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Original article

Association between the quality of life and asymptomatic episodes of paroxysmal atrial fibrillation in the J-RHYTHM II study☆

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ABSTRACT

Background: Paroxysmal atrial fibrillation (AF) patients have a reduced quality-of-life (QoL) despite the fact that the majority of AF episodes are asymptomatic. Asymptomatic AF is likely to be associated with substantial morbidity and mortality rates similar to those with symptomatic AF, whereas its effect on the QoL has not yet been clarified.
Purpose: We studied the specific contribution of asymptomatic AF episodes to reducing the QoL.
Methods: We assessed the QoL in 233 patients with paroxysmal AF and hypertension (age 64.9 ± 9.7 years, 71% male) enrolled in the Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) using an AF-specific QoL questionnaire (AFQLQ). The AFQLQ comprised 3 components: AFQLQ1, the frequency and duration of symptoms; AFQLQ2, severity of symptoms; and AFQLQ3, limitations in daily activities and mental anxiety. Higher scores indicated a better QoL. Each patient transmitted electrocardiograms for 30 s daily at a predetermined time as well as whenever arrhythmia-related symptoms were experienced. We examined the relationship between the 3 AFQLQ components and frequency of symptomatic and asymptomatic AF episodes (days/month) during 12 months of follow-up.
Results: The symptomatic and asymptomatic AF frequencies were 0.9 ± 3.1 days/month and 1.5 ± 3.5 days/month, respectively. AFQLQ1 negatively correlated with the symptomatic AF frequency (Spearman's correlation coefficient: $r = -0.332$, $p < 0.001$). AFQLQ2 and AFQLQ3 correlated with both the symptomatic AF frequency ($r = -0.27$, $p < 0.001$ and $r = -0.265$, $p < 0.001$, respectively) and asymptomatic AF frequency ($r = -0.197$, $p < 0.01$ and $r = -0.229$, $p < 0.005$, respectively).
Conclusion: The asymptomatic AF episode frequency correlates with a reduced QoL in patients with paroxysmal AF, suggesting that there would be psychological benefits to its reduction.

Introduction

Atrial fibrillation (AF) remains the most common sustained arrhythmia in clinical practice and is associated with increased morbidity and mortality [1–4]. AF also causes a significant reduction in the quality of life (QoL) compared to age- or sex-matched healthy subjects [5–7] as well as patients with other cardiac diseases [5,8–11]. This reduced QoL is well known to be associated with the frequency or severity of symptoms such as palpitations, fatigue, or shortness of breath [7,12,13]. Other factors associated with a reduced QoL include demographic factors such as the age and sex, and various comorbidities including heart failure, hypertension, ischemic heart disease, diabetes, and chronic obstructive pulmonary disease. The need to be on chronic medication, as well as dietary or physical activity restrictions are also negatively correlated with the reduced QoL [5–8,10]. However, to the best of our knowledge there have been no corresponding

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studies to date quantifying the relationship between asymptomatic AF burden and the QoL [14]. This is likely due to the difficulty of detecting asymptomatic AF. The studies that have looked at data logs of cardiac implantable electronic devices have shown a high incidence of asymptomatic AF episodes [15–18]. According to three different studies, among patients with symptomatic bradycardia and a history of AF, asymptomatic AF was observed in 38% [16], 65% [15], and more than 90% [17] of patients. The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study showed that 88% of AF episodes stored in the implantable loop recorders were clinically silent [18]. Data from the Canadian Registry of Atrial Fibrillation (CARAF) [19] and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study [20] using AF symptom checklists reported that 12–21% of patients with a diagnosis of AF did not have any overt symptoms. Given the high numbers of AF patients with asymptomatic episodes of AF, it would be useful to know whether asymptomatic AF affects the QoL as much as symptomatic AF does.

Secondly, in patients with paroxysmal AF, there appears to be an inexorable progression to persistent AF at a rate of about 5–9% per year [21,22], so that over time, the majority of patients end up with persistent AF. Previous studies comparing the QoL in different types of AF in a cross-sectional design showed that there were no significant differences in the QoL among patients with paroxysmal, persistent, and permanent AF [23]. To date, few reports have examined the prospective relationship between the QoL and development of persistent AF.

