American Heart Association.

Sex Differences in Quality of Life in Patients With Atrial Fibrillation: A Systematic Review

Linn Arvidsson Strømnes;* Helene Ree, MD;* Knut Gjesdal, MD, PhD; Inger Ariansen, MD, PhD

Background—The goal of this literature review was to assess sex differences in the quality of life (QoL) in patients with atrial fibrillation (AF) and, if possible, to determine if these are due to AF.

Methods and Results—The electronic database PubMed was searched on January 23, 2018, using the search terms "QoL", gender differences, "AF" female, and gender to find potential articles that assessed sex differences in QoL in AF patients. In all, 851 articles were identified, from which 25 original studies were eligible for this systematic review. Female AF patients were found to have poorer QoL and more symptoms than male AF patients. They scored lower, predominantly on the physical component score of the Medical Outcomes Study Short-Form 36 Health Survey.

Conclusions—The available literature consistently describes poorer QoL in female AF patients but does not clearly address whether this is a reflection of sex differences seen in the general population or is related to AF per se. It is also questionable whether the relatively poorer QoL in women is large enough to be of clinical importance. **(*J Am Heart Assoc*. 2019;8:e010992. DOI: 10.1161/JAHA.118.010992.)**

Key Words: atrial fibrillation • female • gender • quality of life

Atrial fibrillation (AF) is a common arrhythmia and, due to its complications, a leading serious cardiovascular disease worldwide. The characteristics of the disease differ between sexes: AF is more prevalent in men than in women; however, the absolute number of women with AF is equal to or greater than that of men, as women live longer.[1] Women are on average 5 years older than men when diagnosed with AF.[2] It is generally established that women have a higher prevalence of hypertension, diabetes mellitus, valvular heart disease, and thyroid disorders,[3] whereas men more frequently have coronary artery disease and idiopathic AF.[4] The risk of stroke is higher in women and significantly related to AF despite the use of anticoagulation therapy.[1] Women also tend to have worse functional outcome after stroke,[5] and women with AF have a higher all-cause mortality compared with men.[1] Women with AF tend to be more symptomatic and seek medical care more frequently but are less likely to receive specialist care and rhythm control therapy.[1] Women also have a series of electrophysiological measures that differ from those of men, including higher resting heart rate and longer heart rate–corrected QT interval.[6]

Health-related quality of life (QoL) encompasses the perceived health as self-reported physical, mental, and social functioning.[7,8] The evaluation of QoL is particularly relevant in patients with chronic disorders such as AF, where QoL may be impaired by both the impact of the disease as well as its management. Several questionnaires measure generic QoL and other disease-specific symptoms. The information thus obtained can support the choice of therapeutic strategy and assess the cost-effectiveness of treatment.[7]

It is well known that QoL is significantly impaired in AF patients compared with the general population,[1] but less attention has been paid to the impact of sex on the QoL in this patient group. The aim of this review is to elucidate whether there is a sex difference in QoL in AF patients and, if so, if this is due to AF per se or just a reflection of sex differences in QoL in the general population.

Methods

Data are available on request, from the authors. The study included results derived from published data, and an institutional review board was not consulted.

From the Faculty of Medicine (L.A.S., H.R.) and Institute of Clinical Medicine (K.G.), Oslo University, Oslo, Norway; Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway (K.G.); Norwegian Institute of Public Health, Oslo, Norway (I.A.).

*Ms Strømnes and Dr Ree contributed equally to this manuscript.

Correspondence to: Inger Ariansen, MD, PhD, Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, PO Box 222 Skøyen, N-0213 Oslo, Norway. E-mail: inger.ariansen@fhi.no

Received October 29, 2018; accepted March 4, 2019.

Clinical Perspective

What Is New?

- Female patients with atrial fibrillation (AF) have poorer quality of life than male patients with AF.
- Few studies, however, compare AF patients with non-AF subjects from the same source population.

What Are the Clinical Implications?

- It is not yet established whether the sex difference in quality of life in AF is greater than it is in the general non-AF population.

Search Strategy

The database PubMed was searched by the Medical Subject Heading terms in 3 searches: Gender OR Female AND Atrial Fibrillation AND Quality of Life; Gender differences AND Atrial Fibrillation AND Quality of Life; and Atrial Fibrillation AND Gender AND Quality of Life.

Inclusion Criteria

Two authors (L.A.S., H.R.) screened the titles and abstracts of all the retrieved articles written in English. The full text of the articles that assessed QoL in AF patients was then screened for the presence of original data on sex differences in QoL, and any article lacking such data was excluded. When several articles examined the same study population, only the article most relevant for sex differences in QoL was included. Furthermore, articles that did not assess QoL by the most widely used generic questionnaires (Short Form-36/12 Health Survey [SF-36/12] and/or EuroQoL [EQ-5D]) were excluded. These questionnaires are validated instruments that can be used across many diseases as well as in healthy population groups and allow comparison of populations. If other questionnaires on symptoms and mental health were used in addition to SF-36/12/EQ-5D, they were taken into account and discussed in light of the QoL findings.

Risk of Bias

Risk of bias was evaluated in studies that addressed differences in QoL between AF patients and control populations within each sex. The bias included the main classes of bias for observational cross-sectional studies: selection bias, information bias, and bias from confounding.

Results

On January 23, 2018, the search in PubMed retrieved 851 citations from the first Medical Subject Heading term search. The subsequent 2 term searches did not give any additional citations. The full text was retrieved for 351 articles. Fifty-six citations fulfilled the inclusion criteria, and 25 articles remained for analysis after the application of exclusion criteria (Figure). The most widely used assessment forms are listed in Table 1.[9-20] Results from the different studies were summarized into separate categories: studies assessing sex differences in QoL in patients with all unspecified AF (paroxysmal, persistent, and permanent) (Table 2), studies assessing sex differences in QoL in patients with paroxysmal and persistent AF (Table 3), studies assessing QoL in AF patients after intervention (Table 4), and sex differences in mental health in patients with AF (Table 5). Baseline results from interventional studies were also incorporated in Tables 2 and 3. Results from some of the studies may thus appear in several tables.

Sex Differences in QoL in Patients With Unspecified AF

Eight observational studies[4,9,10,18,21,22,25,26] and the baseline assessment in 5 interventional studies[11,15,23,24,27] report sex differences in QoL in patients with all forms of AF (paroxysmal, persistent, and permanent AF) (Table 2). The following assessments were used: SF-36/SF-12,[9,10,15,21-27] EQ-5D,[4,9,11,18,21] AFEQT (Atrial Fibrillation Effect on Quality-of-Life),[18,27] University of Toronto Atrial Fibrillation Severity Scale,[15,22] Atrial Fibrillation Symptom Checklist,[22] and Multidimensional Fatigue Inventory-20.[15] Evaluation of the clinical impact of between-group differences in scores was suggested as a minimal important difference (MID) of 2, 0.07, and 7 units for Physical Summary Score (PCS) or Mental Component Summary Score (MCS), EQ-5D Index, and EQ-5D Visual Analogue Scale, respectively,[21] a 10% difference in PCS or MCS,[22] or a difference in mean SF-36 subscale score of 1 standard deviation.[15] Six studies reported significantly lower QoL in female compared with male AF patients,[4,9,11,22,23,25,26] and 3 studies reported numerically lower QoL in female compared with male patients, lower than MID for PCS and MCS or 1 standard deviation for SF-36 subscales,[10,15,21] whereas 2 studies demonstrated no statistically significant sex difference in QoL.[18,24] Three studies revealed that female AF patients reported more symptoms than male AF patients.[4,15,22] Four studies compared results from AF patients with either a control population or with values from a reference population[10,11,21,23]: Roalfe et al and Hoegh et al compared AF male and female patients with men and women in a general population. Both found that female and male AF patients reported clinically significant lower PCS and small and comparable differences in MCS compared with a female and male general population.[10,21] Furthermore, in the study by

