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Factors Predicting Arrhythmia-Related Symptoms and Health-Related Quality of Life in Patients Referred for Radiofrequency Ablation of Atrial Fibrillation

An Observational Study (the SMURF Study)

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ABSTRACT

OBJECTIVES The purpose of this study was to correlate the arrhythmia-related symptoms and health-related quality of life (HRQoL) in patients with atrial fibrillation (AF) who are eligible for radiofrequency ablation (RFA) with a number of objective indicators.

BACKGROUND Although the clinical consequences of AF have been studied extensively, the variation in the symptoms of patients with AF and HRQoL remains under-researched.

METHODS We studied 192 patients eligible for RFA of AF referred to the University Hospital, Linköping, Sweden, between January 2012 and April 2014. The ASTA (Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia) symptom scale was used to assess arrhythmia-related symptoms in the patients. The ASTA HRQoL scale and the short-form 36 (SF-36) physical and mental components summaries (PCS and MCS) were used to express disease-specific and overall HRQoL of the patients, respectively.

RESULTS Anxiety, low-grade inflammation, and left atrial dilatation significantly predicted arrhythmia-related symptoms ($R^2 = 0.313$; $p < 0.001$). Depression was the most important predictor of arrhythmia-specific HRQoL (standardized beta: 0 .406), and the produced model explained a significant proportion of the variation in arrhythmia-specific HRQoL ($R^2 = 0.513$; $p < 0.001$). The most important predictor of PCS was obesity (body mass index >30 kg/m^2) (standardized beta: −0.301), whereas the most important predictor of MCS was anxiety (standardized beta: −0.437).

CONCLUSIONS Anxiety, depression, and low-grade inflammation were the factors that predicted both arrhythmia-related symptoms and HRQoL in patients with AF. Obesity was the most significant predictor of patient general physical status. These factors need to be addressed in patients with AF to improve management of their disease. Intensive risk factor modification can be of great importance. (Reasons for Variations in Health Related Quality of Life and Symptom Burden in Patients With Atrial Fibrillation [SMURF]; NCT01553045) (J Am Coll Cardiol EP 2017;3:494–502)

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is estimated to affect at least 2.9% of the Swedish population (1). AF is associated with increased mortality, increased risk of cerebral thromboembolism, and development of heart failure (2).

The prevalence and the clinical consequences of AF have been studied extensively, but less is known concerning symptoms and health-related quality of life (HRQoL) (3). The most commonly reported symptoms in AF are palpitations, breathlessness during activity, tiredness, and worry/anxiety (4). In the same context, one third of patients with AF have been described as "asymptomatic" (5); however, both categories have experienced reduced HRQoL (3).

A number of studies attempted to explain the variation in AF-related symptoms. There were studies that showed a relationship between perceived symptom burden and rhythm control, AF episode duration, ventricular rate, personality, and sex (6–8). In contrast, another study failed to show that AF characteristics could predict the severity of symptoms of AF (9). Thus, the available data could not fully explain the variation in patients' symptoms and HRQoL.

The aim of this study considered the variety of arrhythmia-related symptoms and HRQoL in patients with AF who were eligible for radiofrequency ablation (RFA) as measured by patient-reported outcome measures, and to correlate these with indicators, such as biomarkers, echocardiographic data, hemodynamics, AF episode frequency and duration, anxiety and depression, obesity, and other comorbidities (10).

METHODS

STUDY DESIGN AND SETTINGS. This was an observational, single-center cohort study conducted between January 2012 and April 2014. Patients referred for RFA due to AF, to the University Hospital in Linköping, Sweden, were considered for participation. The inclusion criteria were: 1) age 18 years or older with paroxysmal or persistent AF; 2) patients referred for first time RFA; and 3) patients with sufficient knowledge of the Swedish language to fill out the study questionnaires independently.

Exclusion criteria were: 1) patients who had previously undergone catheter or surgical AF ablation; 2) patients with previous or expected heart surgery; 3) patients with severe HF with left ventricular ejection fraction (EF) <35%; or 4) patients with acute coronary syndrome during the past 3 months. The protocol of the study was previously published (10).

