

ORIGINAL PAPER

## Atrial fibrillation a benign condition? Quality of life approach

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Nothing to declare

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**Abstract**

Introduction: Atrial fibrillation (AF) is the most frequent cardiac rhythm disorder, considered until recently benign. Due to its major complications (cardio-embolic episodes) patients need to be anticoagulated. Aim: To assess the quality of life (QoL) in patients with new oral anticoagulants (NOAC) versus those using classical anticoagulants (VKA). Methods: A total of

483 patients admitted consecutively in our clinic were evaluated during hospitalization and after discharge. Follow-up visits were conducted: at baseline, 6, 12, 18 and 24 months; the quality of life (QoL) was measured by a specific questionnaire (EQ-5D-3L), and the results were assessed. Patients were divided in two groups considering their anticoagulant use: NOAC or VKA. Baseline characteristics, clinical outcomes as well as QoL indices were compared between the two groups. The current research has been conducted in accordance with the ethical prin-

principles set out in the Helsinki Declaration and Good Clinical Practice Recommendations and was approved by our hospital Ethics Committee. Results: The mean age of our studied group (374 eligible patients) was  $64.7 \pm 8.2$  years ( $p=0.220$ ); 116 patients (31.01%) used NOAC. Patients with NOAC obtained better results in all domains: physical ( $57.0 \pm 8.9$  vs.  $51.1 \pm 12.5$  vs.  $42.0 \pm 6.2$ ;  $p < 0.001$ ), social ( $62.6 \pm 19.8$  vs.  $52.5 \pm 20.0$  vs.  $45.7 \pm 16.0$ ;  $p = 0.019$ ) and environmental ( $62.9 \pm 12.7$  vs.  $52.7 \pm 7.6$  vs.  $60.7 \pm 3.6$ ;  $p = 0.018$ ). Compared to VKAs, NOACs were more commonly prescribed in patients with a history of stroke or with a higher thromboembolic risk ( $p < 0.001$ ). EQ-5D-3L total score:  $75.6 \pm 20.9$ ; visual analogue scale:  $63.1 \pm 20.6$ . Conclusion(s): Satisfaction and QoL with oral anticoagulants were high, although they were both better with NOACs. A worse QoL was associated with comorbidities, polypragmasy, and previous treatment with VKA. Patients strongly expressed their desire to improve their QoL.

## Introduction

The most common arrhythmia, atrial fibrillation (AF), is considered now an epidemic cardiovascular disease and has a major impact on the patient's social life.

It is stated that one in four middle-aged adults from Europe or US will develop AF [1,2]. By 2030, 14–17 million AF patients are anticipated in the European Union, with 120 000 – 215 000 newly diagnosed patients per year [3,4].

The major goals of AF treatment are stroke prevention, rate reduction, rhythm control, minimizing symptoms and eliminating physical limitations. The impairment of QoL associated with AF should also become a major goal in AF treatment and should benefit from equal attention in current and future guidelines. Although until recently considered a benign condition, the distress caused by AF symptom onset can be severe and often result in a major lowering of the quality of life (QoL). This can be attributed to several factors [5]. Typical symptoms that the patients use to describe AF include palpitations, chest constriction, dizziness, sleep disorders or psychosocial distress.

The latest guidelines state that the management of AF aims at reducing symptoms, preventing comorbidities and AF related complications. In order to clarify the patients' expectations and to improve their QoL, we should explain individually, to each patient the expected benefits [6,7]. Current management strategies in AF patients are focused on the rate and rhythm control, thromboembolism prevention

and treatment of underlying diseases. In order to obtain the targeted heart rate of  $< 110$  beats per minute, practitioners often resort to different rate and rhythm control strategies. Moreover, in symptomatic patients, these options improve QoL scale. Over the years, there have been small, short-duration trials that compared different rate control therapies and tried to identify the differences in QoL, exercise capacity, or left ventricular ejection fraction (LVEF) [8,9]. The benefit of different rate control strategies on symptoms, QoL and other intermediate outcomes is still debated and under investigation [1,10]. The impairment of QoL associated with AF should also become a major goal in AF treatment and should benefit from equal attention in current and future guidelines.

Improved quality of life has been noted with both pharmacological and interventional therapies [11], but there are limited data to compare the benefit of different treatments. Assessment of the quality of life is further constrained by a lack of cross-validation of the several AF-specific quality of life tools [12,13].

It is important, however, that the management and treatment of AF take into account not only symptoms, but also individual patients' factors such as psychological well-being [14].

One of the most difficult thing to quantify in AF patients is the relationship between symptoms and actual rhythm. The establishment of an association between these two would be beneficial for the management of AF [15].

The concept of quality of life (QoL) has gained significant importance in the last years as an outcome measure. The QoL scales are used in different trials to evaluate therapeutic options, to plan treatment and to evaluate patient's status and general well-being. Most of the patients with AF have a reduced QoL. There is currently no globally accepted definition for QoL in AF. The term is subjective and may be defined by one or many aspects, including symptoms, functional status, and patients' health perceptions, experiences, or expectations [15]. A measurement tool to accurately and reliably quantify the effect of AF on patient QoL would be useful for both clinical and research purposes. Thus, disease-specific questionnaires must be constructed to become valid measures intended to quantify, to be reproducible in stable patients, and to be sensitive to clinical changes [16].

