, heart failure, stroke, oral anticoagulation, information on AF-related intervention (electrical cardioversion and/or pulmonary vein isolation), current AF type (paroxysmal or nonparoxysmal), smoking, and visit number. To assess the potential influence of sex-specific differences in left ventricular function on our findings, we performed a multivariable logistic regression analysis with baseline data, which was additionally adjusted for left ventricular ejection fraction in the subcohort for which this information was available.

All statistical analyses were performed using SAS 9.4 (SAS Institute). A 2-sided $P<0.05$ was considered to indicate statistical significance.

## Results

Baseline characteristics are presented in Table 1. Overall, 454 (29.4%) study participants were women. Female participants were older than male participants (70±11 versus 67±12 years, $P<0.0001$) and more often had paroxysmal AF (61% versus 54%, $P=0.04$), higher heart rate (71±16 versus 69±15 bpm, $P=0.05$), and higher systolic blood pressure (137±21 versus 134±19 mm Hg, $P=0.007$). Male patients were more likely to have a history of diabetes mellitus (15% versus 10%, $P=0.01$) or myocardial infarction (14% versus 8%, $P=0.0009$). Women had fewer AF-related interventions before enrollment (31% versus 39%, $P=0.002$).

**Table 1.** Baseline Characteristics According to Sex

| Characteristic | Women (n=454) | Men (n=1088) | *P* Value* |
|---|---|---|---|
| Age, y | 70.4±10.7 | 67.2±11.9 | <0.0001 |
| Body mass index, kg/m$^2$ | 26.6±5.7 | 27.4±4.3 | 0.007 |
| Heart rate, beats/min | 71.0±15.7 | 69.3±15.0 | 0.05 |
| Systolic blood pressure, mm Hg | 136.8±21.4 | 133.7±18.9 | 0.007 |
| Diastolic blood pressure, mm Hg | 78.5±13.4 | 79.0±12.8 | 0.5 |
| Type of atrial fibrillation | | | |
| Paroxysmal | 275 (60.6) | 584 (53.7) | 0.04 |
| Persistent | 94 (20.7) | 274 (25.2) | |
| Permanent | 85 (18.7) | 229 (21.1) | |
| Atrial flutter | 64 (14.1) | 228 (21.0) | 0.002 |
| History of myocardial infarction | 37 (8.2) | 155 (14.3) | 0.0009 |
| History of stroke/TIA | 54 (11.9) | 141 (13.0) | 0.6 |
| History of hypertension | 320 (70.5) | 724 (66.5) | 0.1 |
| History of heart failure | 81 (17.8) | 233 (21.4) | 0.1 |
| History of diabetes mellitus | 46 (10.1) | 164 (15.1) | 0.01 |
| History of renal failure | 61 (13.4) | 167 (15.4) | 0.3 |
| Smoking status | | | |
| Current | 37 (8.2) | 101 (9.3) | <0.0001 |
| History | 151 (33.6) | 565 (52.1) | |
| Never | 261 (58.1) | 418 (38.6) | |
| Aspirin as monotherapy | 52 (11.6) | 167 (15.7) | 0.04 |
| Oral anticoagulation | 345 (76.0) | 781 (72.0) | 0.1 |
| History of AF-related intervention† | 139 (30.7) | 422 (38.9) | 0.002 |

Data are means±SD or counts (percentages). Data may not sum to the given number because of missing data. AF indicates atrial fibrillation; TIA, transient ischemic attack.
**P*-values were based on Student *t* tests or $\chi^2$ tests, as appropriate.
†Intervention: either pulmonary vein isolation and/or electrical cardioversion.

## Symptoms According to AF Type

Patients with paroxysmal AF had more symptoms than patients with persistent and permanent AF (80%, 76%, and 51%, respectively, $P<0.0001$), as shown in Table 2. When comparing individual symptoms according to AF type, palpitations, dizziness, and chest pain were more often reported in paroxysmal AF patients ($P<0.0001$, $P=0.009$, and $P=0.02$), whereas dyspnea, fatigue and effort intolerance were more prevalent in patients with nonparoxysmal AF (all $P<0.0001$).