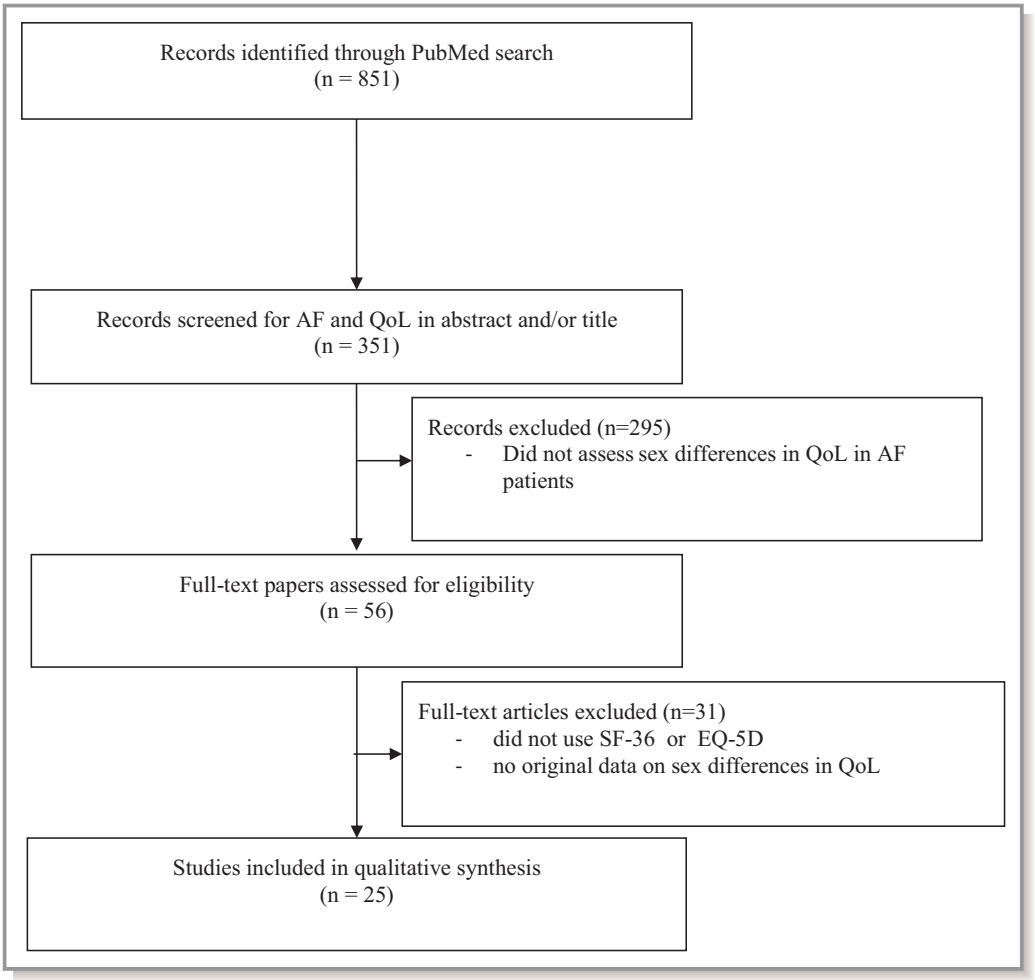

Figure. Flow chart of reviewing process. AF indicates atrial fibrillation; EQ, EuroQoL; QoL, quality of life; SF, Short Form.

Roalfe et al, the AF patients aged 75+ who reported mild total disability (Rankin score <2) had better physical QoL than the general population.[21] One study showed lower QoL scores in women with AF compared with men but did not find a corresponding sex difference in a control population with venous thromboembolism.[11]

Sex Differences in QoL in Patients With Paroxysmal and Persistent AF

QoL was assessed in 3 observational studies[20,28,36] and at baseline in 7 interventional studies[29-35] in patients with paroxysmal or persistent AF (Table 3). The following assessments were used: SF-36/SF-12,[20,29-33,35,36] EQ-5D,[28,34] AFEQT,[33] AF Symptom Checklist,[29,31] AF Severity Scale,[31] AF Symptom and Burden,[20] AF QoL,[28] and the Hospital Anxiety and Depression Scale.[33] Seven studies reported significantly lower QoL in female compared with male AF patients,[20,29-34] with 3 of these only on PCS.[20,31,33] Three studies revealed no statistically significant sex difference in QoL.[28,35,36] Four studies compared results from their AF population with either a healthy control group or values from a reference population.[29-31,35] Substudies of the Rate Control Versus Electrical Cardioversion and the Canadian Trial of Atrial Fibrillation showed that female AF patients had worse QoL than women in a reference population, predominantly on physical health.[30,31] In the Canadian Trial of Atrial Fibrillation, both male and female AF patients had worse QoL than an age-matched reference population; still, female patients had a relatively greater impairment than their age-matched reference population, and than male patients had compared with their reference population.[31] In a study of surgical AF ablation patients, both men and women with AF had lower PCS scores than a sex- and age-stratified reference population.[29] Finally, 4 studies demonstrated that female patients with AF report more symptoms than male AF patients[20,29-31] despite no worse AF burden.[20,31]

Sex Differences in QoL in Patients After Interventions

Ten studies examined QoL in AF patients after various interventions (Table 4). Four studies evaluated the effect of rate or rhythm control,[15,27,30,31] 4 the effect of ablation,[24,29,34,35] and 2 evaluated other interventions in AF patients[11,33] (Table 4).

Sex Differences in QoL After Rate or Rhythm Control in AF Patients

One randomized controlled trial assessed the effect of rate versus rhythm-control on QoL in AF patients: no difference was revealed. Female patients did, however, have worse QoL and higher cardiovascular mortality and morbidity in the rhythm-control

Table 1. Self-Reporting Questionnaires Measuring QoL Used in This Review Article

Generic questionnaires on quality of life	
SF-36: Medical Outcomes Study Short-Form 36 Health Survey	SF-36 is the most commonly used generic health survey. It measures physical and mental QoL by evaluating physical, social, and emotional functioning. It consists of 36 questions and standardized response choices, which are organized into 8 domains: physical functioning (PF), social functioning (SF), role limitation due to physical health problems (RP), role limitation due to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP), and general health perceptions (GH). Items are combined to form the mental component summary (MCS) and the physical component summary (PCS). The MCS measures social functioning and role limitations due to vitality and emotional distress, whereas the PCS estimates physical health and role limitations due to physical difficulties and bodily pain. Scores range from 0 to 100, with higher scores indicating better functioning and higher QoL.[9,10]
EQ-5D Index and VAS: EuroQoL 5D	EQ-5D is a generic questionnaire that consists of 2 parts; EQ-5D Index and EQ-5D Visual Analogue Scale (VAS). EQ-5D Index assesses QoL in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 3 levels of severity: no problems, some/moderate problems, or extreme problems. The EQ-5D questionnaire gives 243 (3^5) possible health states. These states are converted into a single summary index by adding preference weights from population norms. The EQ-5D Index ranges from 0 to 1, with a higher score indicating higher QoL, EQ VAS measures the individuals' perceived health from 0 (worst imaginable health state) to 100 (best imaginable health state).[11]
Questionnaires on mental health and fatigue	
HADS: The Hospital Anxiety and Depression Scale	HADS is a well-established questionnaire developed to provide a reliable and valid rating scale for anxiety and depression in medical settings. Because it omits somatic symptoms of depression such as fatigue and appetite changes, it is widely used to detect false-positive findings in medical patients. It is a 14-item scale with scores ranging from 0 to 42, with higher scores indicating greater distress.[12]
STAI: The State Trait Anxiety Inventory	STAI is a 40-item questionnaire assessing both state anxiety (temporary feeling) and trait anxiety (general feeling). The purpose of the questionnaire is to measure the present level of anxiety and anxiety predisposition. The total score on both subscales ranges from 20 to 80, with higher scores indicating higher levels of anxiety.[13,14]
MFI-20: Multidimensional Fatigue Inventory-20	MFI-20 is a 20-item questionnaire assessing the severity of fatigue. It covers different aspects of fatigue: general, physical, mental fatigue, and reduced activity and motivation. Scores range from 4 to 20, with higher scores indicating more symptoms of fatigue.[15]
BDI: Beck Depression Inventory	BDI is a 21-item questionnaire measuring the severity of depression the past week. Scores range from 0 to 63, with higher scores indicating greater levels of depression.[14,16]
AF disease-specific questionnaires on symptoms and quality of life	
AF-QoL: Atrial Fibrillation Quality of Life	AF-QoL is a questionnaire that contains 18 items with 3 domains: psychological, physical, and sexual activity. Scores range from 0 to 100, with higher scores indicating better QoL.[17]
AFEQT: Atrial Fibrillation Effect on Quality of Life	AFEQT is a 20-item questionnaire assessing 4 domains in AF-related QoL: daily activities, symptoms, treatment concerns, and treatment satisfaction. Scores range from 0 to 100, with higher scores indicating better QoL.[18]
AF-SCL: Symptom Checklist—Frequency and Severity Scale	AF-SCL is a questionnaire that measures the patient's perception of arrhythmia-related symptom frequency and severity over a 1-week interval. Scores range from 0 to 64 on the frequency scale and 0 to 48 on the severity scale, with higher scores indicating greater symptom burden.[19]
AFS/B: Atrial Fibrillation Symptom and Burden	AFS/B is a 2-part questionnaire: atrial fibrillation symptom (AFS) and atrial fibrillation burden (AFB). AFS measures the effect of symptoms on daily life by a set of 8 questions classified into asymptomatic, mild, moderate, or severe. AFB measures disease and health-care utilization by a set of 6 questions. Each question is classified into none, minimal, moderate, and severe burden.[20]
AFSS: University of Toronto Atrial Fibrillation Severity Scale	AFSS is a 7-item questionnaire that measures the patient's perception of AF disease burden including frequency, duration, and severity of episodes. Scores range from 0 to 35, with higher scores indicating greater AF symptoms severity.[15]

AF indicates atrial fibrillation; QoL, quality of life.