INFORMED CONSENT AND ETHICAL CONSIDERATIONS. The Regional Ethical Review Board of the Faculty of Health Sciences, Linköping, Sweden, approved the protocol for this study. All patients gave their written consent, and the study complied with the Declaration of Helsinki (11).

PATIENT-REPORTED OUTCOME MEASURES. Patient-reported outcome measures were assessed with 3 previously described questionnaires (10).

The 36-item short-form health survey. The 36-Item Short-Form Health Survey (SF-36) is a generic questionnaire designed to measure an individual's physical and mental health. It comprises 35 items grouped into 8 scales and 1 question outside the scales (12). The 8 scales are summarized in physical and mental component summaries (PCS and MCS, respectively). PCS and MCS are standardized to a norm, with a mean of 50 ± 10. Scores >50 indicate better PCS and MCS scores compared with the norm, whereas lower scores represent worse PCS and MCS scores (13).

The arrhythmia-specific questionnaire in tachycardia and arrhythmia. The disease-specific questionnaire Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) is a validated questionnaire (14,15) divided into 3 separate parts. Part I evaluates the patient's latest episode of arrhythmia and current medication. Part II assesses symptom burden, including a 9-item symptom scale with a 4-point response scale (ASTA symptom scale) (15). Outside of the symptom scale, there are questions with regard to the frequency of arrhythmia episodes, the average and the longest duration of an arrhythmia episode, and experience of near syncope, syncope, and palpitations in connection with arrhythmias. Part III assesses HRQoL with a 13-item scale, with the same 4-point response scale (ASTA HRQoL scale) as for the symptom scale (14). The ASTA HRQoL scale is divided into a 7-item physical subscale and a 6-item mental subscale. Values range from 0 to 100 and higher scores reflect a higher symptom burden and a worse effect on HRQoL due to the arrhythmia (14,15).

Hospital anxiety and depression scale. The Hospital Anxiety and Depression Scale (HADS) questionnaire consists of 2 subscales, in which anxiety is assessed with 7 questions (HADS-A) and depression with another 7 questions (HADS-D). Responses are scored on a scale of 0 to 3, with higher scores denoting more psychological distress. The score for each

ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

HADS = Hospital Anxiety and Depression Scale

hsCRP = high-sensitivity C-reactive protein

IQR = interquartile range

LA = left atrial

LAV = left atrial volume

MCS = Mental Component Summary of Short-Form 36

MR-proADM = mid-regional portion of pro-adrenomedullin

NT-proBNP = N-terminal pro–B-type natriuretic peptide

PCS = Physical Component Summary of Short-Form 36

RFA = radiofrequency ablation

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

subscale can range from 0 as the lowest to a maximum score of 21. Anxiety and depression severity was categorized as normal: HADS-A: 0 to 7; HADS-D: 0 to 7; possible HADS-A: 8 to 10; HADS-D: 8 to 10; and probable HADS-A: ≥11 and HADS-D: ≥11 (16,17).

ECHOCARDIOGRAPHY. All patients underwent transthoracic and transesophageal echocardiographic examinations (TTE and TEE) before RFA. GE Vivid 7 or GE Vivid E9 system (GE Healthcare, Horten, Norway) was used with a 3.5-MHz transducer for TTE and a 7-MHz transducer for TEE. The measurements and evaluations were performed according to the guidelines of the European Society of Echocardiography (18).

The left atrial volume (LAV) was measured using the biplane area-length method and corrected for body surface area. The left ventricular EF was calculated according to Simpson's biplane method.

BIOMARKERS. The concentrations of the N-terminal pro–B-type natriuretic peptide (NT-proBNP) and mid-regional portion of pro-adrenomedullin (MR-proADM) were measured as previously described (19).

The high-sensitivity C-reactive protein (hsCRP) analysis was performed using the wide range C-reactive protein immunoturbidimetric assay on the ADVIA 1650 system (Siemens Healthcare Gmbh, Erlangen, Germany). The total coefficient of variation was 5.35% at 0.9 mg/l and 1.17% at 12.3 mg/l. The detection limit was 0.12 mg/l, and patients with concentrations >3 mg/l were considered to have a low-grade inflammation (2 to 4 times higher than the normal value) and to be at high cardiovascular risk (20).