Therefore, this prospectively designed Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) post hoc study had two aims. One was to measure the QoL using an AF-specific questionnaire [24–26] in patients with asymptomatic paroxysmal AF episodes. The second was to quantify the changes in the QoL before and after the development of persistent AF.

Methods

Patient population

Details of the J-RHYTHM II study have been reported previously [27,28]. In brief, 318 patients with paroxysmal AF and hypertension, defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg, or requiring any hypertension treatment at enrollment, were randomized to receive either an angiotensin II-receptor blocker (ARB) or calcium channel blocker (CCB). The primary endpoint of the study was the frequency of paroxysmal AF episodes, as days per month. Baseline echocardiography and a QoL assessment were performed during the first 4 weeks after enrollment. After randomization, the assigned therapy for hypertension was initiated in an open-label fashion and continued throughout the whole follow-up period for a maximum of 12 months. Each patient was provided with a transtelephonic monitoring (TTM) device that included a mobile phone system (Nihon Kohden, Tokyo, Japan) and was requested to transmit electrocardiography recordings for 30 s daily at a predetermined time by patients' discretion and also at any time arrhythmia-related symptoms were experienced. The symptomatic and asymptomatic AF episodes were differentiated by the arrhythmia-related symptoms by selecting a button equipped with the device. All electrocardiographic tracings were reviewed by a blinded, independent TTM diagnosis laboratory. Each day was classified as symptomatic AF or asymptomatic AF, or no AF, and the number of AF days was tallied for the 4 weeks. The total AF was defined as the sum of the symptomatic and asymptomatic AF days. If patients transmitted both symptomatic AF and asymptomatic AF episodes in a single day, it was predetermined to use the symptomatic AF episode and not the asymptomatic AF episode. However, we did not have any patients who transmitted both symptomatic AF and asymptomatic AF episodes in a single day. We used two periods, the first month before randomization to an ARB or CCB (baseline), and the final month of the 1-year follow-up on these drugs.

Paroxysmal AF was defined as AF expected to convert spontaneously to sinus rhythm within 48 h of the onset and persistent AF was defined as AF either lasting longer than consecutive 7 days or AF requiring termination by pharmacological or electrical cardioversion. The study protocol was approved by each institution and all patients gave their written informed consent.

Assessment of the QoL

We used a questionnaire formulated specifically for AF patients called the Atrial Fibrillation Quality of Life Questionnaire (AFQLQ) [24,25]. The AFQLQ consisted of 3 components: AFQLQ1 assessed the subjective frequency and duration of symptoms (6 items, 0–24 points); AFQLQ2 assessed the severity of symptoms (6 items, 0–18 points); and AFQLQ3 assessed the limitations in daily and other activities and mental anxiety related to AF (14 items, 0–56 points). A higher score indicated a better QoL in every component. The AFQLQ is considered to be valid and reproducible, with values of a statistical measure for the reliability called Cronbach's alpha of 0.78, 0.81, and 0.89 for AFQLQ1, AFQLQ2, and AFQLQ3, respectively [25]. In general, a Cronbach's alpha of greater than 0.7 indicates reliability [29]. An AFQLQ assessment was performed both at baseline and at the final month of the 1-year follow-up. The AFQLQ was self-administered by the study patients and forwarded to the core laboratory, where analyses were performed.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Differences in the quantitative data and categorical data were evaluated by a Student's *t*-test and chi-square test, respectively. Spearman's rank correlation analysis was applied to test the relationships between the clinical variables and AFQLQ, and the associations between the number of symptomatic AF episodes and asymptomatic AF episodes. The significance of the AFQLQ between those who developed persistent AF and those who remained in paroxysmal AF at baseline and 1 year after enrollment, and the AFQLQ before and after the progression to persistent AF were tested by an analysis of variance (ANOVA). A two-tailed p-value of <0.05 was considered significant.