Table 2. Summary of Studies Assessing Sex Differences in QoL in Patients With Unspecified AF: Paroxysmal, Persistent, and Permanent

Author, Year of Publication	QoL Study Population, Form of AF	% Female	Design, Setting, and Objective	Assessment of QoL*	Results of QoL
Dagres et al (2007)[4]	5333 patients, all forms of AF	42	Ambulant or hospitalized AF patients from 35 European countries. Objective: Investigate sex-related differences.	EQ-5D at baseline and at 1 year follow-up.	Female patients had lower QoL both in EQ-5D and EQ-VAS ($P<0.001$), and were more symptomatic (mainly palpitations and dyspnea) than male patients ($P<0.001$). Age adjustment not specified, and no healthy control group.
Roalfe et al (2012)[21]	1762 patients, all forms of AF	47	Substudy of BAFTA, an RCT of warfarin vs aspirin for stroke prevention in AF patients in primary care. Objective: Compare the QoL in AF with that of the general population.	SF-12, EQ-5D.	Female, but not male, AF patients had significantly lower EQ-5D scores than a reference population (difference below MID), and lower MCS scores (above MID). Both female and male AF patients had (amazingly) higher PCS than a reference population (less than MID). No age-adjusted comparison between sexes, but AF patients with mild disability (Rankin score <2) had higher scores (above MID) for PCS, MCS and ED-5D Index.
Marvig et al (2015)[11]	1003 patients with AF (78%) or venous thromboembolism (VTE) (22%)	38 AF 44 VTE	EU-PACT: European Pharmacogenetics of Anticoagulant Therapy study. Objective: To investigate QoL in patients with VTE and AF.	EQ-5D assessed at baseline and at 3-mo follow-up.	Results before intervention†: AF patients: Female patients had lower scores than male patients on EQ-5D Index (ns) and EQ-VAS ($P<0.05$). VTE patients: No statistically significant sex differences.
Reynolds et al (2006)[22]	963 patients, new-onset AF	40	Multicenter registry of new-onset AF or flutter, the FRACTAL cohort study. Objectives: Characterize symptoms and QoL in AF, and impact of age, sex, and clinical course.	SF-12, AFSS, AF-SCL at baseline and over 2.5 y.	Female patients had 10% lower PCS, slightly lower MCS, and 40% higher symptom frequency and severity scores than male patients. Age adjusted.
Hoegh et al (2016)[10]	873 patients with AF/flutter 41 725 non-AF participants	32 AF 54 non-AF	Danish Diet, Cancer and Health Study cohort: National Patient Registry data from AF patients and controls. Objective: Investigate association between AF and QoL.	SF-36.	After adjustment for age and comorbidity, AF patients of both sexes had lower PCS and slightly lower MCS than non-AF participants. The magnitude of the differences was similar between the sexes.
Hendriks et al (2014)[23]	534 patients with newly diagnosed AF	41	Newly diagnosed AF patients compared with a national reference population. Objective: Evaluate nurse-led outpatient clinic compared with routine care (RCT).	SF-36, HADS assessed baseline and at 2 y.	Results before intervention†: QoL in AF patients was comparable to that in the general population but lower in female compared with male patients. Age adjustment not specified.
Groenveld et al (2011)[15]	437 permanent AF patients	33	Rate Control Efficacy in Permanent Atrial Fibrillation II (RACE II); RCT of AF patients in hospitals randomized to lenient or strict heart rate control. Objective: Investigate rate control influence on QoL.	SF-36, AFSS, MFI-20 assessed at baseline, 1 year, and end of study.	Results before intervention†: Female sex had lower SF-36 subscale scores on PF, RP, BP, SF, and VT and higher symptom score (AFSS). Age adjustment not specified. Sex was associated with high MFI-20 scores (above the mean value +1 SD) on the scales for physical fatigue and reduced active adjustment not explicitly specified.

Continued

Table 2. Continued

Author, Year of Publication	QoL Study Population, Form of AF	% Female	Design, Setting, and Objective	Assessment of QoL*	Results of QoL
Wynn et al (2014)[18]	362 patients with AF	32	AF patients referred to an electrophysiology clinic. Objective: Evalidate EHRA symptom classification in AF.	EQ-5D, AFEQT.	Sex did not have significant effect on any QoL measure. Not age adjusted.
Forleo et al (2007)[24]	170 patients with AF	32	Highly symptomatic, drug-refractory AF patients referred for radiofrequency catheter ablation. Objective: Investigate sex impact on ablation results.	SF-36 at baseline and 6 mo after the procedure.	Results before intervention†: Female AF patients had (ns) lower scores on 6 of 8 scales (PF, RP, BP, GH, SF, and MH). Age adjustment not specified.
Kang (2009)[25]	129 patients with AF	50	AF data analysis from outpatient clinics in United States and Korea. Objectives: Examine sex and culture differences in QoL among American and Korean AF patients.	SF-36.	Americans: female patients had worse physical function but better mental health. In Koreans, female patients had (ns) both worse physical function and worse mental health than male patients. Age adjustment not specified. Americans and Koreans: Female AF patients had significantly lower PCS than male patients when controlling for ethnic group (P=0.02).
Tsounis et al (2014)[9]	108 patients with AF	36	AF patients in tertiary hospital. Objective: Explore the relationship between QoL, functional status and left ventricular function.	SF-36, EQ-5D.	Female patients reported significantly lower scores in 5 of 8 SF-36 scales (PF, RP, BP, SF and RE) and lower scores in EQ-VAS and in the mobility dimension of EQ-5D. Age adjustment not specified.
Jeong et al (2014)[26]	108 patients with AF	26	Interview about QoL and type D personality. Objective: Analyze the determinants of QoL.	SF-12.	More female patients had PCS and MCS below 50 points, and independent predictors for this were female sex and type D personality. Age adjusted.
Sandhu et al (2017)[27]	100 patients with AF	20	Prospective cohort study of AF patients referred for cardioversion. Objective: Investigate impact of DC cardioversion.	SF-36, AFEQT baseline and at 3-mo follow-up.	Results before intervention†: QoL was lower in AF patients compared with norm data from healthy individuals across all domains of SF-36. Sex differences not reported and age adjustment not specified.

Numbers followed by ± indicate mean±SD unless otherwise specified. SF-36 summary scores are physical summary score (PCS) and mental component summary score (MCS). SF-36 subscales referred to include physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE), and mental health (MH). AF indicates atrial fibrillation; AFS/B, Trial Fibrillation Symptom and Burden; AFSS, University of Toronto Atrial Fibrillation Severity Scale; EHRA, European Heart Rhythm Association; EQ-5D, generic questionnaire that consists of 2 parts; EQ-5D Index and EQ-5D Visual Analogue Scale (VAS); MID, minimal important difference; ns, nonsignificantly; QoL, quality of life; RCT, randomized controlled trial. SF-36, Medical Outcomes Study Short-Form 36 Health Survey.
†Articles also included in Table 4.

group.[30] Two studies assessed the effect of rhythm control on QoL: 1 randomized controlled trial compared 3 different antiarrhythmic drug treatments,[31] and 1 study assessed electrical cardioversion.[27] The randomized controlled trial on antiarrhythmic drugs demonstrated an improvement in QoL in both sexes after intervention; although the improvement on PCS was significant only for female patients, the improvement in and MCS was significant only for male patients.[31] The same study also revealed an improvement in symptom frequency and severity in both sexes, but women remained significantly worse. One study assessed rate-control treatment in AF patients. This substudy of Rate Control Versus Electrical Cardioversion II demonstrated no significant effect on QoL in either the lenient or the strict control group, but female sex was associated with lower QoL at all time points.[15]