PRESSURE MEASUREMENTS. The sagittal thoracic diameter was measured in the fourth intercostal space, and the reference pressure (zero level) was placed in the middle of this diameter. The systolic and diastolic pressures in the right ventricle were measured using a multipurpose high flow 5-F catheter (MR A1, Cordis, Miami, Florida). The pressures were recorded at least for 15 s and stored for offline analysis (EP-WorkMate, St. Jude Medical, Saint Paul, Minnesota).

ENDPOINTS. The primary endpoints concern the possible correlation between arrhythmia-related symptoms and HRQoL, with 1 or several factors measured in the SMURF (Reasons for Variations in Health Related Quality of Life and Symptom Burden in Patients With Atrial Fibrillation) study. Examples of these factors are the levels of the 3 biomarkers (NT-proBNP and MR-proADM, and hsCRP), right ventricular pressure, left atrial (LA) dilatation, obesity, AF episode frequency and duration, anxiety and depression, and other comorbidities.

SUBJECT MEASUREMENTS. The subject measurements were described previously (10). All patients were asked to fill out the ASTA, SF-36, and HADS questionnaires. They underwent TTE and TEE according to the clinical routine.

Patients were catheterized, blood samples for the analysis of biomarkers (NT-proBNP, MR-proADM, and hsCRP) were drawn from a peripheral vein, and intracardiac pressures were recorded before the RFA.

STATISTICAL METHODS. For baseline data, continuous variables were expressed as mean ± SD. Variables, not normally distributed, were presented as median (25th, 75th percentile). Categorical data were presented as counts with percentages. Patients with missing values were excluded from the planned analyses.

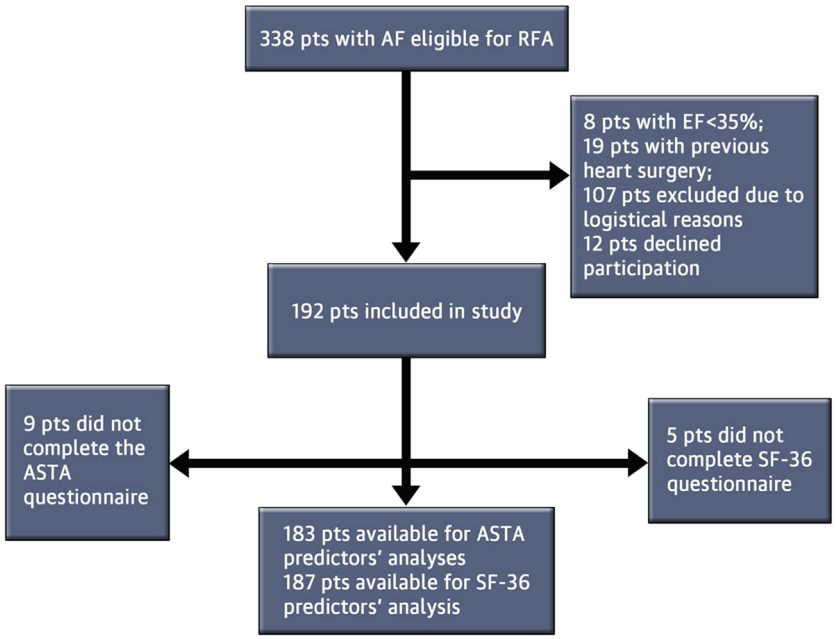
Multiple linear regression analysis was performed to determine possible predictors of arrhythmia-related symptoms and HRQoL. The ASTA symptom scale score was used as a dependent variable to assess arrhythmia-related symptoms in the patients. The disease-specific ASTA HRQoL scale score and the PCS and MCS were used as dependent variables to assess patients' HRQoL. The independent predictors used in the analyses were NT-proBNP, MR-proADM, low-grade inflammation (hsCRP >3 mg/l), the right ventricular systolic and diastolic pressures, left atrial dilatation (body surface area indexed LAV >35 ml/m^2), HF (EF <45%), obesity (body mass index >30 kg/m^2), anxiety and depression (accessed by the HADS questionnaire), CHA_2DS_2 VASc score ≥2 (2), age, frequency of AF episodes (>10 episodes of AF the last month before RFA), and AF episode duration (max AF episode duration >1 h in the last month before RFA). The models were fit by an enter method, in which all variables were entered into the original model and then variables with p values of 0.05 were removed.