Results

From the cohort of the J-RHYTHM II study, a total of 233 patients were included in this post hoc analysis. Patients who failed to complete the AFQLQ protocol ($n = 85$) in the parent study were excluded. The baseline clinical characteristics are shown in Table 1. The mean age was 64.9 ± 9.7 years (range, 38–92 years), and 165 patients (71%) were men. The mean systolic blood pressure was high as expected from the parent study cohort (140.5 ± 15.3 mmHg). The left ventricular ejection fraction (LVEF) was well preserved (67.4 ± 8.3%), and the mean left atrial dimension (LAD) was 39.0 ± 7.0 mm. Few patients had significant structural heart disease.

All patients in the substudy had data for the 12th follow-up month available. The number of AF days/month (both symptomatic and asymptomatic) decreased from 4.5 ± 6.0 days at baseline to 2.4 ± 4.5 days at one year ($p < 0.01$). However, there were no changes in the scores of the 3 components of the AFQLQ between baseline and at one year (Fig. 1A). There was a gender difference

Table 1
Clinical characteristics of the patients.

Characteristics ($n = 233$)	
Age, years	64.9 ± 9.7
Male, %	71
Systolic blood pressure, mmHg	140.5 ± 15.3
Diastolic blood pressure, mmHg	82.1 ± 11.1
Duration of AF, %	
<1 year	25
≥1 year, <5 years	40
>5 years	25
Unknown	10
Development of persistent AF, %	13
Coexisting conditions, %	
Prior embolism	5
Heart failure	3
Myocardial infarction	1
Angina pectoris	2
Dilated cardiomyopathy	0.4
Valve disease	6
Diabetes mellitus	9
Echocardiogram parameter	
LVEF, %	67.4 ± 8.3
LAD, mm	39.0 ± 7.0
Rhythm control drug, %	70

Data represent means ± SD or % of the study population. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LAD, left atrial dimension.

at baseline for the AFQLQ2, with men having a higher score than women (12.7 ± 3.6 vs. 11.3 ± 3.6, $p < 0.05$) (Fig. 1B), although the total number of AF days/month in the men and women did not significantly differ (4.5 ± 6.0 days in men vs. 4.5 ± 6.1 days in women, $p = 0.99$). This gender difference in the AFQLQ2 score was absent at the end of the follow-up (13.5 ± 3.8 vs. 13.2 ± 3.5, $p = 0.55$). No gender difference was observed in the total AF days/month at the end of follow-up (2.6 ± 4.7 days in men vs. 2.0 ± 4.0 days in women, $p = 0.36$).

We also examined potentially confounding variables that could affect the QoL. At baseline, the patients who were not on rhythm control drugs had a higher AFQLQ3 score with near statistical significance ($p = 0.051$) than the patients on rhythm control drugs (Fig. 1C). Spearman's rank correlation analyses failed to reveal any significant relationships between the AFQLQ components and the objective clinical measures such as the age, systolic blood pressure, duration of AF, LVEF, and LAD (data not shown).

Symptomatic AF and asymptomatic AF

The relationship between the AFQLQ and number of AF days/month at baseline and at 1 year after enrollment are summarized in Table 2. At baseline, the symptomatic AF days/month and asymptomatic AF days/month were 1.6 ± 3.2 days and 2.9 ± 5.1 days, respectively. The number of asymptomatic AF days/month accounted for 64% of the total AF days/month. The number of symptomatic AF days was significantly correlated with all 3 components of the AFQLQ (Spearman's correlation coefficient $r = -0.326$, -0.217, and -0.186 for AFQLQ1, AFQLQ2, and AFQLQ3 respectively), but the asymptomatic AF days/month were associated only with the AFQLQ1 only at baseline ($r = -0.170$).