Sex Differences in QoL After AF Ablation

All 4 studies demonstrated an improvement in QoL after ablation of AF,[24,29,34,35] with comparable improvements for female and male patients.[24,34,35] Interestingly, after the surgical ablation procedure in 1 study, AF patients surpassed their age- and sex-norm data on QoL scores: female patients only on PCS and male patients only on MCS. In addition, even though there was a similar improvement in AF symptom frequency, female patients reported greater overall symptom frequency than male patients at all time points.[29]

Table 3. Summary of Studies Assessing Sex Differences in QoL in Patients With Paroxysmal and/or Persistent AF

Authors, Year of Publication	QoL Study Population, Form of AF	% Female	Methods	Assessment of QoL*	Results of QoL
Goette et al (2015)[28]	542 patients with AF	43	IMPULS: a prospective multicenter study on consecutive outpatients treated with dronedarone over 1 y. Objective: Investigate drug tolerability and efficacy.	EQ-5D, AF-QoL at baseline, 6 and 12 mo	Results at baseline†: No important sex difference in QoL. Numeric sex-stratified QoL scores not presented, and age adjustment not specified.
Henry et al (2013)[29]	540 patients with AF	34	Data collected from a hospital-based surgical AF ablation registry (Cox Maze III/IV procedure). Objective: Examine short- and long-term outcomes in female compared with male patients.	SF-12, AF-SCL assessed at baseline and up to 24 mo	Results before intervention†: Female AF patients scored lower on PCS and MCS. Both sexes had lower PCS scores than normative data of similar age and sex. Female patients reported greater frequency and severity of AF symptoms.
Rienstra et al (2005)[30]	458 patients with AF	28	Post-hoc QoL analysis of patients randomized to rate or rhythm control. Objective: Examine whether sex affects the outcome of rate vs rhythm control treatment.	SF-36 at baseline, 12 mo and end of study.	Results before intervention†: QoL in AF patients of both sexes was lower than in healthy age-matched controls, predominantly on the physical health scales. Female patients had more AF-related symptoms (palpitation, fatigue) than male patients despite no significant difference in AF frequency and duration, and they had lower QoL on 6 of 8 SF-36 subscales. Also healthy women had worse QoL than healthy men. AF patients were compared with age- and sex-matched controls.
Paquette et al (2000)[31]	294 patients with symptomatic AF	41	Substudy of the Canadian Trial of Atrial Fibrillation where consecutive AF outpatients were randomized to amiodarone, sotalol, or propafenone treatment. Objectives: Elucidate sex differences in QoL and examine if personality characteristics could explain QoL impairment and QoL differences between sexes.	SF-36, AFSS, AF-SCL at baseline, 3 and 12 mo.	Results before intervention†: AF patients had worse QoL compared to age- and sex-matched controls on 6 of 8 scales for men and 7 of 8 scales for women. Female patients reported more frequent and severe AF symptoms despite similar average AF episode frequency. They had lower QoL on the PCS compared with male patients, but similar on MCS. The impairment in QoL compared with their reference population was greater than in men, most notably on the physical scales.
Pavelková and Bulava (2014)[32]	264 patients with AF	40	Patients referred for catheter ablation at a tertiary clinic. Objective: Assess QoL before and after catheter ablation.	SF-36 at baseline and within 12 mo	Results before intervention†: Significantly more women reported a decreased QoL before ablation. (Sex differences in QoL after ablation were not described.) No numeric sex-stratified QoL scores are presented, age adjustment not specified, and the reference population not described.
Koci et al (2014)[20]	224 patients with AF	26	Consecutive patients from an electrophysiology center. Objective: Develop and validate a patient-generated score and classification scheme for AF-related symptom severity and burden.	SF-12, AFS/B.	Female patients experienced more severe AF-related symptoms, despite no sex difference in frequency and duration of AF episodes. They also reported significantly lower PCS and nonsignificantly lower MCS scores than male patients. Age adjusted.
Wagner et al (2017)[33]	210 patients with AF	28	RCT on catheter ablated AF patients: comprehensive rehabilitation or usual care (CopenHeartRFA trial). Objectives: Investigate sex differences in health status, psychological distress, QoL, rehabilitation outcomes, and factors predicting effect of rehabilitation.	SF-36, HADS, AFEQT.	Results after ablation, but before rehabilitation†: Female patients had lower scores on PCS but not on MCS or HADS scores compared with male patients, and non-significantly lower scores for AFEQT symptoms, daily activity, and global scores. Age adjusted.

Continued

Table 3. Continued

Authors, Year of Publication	QoL Study Population, Form of AF	% Female	Methods	Assessment of QoL*	Results of QoL
Fiala et al (2017)[34]	202 patients with AF	22	Single-center prospective registry of long-standing persistent AF patients who underwent catheter ablation. Objective: Identify global functional improvement 12 mo after successful catheter ablation.	EQ-5D assessed at baseline and 12 mo	Results before intervention†: Female AF patients had worse EQ-5D compared with male patients. Age adjustment not specified.
Berger et al (2016)[35]	99 patients with AF	25	Patients completed SF-36 at baseline and 1 y after catheter ablation. Objective: Examine relation between AF recurrence and QoL.	SF-36 assessed at baseline and 12 mo	Results before intervention†: QoL was lower in patients with AF than in the general population. No sex difference in any subscale on the SF-36. Numeric sex-stratified QoL scores not presented, and age adjustment not specified.
Maryniak et al (2006)[36]	76 patients with AF	29	AF patients referred for catheter ablation. Objective: Relate mode of onset of paroxysmal AF episodes to QoL.	SF-36	No sex difference in any SF-36 subscale. In female but not male patients, maximum ventricular rate during AF correlated negatively with the general physical feeling. Age adjustment not specified.

Mean values followed by ± indicate mean±SD unless otherwise specified. SF-36 summary scores are physical summary score (PCS) and mental component summary score (MCS). SF-36 subscales referred to include physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE), and mental health (MH). AF indicates atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality of Life; AF-SCL, Symptom Checklist–Frequency and Severity Scale; AFS/B, Atrial Fibrillation Symptom and Burden; AFSS, University of Toronto Atrial Fibrillation Severity Scale; EQ-5D, generic questionnaire that consists of 2 parts; EQ-5D Index and EQ-5D Visual Analogue Scale (VAS); HADS, The Hospital Anxiety and Depression Scale; QoL, quality of life; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short-Form 36 Health Survey.
†Articles also included in Table 4.

Sex Differences in QoL After Other Interventions in AF Patients

One study assessed the effect of anticoagulant therapy in AF patients compared with venous thromboembolic patients: in both groups both sexes improved after treatment, but in the AF group female patients had lower EQ-5D scores compared with male patients. This sex difference was not seen in the venous thromboembolic group.[11] The second study assessed the effect of comprehensive rehabilitation versus usual care after catheter ablation. There were improvements in QoL and physical outcome in female patients only, and mental outcomes in male patients only, compared with the groups receiving usual care. No significant sex difference in SF-36 was found in either group.[33]

Sex Differences in Mental Health in Patients With AF

The following assessments were used in the 2 studies: SF-36,[19,37] the Hospital Anxiety and Depression Scale, AF Severity Scale,[37] AF Symptom Checklist, The State Trait Anxiety Inventory, and the Beck Depression Inventory-II[19] (Table 5). Both studies demonstrated that female patients had poorer PCS but similar MCS compared with male patients,[19,37] and for women the PCS was nearly clinically significant as poorer than for normative data, whereas male patients were comparable to normative data.[37] One study revealed that female AF patients reported higher levels of depressive symptoms relative to male patients.[37]

Risk of Bias

Nine studies included some form of sex-stratified comparison of QoL in AF patients versus a normal or control population in strata by sex (Table 6). Systematic evaluation of risk of bias proposed an overall intermediate or high risk of bias in all but 1 study.[10,21]

Discussion

The present overall review demonstrates that female AF patients report poorer QoL,* and are more symptomatic than male AF patients.[4,15,19,20,22,29-31,37] Interestingly, the majority of the studies reveal that female AF patients scored lower, predominantly on the physical component score of the SF-36,[10,19,20,31,33,37] although only a few female patients had significantly lower scores on the mental component score.[22,29] Only 4 studies showed neither a significant sex difference nor a tendency toward women scoring lower in QoL.[18,28,35,36] Female AF patients were also more likely to present with

*References 4, 9-11, 15, 19-23, 25, 26, 29-34, 37.