All reported p values were 2-sided, and a p value < 0.05 was considered statistically significant. The analyses were performed using SPSS version 24.0 (IBM, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. In total, 192 patients with AF were referred to the Department of Cardiology, University Hospital in Linköping, Sweden between January 2012 and April 2014, and were eligible for the study. Of those, 9 did not complete the ASTA

FIGURE 1 Study Inclusion Flowchart



Study flowchart. AF = atrial fibrillation; ASTA = Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; EF = ejection fraction; pts = patients; RFA = radiofrequency ablation; SF-36 = 36-Item Short-Form Health Survey.

and 5 did not complete the SF-36 questionnaire (Figure 1). In total, 39 patients reported episodes of AF with a maximum duration of >1 h, and 77 patients had >10 episodes in the last month before the RFA. Fifty-five patients (30%) had possible or probable anxiety, and 33 (18%) had possible or probable depression as indicated by the HADS questionnaire. There were no differences in the frequency of possible and probable anxiety and depression between women and men (depression frequency: $p = 0.276$; anxiety frequency: $p = 0.763$). The baseline characteristics are presented in Table 1.

ARRHYTHMIA-RELATED SYMPTOMS: ASTA SYMPTOM SCALE. The patients were asked about experience of palpitations, and of the 183 patients, 126 (69%) reported the heart beating rapidly, and 151 (83%) reported the heart beating irregularly. The 2 most commonly reported symptoms were breathlessness during activity and tiredness (Figure 2). The median ASTA symptom scale score was 37 (26 to 52) (Table 2).

Anxiety, low-grade inflammation, and LA dilatation significantly predicted arrhythmia-related symptoms (probable anxiety standardized beta: 0.5; $p < 0.001$; possible anxiety standardized beta: 0.233; $p = 0.001$; low-grade inflammation standardized beta: 0.211; $p = 0.002$; and LA dilatation standardized beta: 0.141; $p = 0.033$). These factors explained a significant proportion of the variation in arrhythmia-related symptoms ($R^2 = 0.313$; $F = 18.303$; $p < 0.001$) (Table 3, Figure 3).

HEALTH-RELATED QUALITY OF LIFE. ASTA HRQoL scale. The median reported ASTA HRQoL scale score, for the total scale was 36 (23 to 51), whereas the median score of the physical subscale was 38 (24 to 57), and the median score of the mental subscale was 28 (17 to 44) (Table 2).

Symptoms of anxiety and depression, as well as low-grade inflammation, age, HF, MR-proADM, and AF episode duration significantly predicted arrhythmia-specific HRQoL in the patients. The most important predictor was depression (probable depression standardized beta: 0.406; $p < 0.001$). These factors explained a significant proportion of variation in arrhythmia-specific HRQoL ($R^2 = 0.513$; $F = 18.696$; $p < 0.001$) (Table 3).

The 36-item short-form health survey. The median reported PCS score was 41.1 (34.3 to 50.7), whereas the median reported MCS score was 47.6 (36.5 to 55.0) (Table 2).

TABLE 1 Baseline Characteristics

Age, yrs (mean)	60.5 ± 10.2
Female	56 (29)
BMI (kg/m^2)	27.4 (24.8, 30.5)
Paroxysmal AF	71 (37)
Hypertension	80 (42)
Diabetes mellitus	15 (8)
Heart failure	17 (9)
CKD (GFR <60 ml/min/1.73 m^2)	40 (20)
Stroke/TIA	19 (10)
CHA_2DS_2VASc	2 (0 to 3)
Beta-blocker	139 (73)
AAD	105 (55)
Amiodarone	42 (22)
Flecainide	35 (18)
Dronedarone	23 (12)
ACEi or ARB	77 (49)
AF at the ablation lab	51 (27)
Statins	56 (30)
Complications*	7 (4)
EF <45%	25 (13)
LA volume/BSA (ml/m^2)	26.6 (22.3, 32.5)
E/E′	11.9 (8.9, 15.1)
RVSP (mm Hg)	30 (26, 34)
RVDP (mm Hg)	11 (9, 15)
NT-proBNP (pg/ml)	170 (71.2, 499.5)
MR-proADM (pmol/l)	0.682 ± 0.184
hsCRP >3 mg/l	44 (23)
Anxiety (n = 185)	
Possible anxiety	35 (19)
Probable anxiety	20 (11)
Depression (n = 188)	
Possible depression	18 (10)
Probable depression	15 (8)

Values are mean ± SD, n (%), or median (25th, 75th percentile). Baseline data are presented for all available patients (N = 192) unless otherwise stated. *Reported complications were cardiac tamponade (1%), pericardial effusion (0.5%), pseudoaneurysm (1.6%), and larger than normal hematoma of the groin (0.5%).