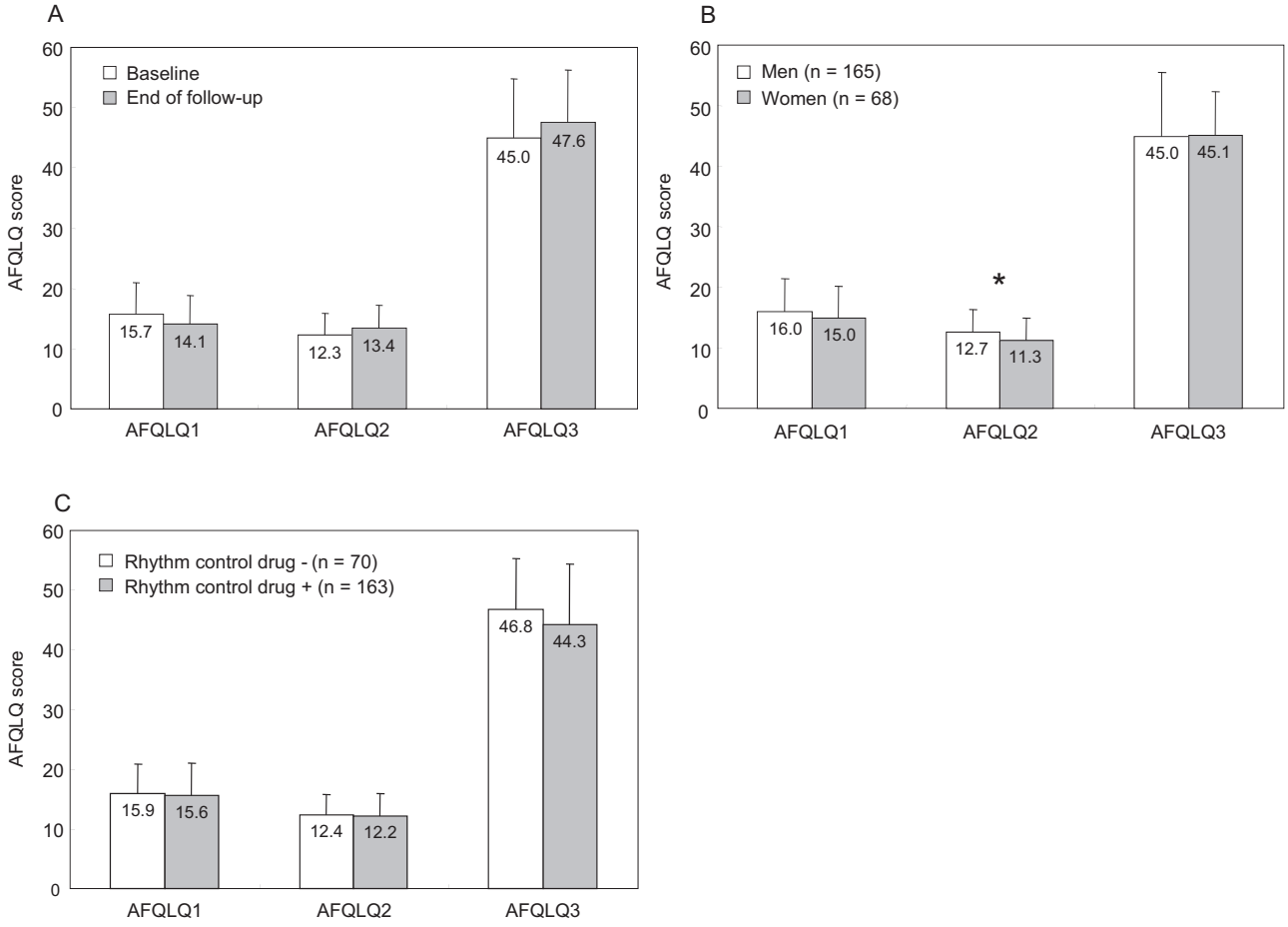

Fig. 1. Atrial Fibrillation Quality of Life Questionnaire (AFQLQ) scores given by paroxysmal AF patients from the J-RHYTHM II substudy. (A) AFQLQ before randomization to drug therapy and 1-year after follow-up. (B) Sex differences at baseline. (C) Rhythm control drug use at baseline. Data represent the mean ± SD. *$p < 0.05$.

Table 2
Relationship between the AFQLQ and AF days per month.