Table 4. Summary of Studies Assessing QoL in AF Patients After Intervention

Authors, Year of Publication	QoL Study Population, Form of AF	% Female	Methods	Assessment of QoL*	Results of QoL
Rate vs rhythm control					
Groenveld et al (2011)[15]	437 patients with AF	34	RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II); RCT of AF patients in hospitals randomized to lenient or strict heart rate control. Objective: Investigate rate control influence on QoL.	SF-36, AFSS and MFI-20 at baseline, 1 y and end of study.	Female sex was associated with worsened SF-36 MH scores (OR 2.3) and Mental Fatigue scores (OR 1.6 compared to male patients), from baseline to end of follow-up study. Age adjustment not specified.
Rienstra, et al (2005)[30]	352 patients with AF	36	Post-hoc QoL analysis of patients randomized to rate or rhythm control. Objective: Examine whether sex affects the outcome of rate- vs rhythm-control treatment.	SF-36 at baseline, 12 mo and end of study.	QoL was unchanged in both sexes in both treatment arms. Baseline sex differences in QoL remained at the end of study, with female patients scoring lower on 7 of 8 SF-36 scales. Age adjustment not explicitly specified.
Paquette et al (2000)[31]	264 symptomatic AF patients	41	Substudy of the Canadian Trial of Atrial Fibrillation in which consecutive AF outpatients were randomized to amiodarone, sotalol, or propafenone treatment. Objectives: Elucidate sex differences in QoL and examine if personality characteristics could explain QoL impairment and QoL differences between sexes.	SF-36, AFSS, AF-SCL at baseline and 3 and 12 mo.	AF symptom frequency and severity at 12 mo had improved significantly for both sexes. PCS had improved significantly for female but not male patients, whereas MCS improved significantly for male but not female patients. Age adjusted.
Sandhu et al (2017)[27]	100 patients with AF	20	Prospective cohort study of AF patients referred for cardioversion. Objective: Investigate impact of DC cardioversion.	SF-36, AFEQT baseline and at 3-mo follow-up.	Multivariable analysis showed that female sex, age, and sinus rhythm at 3 mo were associated with improved QoL after cardioversion. SF-36 MSC improved more in female patients. Age adjustment not specified.
AF patients undergoing ablation					
Henry et al (2013)[29]	148 patients with AF	34	Data collected from a hospital-based surgical AF ablation registry (Cox Maze III/IV procedure). Objective: Examine short- and long-term outcomes in female compared with male patients.	SF-12, AF-SCL assessed at baseline and up to 24 mo.	No sex difference in proportion that regained sinus rhythm. Female AF patients' PCS and MCS scores were lower than those of male patients, and overall symptom frequency and severity scores were higher at all points of time. Both PCS and MCS improved in both sexes, surpassing age and sex group norms for PCS (female) and MCS (male). Overall AF symptom frequency and severity declined similarly in both sexes. PCS: Both male and female patients improved significantly between baseline and 6 mo. Female patients improved significantly from baseline to 12 mo and surpassed their age and sex group norms (by 3.6 points, P=0.003), whereas male patients were similar to their age and sex norms (AF 1.6 points higher than norm, P=0.09).

Continued

Table 4. Continued

Authors, Year of Publication	QoL Study Population, Form of AF	% Female	Methods	Assessment of QoL*	Results of QoL
Forleo et al (2007)[24]	170 patients with AF	32	Highly symptomatic, drug-refractory AF patients referred for radiofrequency catheter ablation. Objective: Investigate sex impact on ablation results.	SF-36 at baseline and 6 mo after the procedure.	At 6-mo follow-up, both sexes had improved SF-36 scores. Women had numerically, but not statistically, better improvement than men. Age adjustment not specified.
Fiala et al (2017)[34]	202 male patients with AF mean age 57±9 y	22	Single-center prospective registry of long-standing persistent AF patients who underwent catheter ablation. Objective: Identify global functional improvement 12 mo after successful catheter ablation.	EQ-5D assessed at baseline and 12 mo.	Female and male patients showed comparable improvement on EQ-5D. Age adjustment not specified.
Berger et al (2016)[35]	99 patients with AF. Mean age 55±9 y	25	Patients completed SF-36 at baseline and 1 y after catheter ablation. Objective: Examine relation between AF recurrence and QoL.	SF-36 assessed at baseline and 12 mo.	QoL improved significantly in all patients. No sex difference in any subscale of SF-36 after ablation. No numeric sex-stratified QoL scores presented.
Other interventions					
Marvig et al (2015)[11]	1003 patients with AF (78%) or VTE (22%)	38 AF 44 VTE	EU-PACT: European Pharmacogenetics of Anticoagulant Therapy study. Objective: To investigate QoL in patients with VTE and AF.	EQ-5D assessed at baseline and at 3-mo follow-up.	Female AF patients had lower score than males on EQ-5D, both at baseline and follow-up. QoL improved after 3 mo on anticoagulant treatment, although less in AF than in VTE. EQ-VAS improved in both sexes, but for EQ-Index score, significantly only in men. No significant difference was seen between female and male patients in the VTE group. QoL data not age adjusted.
Wagner et al (2017)[33]	210 patients with AF	28	RCT on catheter-ablated AF patients: comprehensive rehabilitation or usual care (CopenHeartRFA trial). Objectives: Investigate sex differences in health status, psychological distress, QoL, rehabilitation outcomes, and factors predicting effect of rehabilitation.	SF-36, HADS, AFEQT.	Comprehensive rehabilitation after ablation was better than usual care in women (AFEQT global and treatment concern scores), but in men only HADS-anxiety was better. For SF-36, no significant group difference was found from baseline to follow-up, despite PCS and MCS improved numerically by >2 units for both intervention groups in both sexes. Data are age adjusted.

Values followed by ± indicate mean±SD. SF-36 summary scores are physical summary score (PCS) and mental component summary score (MCS). AF indicates atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality of Life; AF-SCL, Symptom Checklist–Frequency and Severity Scale; AFSS, University of Toronto Atrial Fibrillation Severity Scale; DC, direct current; EQ-5D, generic questionnaire that consists of 2 parts; EQ-5D Index and EQ-5D Visual Analogue Scale (VAS); HADS, The Hospital Anxiety and Depression Scale; OR, odds ratio; QoL, quality of life; RCT, randomized controlled trial; VTE, venous thromboembolism; SF-36, Medical Outcomes Study Short-Form 36 Health Survey.

anxiety and/or depression.[37] Compared with the general population, both men and women with AF had poorer QoL scores,[31] especially for the physical component of QoL.[10,21,29]

Could Poorer QoL in Women in General Explain the Sex Differences in AF?

The most widely used self-reporting questionnaires are SF-36 and EQ-5D/Visual Analogue Scale. These generic questionnaires reflect the individuals' general aspect of physical, mental, and social functioning, which is strongly influenced by other factors such as comorbidity and age. Several studies illustrate that women in the general population report lower QoL than men and that female sex and increasing age are independently associated with reduced QoL.[38-44] In addition to reduced QoL, it seems that older respondents in the AF population,[36] as well as in the general population,[40,41,43] largely score lower on physical QoL. This is consistent with recent normative data from the

Table 5. Sex Difference in Mental Health in Patients With AF

Authors, Year of Publication	QoL Study Population, Form of AF	% Female	Methods	Assessment of QoL*	Results of QoL
Akintade et al (2015)[19]	150 patients with AF (73%) and atrial flutter (27%)	40	Cross-sectional noninterventional study from teaching hospitals. Objective: Evaluate factors that influence QoL in AF/flutter patients.	SF-36, BDI-II, STAI, AF-SCL.	Female patients with AF/flutter reported poorer PCS and higher frequency and severity of AF-related symptoms compared with male patients. Also, depressive symptoms were significant independent predictors of PCS. Symptoms of anxiety and depression were predictors of MCS. Age adjusted.
Ong et al (2006)[37]	93 patients with AF	44	A cross-sectional questionnaire study on AF patients from 2 tertiary-care clinics. Objectives: Investigate sex differences, depression, and QoL in patients with AF.	SF-36, HADS, AFSS.	Female patients had higher depression scores and used more antidepressants. Depression is associated with lower physical and mental QoL. Women scored almost 1 SD below the national norm for SF-36 PCS, whereas men's scores were equal to norm data, as were MCS scores for both sexes. Female patients reported lengthier AF episodes, but episode frequency did not differ. Age adjustment not specified.