AAD = antiarrhythmic drugs; ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; BSA = body surface area; CKD = chronic kidney failure; DC = direct current; EF = ejection fraction; hsCRP = high-sensitivity C-reactive protein; GFR = glomerular filtration rate; LA = left atrium; MR-proADM = mid-regional portion of pro-adrenomedullin; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RVDP = right ventricular diastolic pressure; RVSP = right ventricular systolic pressure; SVT = supraventricular tachycardia; TIA = transient ischemic attack.

The factors that significantly predicted patients' PCS were: obesity, right ventricular diastolic pressure, AF episode frequency, CHA_2DS_2 VASc score ≥2, low-grade inflammation, and depression. The most important predictor was obesity (standardized beta: −0.301; $p < 0.001$). These factors explained a significant proportion of variation in PCS ($R^2 = 0.359$; $F = 12.699$; $p < 0.001$) (Table 3).

Finally, the factors that significantly predicted MCS were anxiety and depression, as well as AF episodes >1 h in duration. The most important predictor was anxiety (probable anxiety standardized beta: −0.437; $p < 0.001$). These factors explained a significant proportion of MCS variance ($R^2 = 0.568$; $F = 43.367$; $p < 0.001$) (Table 3).

DISCUSSION

We examined the role of different factors on arrhythmia-related symptoms and HRQoL in patients who were eligible for RFA. The most important findings were: 1) a significant proportion of symptoms and perception of HRQoL were explained by different indicators; 2) anxiety was the most important predictor of arrhythmia-related symptoms; 3) obesity had a central role in explaining the physical component of patients' general QoL; and 4) psychological factors (anxiety and depression) and low-grade inflammation were proven to have a central role in arrhythmia-related symptoms and HRQoL.

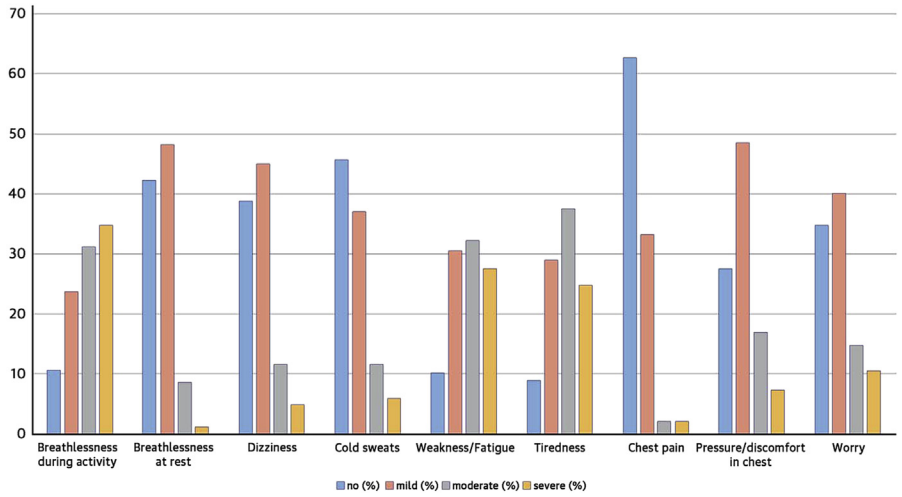
ARRHYTHMIA-RELATED SYMPTOMS. We found anxiety, low-grade inflammation, and LA dilatation significantly predicted arrhythmia-related symptoms.

Anxiety and arrhythmia-related symptoms. Although symptoms have been proven unreliable in predicting AF presence and burden, they can affect HRQoL negatively (21); thus, they remain useful tools for diagnosis and treatment of AF (2,5). Hence, the explanation of symptom variance is of great importance.