	Total AF	Symptomatic AF	Asymptomatic AF
Baseline			
AF days/month, days	4.5 ± 6.0	1.6 ± 3.2	2.9 ± 5.1
Correlation coefficients			
AFQLQ1	−0.338‡	−0.326‡	−0.170*
AFQLQ2	−0.112	−0.217†	0.016
AFQLQ3	−0.034	−0.186**	0.090
1 year after enrollment			
AF days/month, days	2.4 ± 4.5	0.9 ± 3.1	1.5 ± 3.5
Correlation coefficients			
AFQLQ1	−0.342‡	−0.332‡	−0.114
AFQLQ2	−0.181*	−0.270‡	−0.197**
AFQLQ3	−0.123	−0.265‡	−0.229†

Data represent means ± SD. Correlation coefficients were determined by a Spearman's rank correlation analysis. The total AF is the sum of the symptomatic and asymptomatic AF days. AFQLQ, Atrial Fibrillation Quality of Life Questionnaire.
* $p < 0.05$.
** $p < 0.01$.
† $p < 0.005$.
‡ $p < 0.001$.

At one year, the symptomatic AF days/month and asymptomatic AF days/month were 0.9 ± 3.1 days and 1.5 ± 3.5 days, respectively. The number of asymptomatic AF days accounted for 63% of the total AF. Again, the symptomatic AF days/month negatively correlated with all 3 components of the AFQLQ (AFQLQ1: $r = -0.332$, AFQLQ2: $r = -0.270$, and AFQLQ3: $r = -0.265$). The number of asymptomatic AF days/month was also negatively correlated with the AFQLQ2 ($r = -0.197$) and AFQLQ3 ($r = -0.229$). There was no statistical significance between symptomatic AF days/month and asymptomatic AF days/month ($r = -0.122$, $p = 0.06$) when we included the results at baseline and one-year follow-up in the analysis.

Progression to persistent AF

During the follow-up, 30 (13%) patients had progressed to persistent AF. The clinical characteristics and AFQLQ of those who developed persistent AF (persistent AF+) versus those who remained in paroxysmal AF (persistent AF−) are summarized in Table 3. The LAD at baseline was larger in those with progression to persistent AF compared to those who remained in paroxysmal AF (38.5 ± 6.6 mm vs. 43.2 ± 8.8 mm, $p < 0.05$). There were no significant differences in the 3 components of the AFQLQ between those who developed persistent AF and those who remained in paroxysmal AF either at baseline or 1 year after enrollment. Neither were there any significant differences in the 3 components of the AFQLQ before and after the progression to persistent AF.

Table 3
Comparison of paroxysmal AF patients who did and did not develop persistent AF.

	Persistent AF− ($n = 203$)	Persistent AF+ ($n = 30$)
Age, years	64.7 ± 9.7	66.9 ± 9.9
LVEF, %	67.6 ± 8.0	66.2 ± 10.4
LAD, mm	38.5 ± 6.6	43.2 ± 8.8*
$CHADS_2$ score	1.4 ± 0.7	1.5 ± 0.6
Rhythm control drug, %	69	73
AFQLQ (baseline)		
AFQLQ1	15.7 ± 5.3 ($n = 201$)	15.6 ± 5.0 ($n = 26$)
AFQLQ2	12.2 ± 3.7	12.8 ± 3.4
AFQLQ3	44.8 ± 9.6	46.9 ± 9.8
AFQLQ (1 year after enrollment)		
AFQLQ1	14.4 ± 4.5 ($n = 175$)	12.4 ± 5.4 ($n = 23$)
AFQLQ2	13.4 ± 3.7 ($n = 177$)	13.6 ± 3.5 ($n = 22$)
AFQLQ3	47.8 ± 8.4 ($n = 169$)	46.6 ± 10.7 ($n = 21$)
Differences		
AFQLQ1	−1.5 ± 4.9 ($n = 165$)	−3.3 ± 5.2 ($n = 23$)
AFQLQ2	1.3 ± 3.6 ($n = 169$)	0.7 ± 2.8 ($n = 21$)
AFQLQ3	2.0 ± 7.0 ($n = 161$)	0.2 ± 7.0 ($n = 19$)

Data represent means ± SD or the frequency. *n* indicates the number of patients. Persistent AF+: patients who developed persistent AF during the follow up; persistent AF−: those who remained in paroxysmal AF during the follow up. $CHADS_2$: an acronym for congestive heart failure, hypertension, age ≥75, diabetes mellitus, and a prior stroke or transient ischemic attack. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AFQLQ, Atrial Fibrillation Quality of Life Questionnaire.
* $p < 0.05$.