Values followed by ± indicate mean value±SD. SF-36 summary scores are physical summary score (PCS) and mental component summary score (MCS). AF indicates atrial fibrillation; AF-SCL: Symptom Checklist-Frequency and Severity Scale; AFSS: University of Toronto Atrial Fibrillation Severity Scale; BDI: Beck Depression Inventory; HADS: The Hospital Anxiety and Depression Scale; QoL, quality of life; SF-36: Medical Outcomes Study Short-Form 36 Health Survey; STAI: The State Trait Anxiety Inventory.

general Norwegian population.[45] It can therefore be hypothesized that increasing age, more comorbidity, and female sex are associated with reduced QoL, especially with physical health, and that our findings are only a reflection of the sex differences in the general population.

Women in the general population also report more physical symptoms.[46,47] Even though female AF patients experience more severe AF-related symptoms, there does not seem to be a sex effect on AF frequency and duration.[20,30,31] Thus, women may be more sensitive to AF episodes or have a lower threshold for reporting illness burden, and we may therefore speculate if this sex difference in QoL is not due to AF per se but rather to women's perception of illness and style of responding.

The literature reports more anxiety and depression among women in the general population[48] as well as in cardiovascular conditions,[49,50] and it is well known that depression and anxiety are related to poorer QoL.[37] However, it is possible that the sex difference in anxiety and depression prevalence depends on the diagnostic methods used, and use of a symptom scale may yield higher scores in female than in male patients.[48] Because various assessment methods are used to measure anxiety and depression, it is difficult to know whether female AF patients are more prone to depression/anxiety or if women merely are more sensitive to symptoms. Female AF patients might be more worried by their AF episodes, and fear of their next episode might affect anxiety and depression scores.

Could AF Per Se Be Responsible for Lower QoL in Female AF Patients?

Only a few studies support the inference that female AF patients might have lower QoL than males due to AF per se. Paquette et al demonstrated a relatively greater impairment in QoL in female AF patients compared with their age-matched controls than was the case for men with AF, most notably on the physical components. Still, the relative sex difference was <0.5 standard deviation unit and lower than the suggested MID of 1 standard deviation unit.[31] Similarly, the Rate Control Versus Electrical Cardioversion and Canadian Trial of Atrial Fibrillation studies showed that female AF patients had worse QoL than women in the general population, predominantly on physical health.[30,31] Marvig et al found that female AF patients had significantly lower scores on EQ-Index and Visual Analogue Scale compared with male AF patients, although this sex difference was not significant in the control population with venous thromboembolism.[11] In the study by Hoegh et al the difference in PCS between AF patients and a non-AF general population was worse in women than in men. Still, the relative sex difference was <1 score point, and hence it was lower than the MID for

DOI: 10.1161/JAHA.118.010992

Table 6. Risk of Bias in Assessing Differences in QoL in an AF Group Versus a Normal Population/Control Group, in Strata by Sex

Studies	Selection Bias	Information Bias of Exposure and Confounders	Information Bias of Outcome	Bias Due to Confounding	Evaluation and Overall Risk of Bias
Studies comparing QoL in AF patients vs a normal population/ control population in strata by sex	Systematic differences among groups regarding source population, recruitment strategy from source population, and participation rate.	Systematic differences among groups in how the exposure (AF status or control status) or confounders (age, comorbidity) were assessed.	Systematic differences among groups in how outcome (QoL) was measured (setting for filling out questionnaire) and questionnaire data were reported, handled and evaluated (complement rate for QoL questionnaires, method for missing responses, addressing of effect size for difference in QoL among groups).	Relevant confoundersidentified (age, comorbidity) and handled properly in analysis (such as adjusting or stratification).	Proper design to assess differences in QoL in an AF vs control population in strata by sex. Ability to consider bias and evaluation of bias.
Roalfe et al (2012)[21]	High Risk Different source populations and recruitment methods. AF patients recruited from general practice vs population-based normative data. Participation only reported in AF group (38%).	Low Risk AF diagnosis extracted from electronic records of known AF patients and from opportunistic pulse screening. Clinically confirmed AF diagnosis. Differing assessment of confounders; comorbidity and age-distribution only in AF-group.	Intermediate/high Risk Similar assessment of QoL questionnaires in both groups. Differing settings for AF patients (at randomization clinic and control group (participants' homes). Missing completions of questionnaires only reported in AF group. Sex-specific missing completions not reported. QoL effect size between groups calculated, and MID discussed.	Intermediate Risk Similar, broad age range in both groups. Comorbidity between groups discussed. No adjustment for comorbidity or age distribution.	Intermediate Risk The study aimed to compare QoL in AF population with the general population. Sources of bias partially addressed.
Marvig et al (2015)[11]	Low/intermediate Risk Same source population (either general practitioners, anticoagulation clinics, or hospitals from 4 European countries) and recruitment method for both groups. Participation rates not reported.	Intermediate Risk Similar detection of diagnoses and clinical setting for both groups: Recently diagnosed by clinicians at start of oral anticoagulant therapy. Comorbidity not assessed.	Low/intermediate Risk Same assessment of QoL questionnaires in both groups. Assessment setting not described. Similar completion rate for both groups. More female patients with noncompleted QoL questionnaires in control group. Difference in QoL score only assessed within but not between groups.	High Risk No adjustment for confounding factors.	High Risk The study did not aim to specifically compare sex differences in QoL between AF and control group. Sources of bias poorly reported.
Hoegh et al (2016)[10]	Low Risk Same source population (general population without cancer), same recruitment method and same participation rate (28%) for both groups.	Intermediate/Low Risk Registry- based AF diagnosis. Validity of AF diagnosis addressed. Potential differing time since AF diagnosis to QoL assessment was addressed.	Low Risk Same method for QoL questionnaire assessment and assessment setting for all participants. Same proportion of missing completions in both groups. Sex-specific missing completions not reported. Difference in QoL score between groups calculated, and MID discussed.	Low Risk Analyses adjusted for age and comorbidity.	Low Risk The study aimed to compare QoL in AF population with the general population in strata by sex. Excellent design. Satisfactory identification and handling of bias.

Continued

Table 6. Continued

Studies	Selection Bias	Information Bias of Exposure and Confounders	Information Bias of Outcome	Bias Due to Confounding	Evaluation and Overall Risk of Bias
Studies comparing QoL in AF patients vs a normal population/ control population in strata by sex	Systematic differences among groups regarding source population, recruitment strategy from source population, and participation rate.	Systematic differences among groups in how the exposure (AF status or control status) or confounders (age, comorbidity) were assessed.	Systematic differences among groups in how outcome (QoL) was measured (setting for filling out questionnaire) and questionnaire data were reported, handled and evaluated (complement rate for QoL questionnaires, method for missing responses, addressing of effect size for difference in QoL among groups).	Relevant confoundersidentified (age, comorbidity) and handled properly in analysis (such as adjusting or stratification).	Proper design to assess differences in QoL in an AF vs control population in strata by sex. Ability to consider bias and evaluation of bias.
Hendriks et al (2014)[23]	High Risk Different source populations. Newly diagnosed AF patients enrolled in RCT study vs population-based normative database. Participation rate not clearly reported for any of the groups.	Intermediate Risk Clinically confirmed AF. Comorbidity and age assessed only in the AF group.	Unknown Questionnaire assessment, assessment setting, and missing questionnaire completions reported only for the AF group. Difference in QoL score between groups not calculated.	High Risk Confounding factors not adjusted for.	High Risk Comparison of sex differences in QoL between AF and a normal population was not the main aim of the study. Sources of bias poorly reported.
Henry et al (2013)[29]	High Risk Different source populations. AF-population underwent ablation. Compared with age- and sex-stratified population-based normative data.	Low Risk Clinically confirmed AF. Comorbidity only assessed in AF group.	Unknown/Intermediate Risk Questionnaire assessment and assessment setting only reported for AF group. Missing completions of questionnaires not clearly specified. Difference in QoL score between groups addressed.	Low/Intermediate Risk Probably similar age range in both groups. Outcome assessed within sex strata for both groups. Adjustment for comorbidity not specified.	Intermediate/High Risk Comparison of sex differences in QoL between AF and a normal population was not the main aim of the study. Sources of bias poorly reported but addressed.
Rienstra et al (2005)[30]	Unknown/High Risk Different source populations. AF patients enrolled in RCT compared with age-matched controls from general population. Inclusion in control group not specified. Participation rate not clearly reported for any of the groups.	High Risk Clinically confirmed AF. Comorbidity assessed only in AF group.	Unknown/High Risk Questionnaire assessment, assessment setting, and missing questionnaire completions not reported in any group. Difference in QoL score between groups addressed.	High Risk Similar age range in both groups. Outcome assessed within sex strata for both groups. Adjustment for comorbidity not specified.	Intermediate/High Risk Comparison of sex differences in QoL between AF and a normal population was not the main aim of the study. Sources of bias poorly reported but addressed.