We found anxiety to be the strongest predictor of arrhythmia-related symptoms. Several studies demonstrated a strong correlation between AF symptoms and anxiety (17,22), although it was unclear whether anxiety was the cause of AF-related symptoms or the result of AF. Although antiarrhythmic drugs and catheter ablation significantly improved symptoms (4), they did not have any effect on symptoms of anxiety and depression when adjusted for confounders (17). Thus, more comprehensive symptom relief (i.e., treatment of both AF and physiological comorbidities) may be beneficial (17).

Low-grade inflammation and arrhythmia-related symptoms. In our study, low-grade inflammation was found to predict some of the variation in symptoms. Low-grade inflammation has been linked to a variety of cardiovascular conditions, including AF (23). Nevertheless, it is unclear whether inflammation is an initiator or a consequence of AF. It has been demonstrated that levels of hsCRP are higher in patients with AF compared with those in sinus rhythm, and in those with persistent AF compared with those with paroxysmal AF (24). Hence, it can be assumed that low-grade inflammation can be a marker of a

FIGURE 2 Symptoms Reported by Study Participants Before Ablation



The nine symptoms in the ASTA (Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia) symptom scale are shown on the x-axis and the percent of the symptom severity is shown on the y-axis (n = 183).

longer duration and more active disease (i.e., AF) or of the existence of other comorbidities (e.g., obesity) (25), which may explain a part of the variation in symptoms in patients with AF.

LA dilatation and arrhythmia-related symptoms. LA dilatation was a minor but significant predictor of AF symptoms. Sixty years ago, Fraser et al. (26) illustrated the relationship between LA dilatation and AF, by showing that an increased LA diameter leads to a higher incidence of AF. Furthermore, LA size was proved to increase with persistent AF (27). Hence, LA dilatation can act as a marker of AF progression and can thus be a predictor of more severe symptoms.

TABLE 2 Arrhythmia-Related Symptoms and HRQoL Measured by the ASTA and the SF-36

ASTA (n = 183)	
$ASTA_{symptom\ score}$	37 (26, 52)
$ASTA_{HRQoL\ score}$	36 (23, 51)
$ASTA_{physical\ subscale\ score}$	38 (24, 57)
$ASTA_{mental\ subscale\ score}$	28 (17, 44)
36-SF (n = 187)	
Physical functioning	75 (55, 90)
Role: physical	50 (0, 100)
Bodily pain	74 (41, 100)
General health	60 (45, 77)
Vitality	50 (30, 70)
Social functioning	75 (62.5, 100)
Role: emotional	100 (33.3, 100)
Mental health	76 (60, 88)
Physical component summary	41.1 (34.3, 50.7)
Mental component summary	47.6 (36.5, 55)

Values are median (25th, 75th percentile). The 36-Item Short form Health Survey (SF-36) weighted scores ranged between 0 and 100, in which higher scores indicate better health. Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) scores ranged between 0 and 100, where higher scores reflect a higher symptom burden and a worse effect on health-related quality of life (HRQoL).

HRQoL. Assessment of HRQoL is used for several purposes in a healthcare setting. In particular, HRQoL is relevant to the treatment of AF, and is the primary indication, together with symptom relief, for AF ablation (2). Furthermore, patients with AF have significantly reduced HRQoL compared with healthy subjects and compared with patients with coronary disease (3).

In our study, HRQoL was mainly linked to psychological factors, low-grade inflammation, and obesity.

Anxiety and/or depression and HRQoL. It was shown that one-third of patients with AF had elevated levels of depression and anxiety, whereas depression and anxiety traits emerged as significant predictors of QoL (22); these are results that concur with the results of our study. Poorer physical and mental functioning, and worse AF-related symptoms might be a result of anxiety and depression through related cognitive and behavioral processes. Perceptions of arrhythmia burden might be increased by a depressed mood, whereas disengaging from daily activities might be caused by worry and sadness (28). Another explanation could be that anxiety and depression strongly predicted the overestimation of

TABLE 3 Factors Predicting Arrhythmia-Related Symptoms and HRQoL Variation in Patients Eligible for Radiofrequency Ablation