## Symptoms According to Sex

Health perception and prevalence of various symptom categories according to sex at baseline and up to 3 years of follow-up are shown in Table 3. At baseline, health perception on a VAS was significantly worse in women compared with men (70 [IQR: 50–80] versus 76 [IQR: 60–85], $P<0.0001$). Women reported symptoms significantly more often than men (85% versus 68%, $P<0.0001$). When the different symptom categories were assessed individually, women more often indicated palpitations (65% versus 44%, $P<0.0001$), dizziness (26% versus 14%, $P<0.0001$), fatigue (25% versus 19%, $P=0.006$), and dyspnea (36% versus 22%, $P<0.0001$), whereas men more often reported effort intolerance (14% versus 9%, $P=0.005$). No significant differences were observed for chest pain (12% of women versus 9% of men, $P=0.12$) and syncope (4% of women versus 3% of men, $P=0.26$).

**Table 2.** Symptom Status According to AF Type and Sex

| Characteristic | Paroxysmal | | | Persistent | | | Permanent | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Women | Men | *P* Value* | Women | Men | *P* Value* | Women | Men | *P* Value* | *P* Value† |
| Any symptoms | 247 (89.8) | 442 (75.7) | <0.0001 | 82 (87.2) | 198 (72.3) | 0.003 | 57 (67.1) | 103 (45.0) | 0.0005 | <0.0001 |
| Palpitations | 210 (76.4) | 328 (56.2) | <0.0001 | 57 (60.6) | 105 (38.3) | 0.0002 | 29 (34.1) | 50 (21.8) | 0.03 | <0.0001 |
| Dyspnea | 87 (31.6) | 111 (19.0) | <0.0001 | 42 (44.7) | 86 (31.4) | 0.02 | 33 (38.8) | 40 (17.5) | <0.0001 | <0.0001 |
| Fatigue | 60 (21.8) | 104 (17.8) | 0.2 | 38 (40.4) | 70 (25.6) | 0.006 | 17 (20.0) | 34 (14.9) | 0.3 | <0.0001 |
| Dizziness | 77 (28.0) | 90 (15.4) | <0.0001 | 23 (24.5) | 35 (12.8) | 0.007 | 16 (18.8) | 22 (9.6) | 0.03 | 0.009 |
| Effort intolerance | 18 (6.6) | 84 (14.4) | 0.0009 | 18 (19.2) | 56 (20.4) | 0.8 | 4 (4.7) | 13 (5.7) | 1.0 | <0.0001 |
| Chest pain | 35 (12.7) | 64 (11.0) | 0.4 | 9 (9.6) | 16 (5.8) | 0.2 | 8 (9.4) | 17 (7.4) | 0.6 | 0.02 |
| Syncope | 12 (4.4) | 19 (3.3) | 0.4 | 3 (3.2) | 6 (2.2) | 0.7 | 2 (2.4) | 4 (1.8) | 0.7 | 0.2 |

Data are numbers (percentages). AF indicates atrial fibrillation.
*$P$ values were based on $\chi^2$ or Fisher exact tests, as appropriate, and indicate differences in symptoms according to sex within the same atrial fibrillation type.
†$P$ values are based on $\chi^2$ tests and indicate differences in symptoms across different atrial fibrillation types.

After 1 year of follow-up, health perception increased from 70 (IQR: 50–80) to 74 (IQR: 60–80) among women and from 76 (IQR: 60–85) to 80 (IQR: 65–90) among men, such that the significant sex-specific differences persisted ($P$<0.0001), as shown in Table 3. Similar findings were observed after 2 years of follow-up (75 [IQR: 60–85] for women versus 80 [IQR: 65–90] for men, $P$=0.0004).

After 1 year of follow-up, the overall prevalence of symptoms decreased to 49% among women and 33% among men, but the sex-specific difference remained highly significant ($P$<0.0001). After 1 year of follow-up, women still had a higher prevalence of palpitations (35% versus 21%, $P$<0.0001), dyspnea (13% versus 9%, $P$=0.01), and dizziness (14% versus 7%, $P$<0.0001) compared with men. The higher symptom burden in women also persisted after 2 years of follow-up (48% versus 32% for men, $P$<0.0001) and after 3 years of follow-up (41% versus 31%, $P$=0.02). Differences in symptom categories remained generally consistent over time, although not all comparisons were statistically significant (Table 3).

Between baseline and 1 year of follow-up, a total of 405 (26.3%) patients had either pulmonary vein isolation or electrical cardioversion, with similar percentages among women and men (25.7% versus 30.6%, $P$=0.07). The symptom burden declined overall by 28.4% among patients without intervention and by 56.3% among those with intervention, as shown in Table 4.