Continued

DOI: 10.1161/JAHA.118.010992

Table 6. Continued

Studies	Selection Bias	Information Bias of Exposure and Confounders	Information Bias of Outcome	Bias Due to Confounding	Evaluation and Overall Risk of Bias
Studies comparing QoL in AF patients vs a normal population/ control population in strata by sex	Systematic differences among groups regarding source population, recruitment strategy from source population, and participation rate.	Systematic differences among groups in how the exposure (AF status or control status) or confounders (age, comorbidity) were assessed.	Systematic differences among groups in how outcome (QoL) was measured (setting for filling out questionnaire) and questionnaire data were reported, handled and evaluated (complement rate for QoL questionnaires, method for missing responses, addressing of effect size for difference in QoL among groups).	Relevant confoundersidentified (age, comorbidity) and handled properly in analysis (such as adjusting or stratification).	Proper design to assess differences in QoL in an AF vs control population in strata by sex. Ability to consider bias and evaluation of bias.
Paquette et al (2000)[31]	High Risk Different source populations. Consecutive AF outpatients were compared with a population-based normative database. Participation rate not clearly reported for any of the groups.	High Risk Clinically confirmed AF. Comorbidity assessed only in AF group.	Unknown/Intermediate Questionnaire assessment and assessment setting not reported in any group. Missing questionnaire completions reported only for AF group. Difference in QoL score between groups calculated.	Low/Intermediate Age matching. Outcome assessed within sex strata for both groups. No adjustment for comorbidity.	Intermediate Risk The study aimed to compare QoL in AF population with the general population in strata by sex. Sources of bias poorly reported, but addressed.
Berger et al (2016)[35]	High Risk Different source populations. AF patients who underwent pulmonary vein isolation were compared with a population-based normative database. Participation rate not clearly reported for any of the groups.	Low Risk Clinically confirmed AF. Comorbidity assessed only in AF group.	Unknown/Intermediate Questionnaire assessment, assessment setting, and missing questionnaire completions not reported in either group. Difference in QoL score between groups calculated.	High Risk Confounding factors not adjusted for.	High Risk The study did not aim to compare sex differences between AF patients and the general population. Sources of bias poorly reported.
Ong et al (2006)[37]	High Risk Different source populations. A convenience sample of AF patients from tertiary care clinics was compared with age-matched population-based normative data. Participation rate not clearly reported for any of the groups.	Intermediate Risk Clinically confirmed AF. Comorbidity assessed only in AF group.	Low/Intermediate Risk Questionnaire assessment and questionnaire completions reported only for AF group. Difference in QoL score between groups addressed but poorly quantified.	Low/Intermediate Risk Age matching. Outcome addressed within sex strata for both groups. No adjustment for comorbidity.	Intermediate/High Risk Comparison of differences in QoL between AF and a normal population was not the main aim of the study. Sources of bias poorly reported but addressed.

AF indicates atrial fibrillation; QoL, quality of life; MID, minimal important difference; RCT, randomized controlled trial.

DOI: 10.1161/JAHA.118.010992

PCS of 2 score points.[10] Also, in the study by Roalfe et al the between-sex difference in QoL relative to normative data was 1.9 MCS score units poorer in women and below the MID.[21] These results both support the fact that AF has a relatively greater impact on physical QoL in women than in men but that this reduction in QoL may be too small to have clinical relevance. The interventional studies included in this review (Table 4) show an improvement in QoL in both sexes, independent of the type of intervention. Henry et al found that female AF patients who underwent Cox-maze surgery for AF had a relatively greater improvement in PCS and even surpassed their age and sex norms, whereas male AF patients improved to the norm level.[29] Paquette et al revealed a similar trend, with female AF patients improving more in PCS than did male patients. However, there is no clear trend suggesting more improvement after intervention in female compared with male AF patients.

It is important to note that only 1 of the studies included in this review compared sex differences in their AF population with sex differences in non-AF patients recruited in the same way from the same source population[10] (Table 5). A few studies compared their AF population with a control group[10,11,30] to normative values from a database[21,23,29,31,35,37] or to reference values from other publications,[9,22,27] and selection bias may be present because inclusion into these studies may differ from that of the comparator population. This comparison is important to clarify if the sex difference seen in QoL in AF patients is due to the disease per se, but such clarification may be difficult, particularly in interventional studies.

The major limitation of this review is that very few authors have focused on sex differences in QoL in AF compared with sex differences in QoL in a control group. Even though some studies used normative data or a control group, their data are not always age or sex adjusted. As shown in Table 6, even the most relevant studies had an intermediate to high risk of bias. Only 1 study provided the optimal design: to select reference participants from the same source population as the AF patients.[10]

In addition, the majority of the studies did not distinguish among the various forms of AF and used different inclusion criteria. Samples from different AF populations were also used, mainly from either primary-care or from tertiary-care units. This makes it difficult to generalize the results because the majority of the patients referred to tertiary clinics have a greater sickness burden than the average AF patient. It is also noteworthy that age adjustment for QoL often is not clearly described. Women with AF are generally older with more comorbidity, and age adjustment is therefore essential. Despite equal numbers of male and female AF patients, men tend to be overrepresented in the clinical studies. The limitations listed above make it hard to draw a conclusion as to whether female AF patients fare worse than male patients compared with the sex differences in the general population.

In conclusion, the present review demonstrates that women consistently report lower QoL, both in AF and in the general population. So far, the evidence slightly supports the hypothesis that women's QoL is more affected by AF than is the case in men. At present, however, it is questionable whether the relatively poorer QoL in women is large enough to be of clinical importance.

Disclosures

None.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
2. Humphries KH, Kerr CR, Connolly SJ, Klein G, Boone JA, Green M, Sheldon R, Talajic M, Dorian P, Newman D. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. *Circulation*. 2001;103:2365–2370.
3. Anselmino M, Battaglia A, Gallo C, Gili S, Matta M, Castagno D, Ferraris F, Giustetto C, Gaita F. Atrial fibrillation and female sex. *J Cardiovasc Med*. 2015;16:795–801.
4. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S, Kremastinos DT, Breithardt G, Cokkinos DV, Crijns HJ. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol*. 2007;49:572–577.
5. Tomita H, Hagii J, Metoki N, Saito S, Shiroto H, Hitomi H, Kamada T, Seino S, Takahashi K, Baba Y, Sasaki S, Uchizawa T, Iwata M, Matsumoto S, Shoji Y, Tanno T, Osanai T, Yasujima M, Okumura K. Impact of sex difference on severity and functional outcome in patients with cardioembolic stroke. *J Stroke Cerebrovasc Dis*. 2015;24:2613–2618.
6. Gillis AM. Atrial fibrillation and ventricular arrhythmias: sex differences in electrophysiology, epidemiology, clinical presentation, and clinical outcomes. *Circulation*. 2017;135:593–608.
7. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119:448.e1–448.e19.
8. Lane DA, Langman CM, Lip GY, Nouwen A. Illness perceptions, affective response, and health-related quality of life in patients with atrial fibrillation. *J Psychosom Res*. 2009;66:203–210.
9. Tsounis D, Ioannidis A, Bouras G, Raikou M, Giannopoulos G, Deftereos S, Kossyvakis C, Toutouzas K, Tousoulis D, Synetos A, Pyrgakis V, Niakas D, Stefanadis C. Assessment of health-related quality of life in a Greek symptomatic population with atrial fibrillation: correlation with functional status and echocardiographic indices. *Hellenic J Cardiol*. 2014;55:475–485.
10. Hoegh V, Lundbye-Christensen S, Delmar C, Frederiksen K, Riahi S, Overvad K. Association between the diagnosis of atrial fibrillation and aspects of health status: a Danish cross-sectional study. *Scand J Caring Sci*. 2016;30:507–517.
11. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, Daly AK, Manolopoulos VG, Wadelius M, Bouvy M, Maitland-van der Zee AH. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. *Thromb Res*. 2015;136:69–75.
12. Ong L, Cribbie R, Harris L, Dorian P, Newman D, Mangat I, Nolan R, Irvine J. Psychological correlates of quality of life in atrial fibrillation. *Qual Life Res*. 2006;15:1323–1333.
13. Sears SF, Serber ER, Alvarez LG, Schwartzman DS, Hoyt RH, Ujhelyi MR. Understanding atrial symptom reports: objective versus subjective predictors. *Pacing Clin Electrophysiol*. 2005;28:801–807.
14. Lioni L, Vlachos K, Letsas KP, Efremidis M, Karlis D, Asvestas D, Kareliotis V, Xydonas S, Dimopoulos N, Korantzopoulos P, Trikas A, Sideris A. Differences in quality of life, anxiety and depression in patients with paroxysmal atrial fibrillation and common forms of atrioventricular reentry supraventricular tachycardias. *Indian Pacing Electrophysiol J*. 2014;14:250–257.