Discussion

Major findings

We investigated the QoL in patients with paroxysmal AF enrolled in the J-RHYTHM II study using an AF-specific questionnaire, the AFQLQ. Based on the data gathered using periodic and symptom-related transtelephonic ECG monitoring, we discovered that the QoL was negatively associated with the number of asymptomatic AF days. Further, we found that the progression to persistent AF did not decrease the QoL in patients with paroxysmal AF. Our study also confirmed the results of studies in the literature showing that the burden of symptomatic AF negatively affects the QoL [7,12], and women experienced a subjectively greater severity of AF symptoms relative to men [9], although there was no difference in the number of AF days between the sexes in our study. Objective measures of disease severity were not associated with the QoL, a finding that has been observed in other studies.

AF-specific QoL measure

The administration of an AF-specific QoL test, the AFQLQ, provided evidence for a reduced QoL in patients with asymptomatic episodes of AF. In this respect, the scores obtained in the limitations of daily and other activities and the mental anxiety of the AF-QoL questionnaire (AFQLQ3) would indicate that it is precisely the patients with asymptomatic episodes of AF who experience a worse QoL. Internal consistency and reproducibility of AFQLQ was validated by Yamashita et al. [25]. In that study the completed questionnaire was obtained twice from 172 stable AF patients at 3–6 months interval. Spearman's rank correlation coefficients of 3 items were all above 0.7, indicating a positive result. Also, as presented in Fig. 1 there were no significant differences in the average scores of the 3 components of AFQLQ between baseline and the end of follow up. We believe that difference in the span of evaluation of this study might not influence the outcomes. To date, the AFQLQ has been used for AF studies involving the J-RHYTHM study [26] and the J-RHYTHM II study [28]. While multiple reports on the QoL in AF patients have been published, most of them used generic QoL questionnaires [7,8,10,14], rather than AF-specific ones [11,23,30]. The strengths of the generic tools used to assess the QoL in AF include their extensive validation, generalizability, and the wealth of data already collected on AF patients. The weakness of the generic measures is, however, that scores among AF patients are markedly influenced by patient demographics and comorbid conditions, because they include questions about general health and function [10]. We believe AF-specific questionnaires focused on domains or symptoms relevant to AF can be more illuminating

because AF patients often have multiple health problems, and are heterogeneous [31].

QoL in AF patients

In the present study, we examined the association between the AFQLQ and symptomatic AF and asymptomatic AF independently. As expected, the number of symptomatic AF days correlated negatively with all 3 components of the AFQLQ. Interestingly, the number of asymptomatic AF days was also negatively associated with the AFQLQ2 and AFQLQ3, representing perceived severity of symptoms, and limitations in daily activities and mental anxiety. We found that there was no statistical significance between the number of symptomatic AF days and asymptomatic AF days; however, we could not completely exclude the associations between symptomatic AF episodes and asymptomatic AF episodes because of the marginal significance. This finding suggests that the inverse correlation between asymptomatic AF episodes and QoL score may be partly mediated by the symptomatic AF episodes. Further, if the patients who experienced no symptomatic AF episodes but had only asymptomatic AF episodes throughout the study period had reduced QoL, it may support our conclusion; however, we did not have such a patient.