After multivariable adjustment in the longitudinal models, female sex remained a strong predictor of overall symptoms (OR: 2.6; 95% CI, 2.1–3.4; $P$<0.0001), palpitations (OR: 2.6; 95% CI, 2.1–3.2; $P$<0.0001), dizziness (OR: 2.9; 95% CI, 2.1–3.9; $P$<0.0001), dyspnea (OR: 2.1; 95% CI, 1.6–2.8; $P$<0.0001), fatigue (OR: 1.6; 95% CI, 1.2–2.2; $P$=0.0008), and chest pain (OR: 1.8; 95% CI, 1.3–2.6; $P$=0.001), as shown in Table 5. No association was observed for effort intolerance (OR: 0.7; 95% CI, 0.5–1.0; $P$=0.051). Similarly, lower health perception among women also persisted after multivariable adjustment (ß=−4.8; 95% CI, −6.5 to −3.1; $P$<0.0001).

Additional adjustment for left ventricular function among those patients with this information available did not influence our results, as shown in Table 6. In these baseline models, female sex remained a significant predictor of overall symptoms (OR: 2.3; 95% CI, 1.3–4.0; $P$=0.004), palpitations (OR: 2.3; 95% CI, 1.5–3.7; $P$=0.0002), dyspnea (OR: 1.8; 95% CI, 1.2–2.8; $P$=0.008), fatigue (OR: 1.7; 95% CI, 1.1–2.6; $P$=0.03), and dizziness (OR: 2.5; 95% CI, 1.5–4.1; $P$=0.0003).

## Discussion

In this large prospective cohort study of patients with AF, we found that women had substantially lower health perception and a higher symptom burden compared with their male counterparts. Most individual symptoms potentially related to AF were more frequent in women than in men. These findings remained statistically significant after extensive multivariable adjustment and persisted during prospective follow-up, despite the fact that the overall symptom burden substantially decreased over time.

Prior studies have shown that female participants with AF were older and had more frequent paroxysmal AF and a higher symptom burden than male participants.[10,11,17,18] In a study of patients with new-onset AF and normal echocardiogram, Potpara et al showed that women more often had palpitations, fatigue, and chest pain.[17] Another study also found that women had a more symptomatic European Heart Rhythm Association class compared with men.[11]

Our data extend these findings in several respects. First, the observed difference of 5 points in the VAS between men and women is clinically meaningful; for example, the post-procedural VAS score improved by 5 points in patients with paroxysmal AF who underwent pulmonary vein isolation.[19]

**Table 3.** Symptom Status and Health Perception According to Sex

| | Baseline | | | 1-Y Follow-up | | | 2-Y Follow-up | | | 3-Y Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Women | Men | *P* Value* | Women | Men | *P* Value* | Women | Men | *P* Value* | Women | Men | *P* Value* |
| n | 454 | 1088 | | 409 | 981 | | 292 | 708 | | 177 | 411 | |
| Any symptoms, n (%) | 386 (85.0) | 743 (68.3) | <0.0001 | 201 (49.1) | 320 (32.6) | <0.0001 | 140 (48.0) | 226 (31.9) | <0.0001 | 73 (41.2) | 128 (31.1) | 0.02 |
| Palpitations | 296 (65.2) | 483 (44.4) | <0.0001 | 142 (34.7) | 203 (20.7) | <0.0001 | 92 (31.5) | 138 (19.5) | <0.0001 | 49 (27.7) | 71 (17.3) | 0.004 |
| Dyspnea | 162 (35.7) | 237 (21.8) | <0.0001 | 55 (13.4) | 87 (8.9) | 0.01 | 41 (14.0) | 49 (6.9) | 0.0003 | 20 (11.3) | 28 (6.8) | 0.07 |
| Fatigue | 115 (25.3) | 208 (19.1) | 0.006 | 50 (12.2) | 71 (7.2) | 0.003 | 18 (6.2) | 50 (7.1) | 0.6 | 12 (6.8) | 27 (6.6) | 0.9 |
| Dizziness | 116 (25.6) | 147 (13.5) | <0.0001 | 58 (14.2) | 66 (6.7) | <0.0001 | 31 (10.6) | 41 (5.8) | 0.007 | 14 (7.9) | 22 (5.4) | 0.2 |
| Effort intolerance | 40 (8.8) | 153 (14.1) | 0.005 | 14 (3.4) | 46 (4.7) | 0.3 | 8 (2.7) | 29 (4.1) | 0.3 | 4 (2.3) | 16 (3.9) | 0.3 |
| Chest pain | 52 (11.5) | 97 (8.9) | 0.12 | 23 (5.6) | 29 (3.0) | 0.02 | 17 (5.8) | 14 (2.0) | 0.001 | 7 (4.0) | 7 (1.7) | 0.1 |
| Syncope | 17 (3.7) | 29 (2.7) | 0.26 | 12 (2.9) | 5 (0.5) | 0.0002 | 7 (2.4) | 1 (0.1) | 0.0003 | 2 (1.1) | 1 (0.2) | 0.2 |
| Health perception, 0–100, median (IQR) | 70.0 (50.0–80.0) | 76.0 (60.0–85.0) | <0.0001 | 74.0 (60.0–80.0) | 80.0 (65.0–90.0) | <0.0001 | 75.0 (60.0–85.0) | 80.0 (65.0–90.0) | 0.0004 | ns | | |