15. Groenveld HF, Crijns HJ, Van den Berg MP, Van Sonderen E, Alings AM, Tijssen JG, Hillege HL, Tuininga YS, Van Veldhuisen DJ, Ranchor AV, Van Gelder IC. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. *J Am Coll Cardiol*. 2011;58:1795–1803.
16. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest*. 2007;132:1259–1264.
17. Arribas F, Ormaetxe JM, Peinado R, Perulero N, Ramirez P, Badia X. Validation of the AF-QoL, a disease-specific quality of life questionnaire for patients with atrial fibrillation. *Europace*. 2010;12:364–370.
18. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace*. 2014;16:965–972.
19. Akintade BF, Chapa D, Friedmann E, Thomas SA. The influence of depression and anxiety symptoms on health-related quality of life in patients with atrial fibrillation and atrial flutter. *J Cardiovasc Nurs*. 2015;30:66–73.
20. Koci F, Forbes P, Mansour MC, Heist EK, Singh JP, Ellinor PT, Ruskin JN. New classification scheme for atrial fibrillation symptom severity and burden. *Am J Cardiol*. 2014;114:260–265.
21. Roalfe AK, Bryant TL, Davies MH, Hackett TG, Saba S, Fletcher K, Lip GY, Hobbs FD, Mant J. A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study. *Europace*. 2012;14:1420–1427.
22. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse Events and Lifestyle (FRACTAL) study. *Am Heart J*. 2006;152:1097–1103.
23. Hendriks JM, Vrijhoef HJ, Crijns HJ, Brunner-La Rocca HP. The effect of a nurse-led integrated chronic care approach on quality of life in patients with atrial fibrillation. *Europace*. 2014;16:491–499.
24. Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V, Clementi F, Fagundes RL, Leo R, Romeo F, Mantica M. Gender-related differences in catheter ablation of atrial fibrillation. *Europace*. 2007;9:613–620.
25. Kang Y. Gender and culture differences in the quality of life among Americans and Koreans with atrial fibrillation. *Nurs Health Sci*. 2009;11:301–305.
26. Jeong HK, Cho JG, Lee KH, Park HW, Kim MR, Lee KJ, Jang SY, Park KH, Sim DS, Yoon NS, Yoon HJ, Kim KH, Hong YJ, Kim JH, Ahn Y, Jeong MH, Park JC. Determinants of quality of life in patients with atrial fibrillation. *Int J Cardiol*. 2014;172:e300–e302.
27. Sandhu RK, Smigorowsky M, Lockwood E, Savu A, Kaul P, McAlister FA. Impact of electrical cardioversion on quality of life for the treatment of atrial fibrillation. *Can J Cardiol*. 2017;33:450–455.
28. Goette A, Benninger G, Pittrow D, Paar WD, von Stritzky B, Bosch RF. One-year safety and quality of life outcomes in patients with atrial fibrillation on dronedarone: prospective, non-interventional study in German ambulatory care. *Herzschrittmacherther Elektrophysiol*. 2015;26:148–154.
29. Henry L, Hunt S, Holmes SD, Martin LM, Ad N. Are there gender differences in outcomes after the Cox-Maze procedure for atrial fibrillation? *Innovations (Phila)*. 2013;8:190–198.
30. Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, Van Gelder IC. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *J Am Coll Cardiol*. 2005;46:1298–1306.
31. Paquette M, Roy D, Talajic M, Newman D, Couturier A, Yang C, Dorian P. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *Am J Cardiol*. 2000;86:764–768.
32. Pavelkova Z, Bulava A. Nursing and quality of life in patients with atrial fibrillation before and after radiofrequency ablation. *Neuro Endocrinol Lett*. 2014;35(suppl 1):49–53.
33. Wagner MK, Zwisler A-DO, Risom SS, Svendsen JH, Christensen AV, Berg SK. Sex differences in health status and rehabilitation outcomes in patients with atrial fibrillation treated with ablation: results from the CopenHeartRFA trial. *Eur J Cardiovasc Nurs*. 2017;17:123–135.
34. Fiala M, Bulkova V, Sknouril L, Nevralova R, Toman O, Januska J, Spinar J, Wichterle D. Functional improvement after successful catheter ablation for long-standing persistent atrial fibrillation. *Europace*. 2017;19:1781–1789.
35. Berger WR, Krul SP, van der Pol JA, van Dessel PF, Conrath CE, Wilde AA, de Groot JR. Documented atrial fibrillation recurrences after pulmonary vein isolation are associated with diminished quality of life. *J Cardiovasc Med*. 2016;17:201–208.
36. Maryniak A, Walczak F, Bodalski R, Szumowski L, Derejko P, Urbanek P, Orczykowski M, Szufladowicz E. Atrial fibrillation onset circumstances and their relation to patients' quality of life. *Kardiol Pol*. 2006;64:1102–1109.
37. Ong L, Irvine J, Nolan R, Cribbie R, Harris L, Newman D, Mangat I, Dorian P. Gender differences and quality of life in atrial fibrillation: the mediating role of depression. *J Psychosom Res*. 2006;61:769–774.
38. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ*. 1993;306:1437–1440.
39. Audureau E, Rican S, Coste J. Worsening trends and increasing disparities in health-related quality of life: evidence from two French population-based cross-sectional surveys, 1995–2003. *Qual Life Res*. 2013;22:13–26.
40. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51:1055–1068.
41. Konig HH, Heider D, Lehnert T, Riedel-Heller SG, Angermeyer MC, Matschinger H, Vilagut G, Bruffaerts R, Haro JM, de Girolamo G, de Graaf R, Kovess V, Alonso J. Health status of the advanced elderly in six European countries: results from a representative survey using EQ-5D and SF-12. *Health Qual Life Outcomes*. 2010;8:143.
42. Bernert S, Fernandez A, Haro JM, Konig HH, Alonso J, Vilagut G, Sevilla-Dedieu C, de Graaf R, Matschinger H, Heider D, Angermeyer MC. Comparison of different valuation methods for population health status measured by the EQ-5D in three European countries. *Value Health*. 2009;12:750–758.
43. Kontodimopoulos N, Pappa E, Niakas D, Yfantopoulos J, Dimitrakaki C, Tountas Y. Validity of the EuroQoL (EQ-5D) instrument in a Greek general population. *Value Health*. 2008;11:1162–1169.
44. Cherepanov D, Palta M, Fryback DG, Robert SA. Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. *Qual Life Res*. 2010;19:1115–1124.
45. Garratt AM, Stavem K. Measurement properties and normative data for the Norwegian SF-36: results from a general population survey. *Health Qual Life Outcomes*. 2017;15:51.
46. van Wijk CM, Kolk AM. Sex differences in physical symptoms: the contribution of symptom perception theory. *Soc Sci Med*. 1997;45:231–246.
47. Williams JB, Spitzer RL, Linzer M, Kroenke K, Hahn SR, deGruy FV, Lazev A. Gender differences in depression in primary care. *Am J Obstet Gynecol*. 1995;173:654–659.
48. Stordal E, Bjartveit Kruger M, Dahl NH, Kruger O, Mykletun A, Dahl AA. Depression in relation to age and gender in the general population: the Nord-Trondelag Health Study (HUNT). *Acta Psychiatr Scand*. 2001;104:210–216.
49. Gottlieb SS, Khatta M, Friedmann E, Einbinder L, Katzen S, Baker B, Marshall J, Minshall S, Robinson S, Fisher ML, Potenza M, Sigler B, Baldwin C, Thomas SA. The influence of age, gender, and race on the prevalence of depression in heart failure patients. *J Am Coll Cardiol*. 2004;43:1542–1549.
50. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA*. 2003;290:215–221.