Scales/Predictors	Standardized Beta	Predictor's p Value	Model's R^2	Model's p value
ASTA symptom scale score (n = 166)			0.313	<0.001
Anxiety				
Probable anxiety	0.50	<0.001		
Possible anxiety	0.233	0.001		
Low-grade inflammation*	0.211	0.002		
LA dilation†	0.141	0.033		
ASTA HRQoL scale score (n = 170)			0.513	<0.001
Depression				
Probable depression	0.406	<0.001		
Possible depression	0.127	0.076		
Anxiety				
Probable anxiety	0.343	<0.001		
Possible anxiety	0.288	<0.001		
Age	0.227	0.001		
MR-proADM	−0.218	0.004		
HF‡	0.156	0.011		
Low-grade inflammation*	0.15	0.012		
AF episode duration >1 h	0.131	0.026		
PCS (SF-36) (n = 167)			0.359	<0.001
Obesity§	−0.301	<0.001		
RVDP	0.244	0.001		
>10 AF episodes/month	−0.233	0.001		
CHA_2DS_2 VASc ≥2	−0.223	0.001		
Low-grade inflammation*	−0.204	0.002		
Depression				
Probable depression	−0.135	0.039		
Possible depression	−0.04	0.558		
MCS (SF-36) (n = 171)			0.568	<0.001
Anxiety				
Probable anxiety	−0.437	<0.001		
Possible anxiety	−0.23	<0.001		
Depression				
Probable depression	−0.256	<0.001		
Possible depression	−0.232	<0.001		
AF episode duration >1 h	−0.158	0.003		

Multiple linear regression analysis was performed to determine possible predictors of variation in patients' symptoms and HRQoL. The models were fit by an enter method, in which all variables were entered into the original model and then variables with p values of 0.05 were removed. ASTA symptom scale score was used as a dependent variable to express symptom variation. The disease-specific ASTA HRQoL and the generic SF-36 component summaries (PCS and MCS) were used to express the variation in HRQoL. All reported p values are 2-sided, and a p value < 0.05 was considered statistically significant. *Low-grade inflammation was defined as hsCRP >3 mg/l. †LA dilatation was defined as left atrial volume >35 ml/m^2. ‡HF was defined as EF <45%. §Obesity was defined as BMI >30 kg/m^2.

MCS = mental component summary; PCS = physical component summary; other abbreviations as in Tables 1 and 2.

the frequency and duration of AF episodes by patients with previously diagnosed AF (29), which led to misinterpretation of their AF-related symptoms.

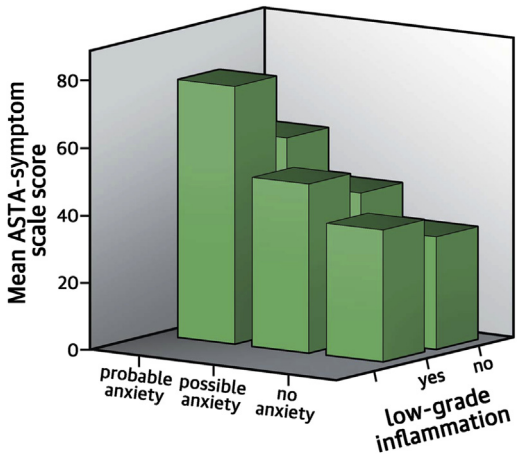
Low-grade inflammation and HRQoL. Low-grade inflammation evaluated by CRP and interleukin-6 was negatively associated with all SF-36 subscales in a randomly selected sample of middle-aged Swedish general population in a recent study by Garvin et al (30). Our results also concurred with the results by Son et al. (31), which showed that hsCRP was an independent predictor of impaired HRQoL in patients with AF.

Obesity and HRQoL. Obesity was the strongest predictor of the patient PCS. Obesity is a lifestyle factor that has been observed to contribute to AF development and progression (25). Several mechanisms have been suggested to explain the association between obesity and AF, such as impaired diastolic function, inflammation, pericardial fat, and the effect of weight loss on other established AF risk factors (25). Furthermore, obesity in a general population was shown to have an adverse impact on HRQoL among subjects with and without metabolic comorbidities (i.e., diabetes, hypertension, hypercholesterolemia, or cardiovascular disease) (32). Obese patients with AF who were eligible for catheter ablation were reported to have significantly lower HRQoL scores compared with normal weight patients, which was a result consistent with our findings concerning the link between obesity and the physical score (33). In addition, obesity has been shown to impair RFA results (33); nonetheless, HRQoL in obese patients with AF was significantly improved after catheter ablation (33). In our study, the median body mass index was 28 kg/m^2 (24.8 to 30.5), and 52 (27%) patients had a body mass index >30 kg/m^2. Hence, a more intensive weight management approach is needed to achieve better physical capacity in patients with AF.