IQR indicates interquartile range; ns indicates not surveyed.
*P-values were based on the $\chi^2$ test or Wilcoxon rank sum test, as appropriate.

Given that this intervention is the most effective for symptom control among patients with symptomatic paroxysmal AF, we consider this difference as clinically meaningful. Second, we showed that sex-specific differences persist over time, despite the fact that a sizable number of enrolled participants received AF-related interventions and that the overall symptom burden decreased substantially. In contrast, our study is in line with previous reports showing that symptom burden among AF patients can be substantially reduced with currently available treatment tools.[20] Previous studies suggested that women were less likely to receive AF-related interventions,[10,21,22] and our results are in line with this finding. The totality of evidence suggests that symptomatic women should be considered for interventions to reduce their symptom burden. This hypothesis should be tested in a randomized trial.

It is also interesting that patients with no interventions during follow-up had considerably fewer symptoms at 1-year follow-up. A possible explanation for this finding is the development of tolerance to the arrhythmia over time. In addition, this could reflect the dynamic nature of symptoms and the many factors contributing to the interaction between symptoms and AF.[9] Improvement in antiarrhythmic or rate control treatment may be another potential explanation. Unfortunately, detailed data on changes in medical treatment over time are currently unavailable in our database.

Third, our study is one of the first to show that sex-specific differences in AF-related symptoms persisted after multivariable adjustment. Most studies published on patients with AF have shown important sex-specific differences in baseline characteristics; therefore, adjustment for potential confounders in multivariable models is crucial to determine whether differences in symptoms are related to differences in baseline characteristics or whether there may be real sex-specific differences in symptom status. Our study clearly suggests that there are differences related to sex.

Several factors that might explain the persistent sex-related differences have to be considered. Increased heart rate is an important predictor of symptoms.[15] Although we adjusted for resting heart rate, women with paroxysmal AF

**Table 4.** Symptom Status Over Time Stratified by Intervention

| Characteristic | Symptoms Baseline | Symptoms at 1-Y Follow-up | *P* Value* |
|---|---|---|---|
| No intervention | 652 (66.3) | 373 (37.9) | <0.0001 |
| Intervention | 376 (92.8) | 148 (36.5) | 0.008 |
| *P* value* | <0.0001 | 0.6 | |

Data are numbers (percentages).
**P*-values were based on $\chi^2$ tests; intervention was pulmonary vein isolation and/or electrical cardioversion between baseline and 1-year follow-up.

**Table 5.** Differences in Symptom Status in Women Vs Men

| Characteristic | OR (95% CI) Univariate | *P* Value* | OR (95% CI) Multivariate | *P* Value* |
|---|---|---|---|---|
| Any symptoms | 2.6 (2.1–3.3) | <0.0001 | 2.6 (2.1–3.4) | <0.0001 |
| Palpitations | 2.6 (2.1–3.3) | <0.0001 | 2.6 (2.1–3.2) | <0.0001 |
| Dizziness | 2.7 (2.0–3.6) | <0.0001 | 2.9 (2.1–3.9) | <0.0001 |
| Dyspnea | 2.2 (1.7–2.8) | <0.0001 | 2.1 (1.6–2.8) | <0.0001 |
| Fatigue | 1.5 (1.2–2.0) | 0.0014 | 1.6 (1.2–2.2) | 0.0008 |
| Chest pain | 1.8 (1.3–2.5) | 0.0009 | 1.8 (1.3–2.6) | 0.001 |
| Effort intolerance | 0.6 (0.4–0.8) | 0.002 | 0.7 (0.5–1.0) | 0.051 |
| | β (95% CI) | *P* Value† | β (95% CI) | *P* Value† |
| Health perception, 0–100 | −4.5 (−6.3 to −2.7) | <0.0001 | −4.8 (−6.5 to −3.1) | <0.0001 |