Previous studies have reported that AF patients live in fear of AF episodes, and that depression, anxiety, and perceived stress are associated with a reduced QoL in AF patients [32–35]. One of these studies by Kupper et al. [35] examined the prospective relationship between AF symptoms and emotional distress before and after electrical cardioversion in patients with persistent AF. They found that higher levels of emotional distress including anxiety and perceived stress continued even in the absence of AF recurrences after electrical cardioversion. The QoL in patients with asymptomatic AF has also been reported in a different study design. Savelieva et al. [14] compared the QoL using the Medical Outcomes Study Short Form Health Survey (SF-36) in healthy subjects, patients with asymptomatic AF and symptomatic AF, in which a subset of the Bubien and Kay's symptom checklist [12] was used to categorize whether patients were asymptomatic. They reported that although most of the SF-36 scale scores did not differ much between healthy subjects and asymptomatic AF patients, the perception of their general health and global life satisfaction were nevertheless significantly decreased in the asymptomatic AF patients compared with healthy subjects. They interpreted their results as suggesting that AF itself could significantly decrease the overall perception of well-being in asymptomatic AF patients, even though the perception of the QoL was similar to healthy subjects for specific social, emotional, and physical questions. Our results confirm the findings of these multiple studies, and suggest that persistence of anxiety and depression decrease the QoL in AF patients even in the absence of AF-related symptoms.

Why should asymptomatic AF reduce the QoL? One possibility is that merely receiving a diagnosis of a chronic disease such as AF that can lead to serious consequences such as embolic or hemorrhagic strokes can induce anxiety and a depressed outlook. Another is that underlying morbidities leading to atrial enlargement and AF contribute to a reduced sense of health and vigor. A third is that both asymptomatic and symptomatic AF episodes directly affect the QoL via a reduced cardiac output or exercise intolerance, for example, even when the episodes themselves are not perceived. Our results that showed a correlation between the number of days of AF and the QoL scores would flatly rule out the first hypothesis, and make the third hypothesis more likely than the second, since diseases accompanying AF vary, giving no reason for a linear relationship between the AF episode frequency and a reduced QoL.

Our data showed that there were no significant changes in the average scores of the 3 components of the AFQLQ between that at baseline and at one year. However, there were correlations between the asymptomatic episode frequency and AFQLQ2 and AFQLQ3 at one year which were not observed at baseline. The exact reason for this finding is unknown, but we speculate that AF patients may have some feeling of deterioration of their QoL because of either symptomatic or asymptomatic AF episodes, as mentioned above [35]. Symptomatic AF episodes directly reduce the QoL, but if the symptomatic AF episodes reduced, the asymptomatic episodes may cause a decrease in the QoL. In other words asymptomatic AF usually hides behind symptomatic AF, but if the symptomatic AF decreases, asymptomatic AF may become unveiled and influence the AFQLQ2 (the severity of symptoms) and AFQLQ3 (the limitations in the activities and mental anxiety).

Persistent AF

After the initial diagnosis of paroxysmal AF, there is a slow but steady progression to persistent AF. Our data showed that 13% of patients progressed to persistent AF in 1 year but they did not report a decrease in the QoL as compared to baseline. A previous study by Peinado et al. [23] compared the QoL in 3 different types of AF (paroxysmal, persistent, and permanent). They showed, in addition to no significant difference in the QoL among the different types of AF, that patients with permanent AF were less symptomatic and had better preserved psychological dimensions than those with paroxysmal AF, which they attributed to a better adaptation to the condition. Patients in whom the disease is chronic may have the perception that the symptoms have become milder or that they have even disappeared [23].

Study limitations

The present study has several limitations. Our substudy was based on the J-RHYTHM II study data, in which all patients had hypertension in addition to paroxysmal AF, and therefore may not represent AF patients without hypertension. We did not have control subjects and did not use a generic health-related QoL questionnaire. The period of follow-up was short at 12 months. Therefore, we cannot draw conclusions about the QoL for patients with AF with long-standing disease. We used counts of AF from TTM of a 30 s duration daily for over a month as a measure of the AF burden, which obviously underestimated the actual number and duration of AF episodes. However, asymptomatic episodes of AF still accounted for 64% of the total AF episodes detected in this manner, which is not that much smaller than, say, the 88% found in the CARISMA study that used a cardiac implantable electronic device to detect asymptomatic AF episodes [18].

Conclusions

In patients with paroxysmal AF, asymptomatic AF episodes appear to reduce aspects of the QoL associated with mental anxiety/limitations in daily activities, and the perception of the AF symptom severity. Our study suggests that asymptomatic AF also contributes to a detriment in the QoL, and that elimination of all AF whether perceived or not, is beneficial not only from a clinical, prognostic point as is well known, but likely also for the psychological well-being of the patient.

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