Other predictors of HRQoL. AF episode duration of >1 h predicted MCS and arrhythmia-specific HRQoL, whereas >10 AF episodes per month predicted PCS. Our results agree with the results of Kochhauser et al. (34), that an AF burden of >2 h had a significant impact on QoL, and a study by van den Berg et al. (35) showed that the frequency of AF paroxysms was predictive of physical functioning.

We found that MR-proADM was inversely related to the arrhythmia-specific HRQoL, that is, higher MR-proADM levels were related to better arrhythmia-specific HRQoL. MR-proADM is a product of the parental molecule of adrenomedullin (ADM). ADM is an extracardiac peptide with vasoactive and natriuretic properties that has emerged as a biomarker of potential interest in the prediction of cardiovascular disease risks (36). A study by Kerkela et al. (37) showed that atrial stretch significantly decreased ADM levels, suggesting a downregulation of the local ADM system, which was a result that possibly explained this inverse relationship between MR-proADM and arrhythmia-related HRQoL.

FIGURE 3 Changes in ASTA Symptom Scale Score Depending on Low-Grade Inflammation and the Level of Anxiety



Low-grade inflammation was high-sensitivity C-reactive protein >3 mg/l. Abbreviation as in Figure 1.

CLINICAL IMPLICATIONS. We found an important association between depression, anxiety, and obesity, and arrhythmia-related symptoms and HRQoL. There is evidence that physical activity can be beneficial not only for weight reduction but also for reduction of symptoms of depression and anxiety (38). Furthermore, Pathak et al. (39) showed that aggressive risk factor modification improved the long-term success of AF ablation, and that cardiorespiratory fitness predicted arrhythmia recurrence in obese patients with symptomatic AF (40). Hence, our results reinforced the importance of these recently published studies, in which it was clearly shown that patients with AF could benefit from an intensive risk factor modification, including weight loss and improvement of cardiorespiratory fitness. In that way, factors such as anxiety, depression, and obesity that are correlated with disabling symptoms and poor quality of life can be treated.

STUDY LIMITATIONS. There were some limitations to our study. One was that our study was a single-center observational cohort study with a moderate sample size and no control group. Our sample consisted of patients with AF who were eligible for RFA, that is, patients who were supposed to have a high symptom burden and impaired HRQoL in order to be referred for catheter ablation. Nevertheless, we observed quite a wide variation in symptoms and HRQoL. Furthermore, our sample consisted of a heterogenic group of patients, and included those with both paroxysmal or persistent AF, and patients with normal or reduced EF. In addition, follow-up data on the effect of RFA on the contributing factors to symptoms and HRQoL would have been of interest, but was outside the scope of this study.

CONCLUSIONS

Our study showed that both anxiety and depression, as indicated by the HADS questionnaire, and low-grade inflammation played a central role in arrhythmia-related symptoms and HRQoL in patients with AF who were eligible for RFA. Obesity was the most significant predictor of general physical status. All these factors need to be addressed to improve the management of patients with AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Both anxiety and depression, and low-grade inflammation play a central role in arrhythmia-related symptoms and HRQoL, whereas obesity is a strong predictor of general physical status in patients with atrial fibrillation eligible for radiofrequency ablation.

TRANSLATIONAL OUTLOOK: Treatable factors, such as anxiety, depression, and obesity, which are closely correlated to disabling symptoms and poor quality of life in patients with atrial fibrillation eligible for radiofrequency ablation should be addressed by treating physicians even before the planned intervention. An intensive risk factor modification can be a possible way. More studies are needed to clarify the mechanisms behind the association among anxiety, depression, obesity, and atrial fibrillation.

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KEY WORDS anxiety, arrhythmia-related symptoms, atrial fibrillation, health-related quality of life, obesity