ORs (95% CIs) are for women compared with men. *P* values were based on mixed logistic regression models or mixed linear models, as appropriate. Univariate models were adjusted for visit number; multivariable models were adjusted for baseline body mass index, systolic blood pressure, heart rate (>100 and <100 bpm), and updated information on age, current smoking, oral anticoagulation, intervention (pulmonary vein isolation and/or electrical cardioversion), coronary heart disease (myocardial infarction, percutaneous transluminal coronary angioplasty, or aortocoronary bypass), diabetes mellitus, hypertension, heart failure, history of stroke, atrial fibrillation type (paroxysmal or nonparoxysmal), and visit number. CI indicates confidence interval; OR, odds ratio.
*Mixed logistic regression model.
†Mixed linear model.

may still have higher ambulatory heart rates, as has been observed previously on Holter-ECG recordings in patients with paroxysmal AF.[23] A decreased vagal tone and a greater prevalence of thyroid dysfunction in women may be a mechanistic explanation for this observation.[13] Total heart rate variability was higher in postmenopausal women who were on estrogen replacement therapy compared with those without hormone therapy.[24] In addition, resting and ambulatory heart rates were higher in young and healthy women,[25] another observation that is in line with this hypothesis. Other factors that may explain sex-specific differences but that were not assessed in this study include drug adherence, emotional stress, sleep quality, and sex-specific treatment strategies by healthcare providers. Finally, residual confounding remains an issue in every observational cohort.

**Table 6.** Differences in Symptom Status in Women Vs Men in a Subset of Patients With Echocardiographic Baseline Information

| Characteristic | OR (95% CI) | *P* Value* |
|---|---|---|
| Any symptoms | 2.3 (1.3; 4.0) | 0.004 |
| Palpitations | 2.3 (1.5; 3.7) | 0.0002 |
| Dyspnea | 1.8 (1.2; 2.8) | 0.008 |
| Fatigue | 1.7 (1.1; 2.6) | 0.03 |
| Dizziness | 2.5 (1.5; 4.1) | 0.0003 |
| Chest pain | 1.7 (0.9; 3.1) | 0.08 |
| Effort intolerance | 0.7 (0.4; 1.3) | 0.3 |
| Syncope | 0.8 (0.2; 2.7) | 0.7 |

ORs (95% CIs) are for women compared to men. CI indicates confidence interval; OR, odds ratio.
**P* values were based on logistic regression. Models were adjusted for left ventricular ejection fraction, age, body mass index, systolic blood pressure, heart rate (>100 and <100 bpm), coronary heart disease (myocardial infarction, percutaneous transluminal coronary angioplasty, or aortocoronary bypass), diabetes mellitus, hypertension, heart failure, history of stroke, oral anticoagulation at baseline, history of intervention (electrical cardioversion and/or pulmonary vein isolation), atrial fibrillation type (paroxysmal or nonparoxysmal), and current smoking.

Main strengths of this study are the large sample size of an unselected and well-characterized AF population, the prospective follow-up with updating of symptom status and health perception over time, and a clinically relevant main finding. Several limitations need to be taken into account in the interpretation of our findings. Given the observational study design, we were not able to prove causality, and residual confounding may be present despite extensive multivariable adjustment, Nevertheless, our study suggests that differences in symptoms are not explained by the covariates added to the models. Finally, data on cardiac structure and function were not systematically collected in this study. Adjustment for left ventricular function among those with this information available did not change our findings; however, differences in cardiac function may still have influenced our results. Patients with available information on left ventricular function may be different from the overall study population and thus may have experienced symptoms differently or for a reason other than AF.

## Conclusion

In this large prospective study of patients with AF, we found that women had a significantly higher symptom burden and lower health perception than men. These findings persisted

over time and after comprehensive multivariable adjustment. Future studies need to elaborate the mechanisms underlying these important differences.

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## Disclosures

Shah received honoria from Daiichi-Sankyo and Pfizer; Schläpfer served in the advisory boards for Daiichi-Sankyo, Bayer & Boehringer-Ingelheim; Kühne has served on the speakers' bureau for Boston Scientific, St. Jude Medical and Biotronik. He has received lecture/consulting fees from Sorin, Boehringer Ingelheim, Bayer, Sanofi Aventis, Novartis and MSD and has received unrestricted grants from Sanofi Aventis, Bayer and Boehringer Ingelheim. He is a proctor for Medtronic (Cryoballoon); Conen has received research support from Bayer, Bristol-Myers-Squibb, Pfizer and Daiichi-Sankyo; he also received consultant and/or speaker fees from Bayer, Bristol-Myers-Squibb, Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. The remaining authors have no disclosures to report.

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