The FRACTAL (Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle) study concluded that generic tools are not ideal for measuring AF-specific QoL. There is a need for a comprehensive, validated AF-specific questionnaire to measure the spectrum of QoL domains [17].

Older population represents a challenge in terms of treating AF, due to their associated comorbidities (heart failure, arterial hypertension, diabetes mellitus, metabolic dysfunction, anaemia, chronic renal disease, syncope, cognitive disorder). Such conditions may limit the quality of life more than AF-related symptoms.

This single-centre clinical study was aimed, using Euro-QoL 5-Dimensional questionnaire (EuroQoL/EQ-5D), to assess QoL in AF patients with new oral anticoagulation (NOAC) versus those using vitamin K antagonists (VKA).

## Material and Methods

### Study population

We conducted a cohort retrospective study among adult patients, who have the clinical diagnosis of AF. A total of 483 patients admitted consecutively in our clinic between January 2014 and December 2014, were periodically evaluated during hospitalization and after discharge. Exclusion criteria involved patients who were not anticoagulated. Follow-up visits were conducted as follows: at baseline, 6, 12, 18 and 24 months. The quality of life (QoL) was measured by a specific questionnaire, and we assessed it through out QoL score.

The EuroQoL (EQ-5D) is a well-validated, generic health-related quality-of-life measure. It is self-administered and has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It also includes a visual analogue scale that asks respondents to rate their current health from 0 to 100, with 0 representing death and 100 indicating perfect health. The 5-item questionnaire can also be transformed to a social-based utility score, ranging from 0 to 1, with higher scores reflecting better health status. The scores are rated on three levels ranging from 'no problems' to 'severe problems' [18].

Patients were divided in two groups considering their anticoagulant use: NOAC or VKA. Baseline characteristics, clinical outcomes as well as QoL indices (EQ-5D-3L questionnaire) were compared between the two groups.

The current research has been conducted in accordance with the ethical principles set out in the Helsinki Declaration and Good Clinical Practice Recommendations and was approved by our hospital Ethics Committee.

### Monitoring, evaluation, data acquisition:

Data from the patient's medical charts and demographic information were obtained and clinical assessment and comorbidities were extracted. Laboratory findings in conjunction with physician notes as well as medication from

the patient's medical charts, were used to determine whether or not they have a specific comorbidity. In addition, we defined comorbidity as the presence of one or more diseases, associated with AF condition. Patients who met the inclusion criteria but died during the specified observation range were also included in the study.

Statistical methodology of the data obtained:

All statistical analyses were conducted using SPSS 18 and Microsoft Excel Analyse-it software. Results are presented as mean  $\pm$  standard deviation SD (for numerical variables) or percentages. Continuous variables were analysed for normalization and compared using the t Student test; they were expressed by mean value  $\pm$  standard and median deviation. For comparison of parameter averages in the two groups, the Mann-Whitney U method and the Wilcoxon method W were used. The degree of correlation (r) between the studied parameters was evaluated by calculating the correlation coefficient Pearson. A cut-off value of  $p < 0.05$  was considered for statistical significance.

## Results

From a total of 483 patients, a group of 109 patients were excluded from the study due to missing data, non-anticoagulation or they were lost-to follow-up.

The mean age of our studied group (374 eligible patients) was  $64.7 \pm 8.2$  years ( $p=0.220$ ), with slightly more men than women included (51.06%). Baseline characteristics are highlighted in table 1.

Associated comorbidities of AF in our patients were: stroke (12.03%), congestive heart failure (67.64%), ischemic heart disease (54.81%), hypertension (73.26%), valvular heart disease (31.55%), chronic obstructive pulmonary disease (24.59%), diabetes mellitus (33.95%), anaemia (10.42%), chronic kidney disease (26.20%), cardiomyopathy (20.32%) and endocrine disorders (12.56%). More than one-third (37.96 %) of AF patients have at least three associated comorbidities. Approximately 25% of all patients with AF had no cardiac impairment. Only 18.71% of the studied group have no comorbidity.

Only in one third of our patients NOAC (apixaban, dabigatran, rivaroxaban) was introduced in AF management. The rest of the group had prescription of VKA (68.98%).

At discharge (baseline), 77.80% from all patients were prescribed beta-blockers, 80.74% on angiotensin converting enzyme inhibitors or angiotensin II receptor blocker, 31.81% on digoxin, 32.08% on calcium antagonists, 62.29%

Baseline characteristics by admission					
Criteria		Total number of patients (n=374)	NOAC (n=116)	VKAs (n=258)	p
Gender (male vs female, (n%))		191 (51.06%) vs 183 (48.93%)	62 (53.44%) vs 54 (46.55%)	129 (50.0%) vs 129 (50%)	0.310
Age (yo)		64.7; SD: 8.2	66.3; SD: 7.3	64.1; SD: 7.2	0.220
Type of AF	First diagnosed AF (n, (n%))	34 (9.09%)	11 (9.48%)	23 (8.91%)	0.45
	Paroxysmal AF(n, (n%))	89 (23.79%)	29 (25.0%)	60 (23.25%)	0.002
	Persistent AF (n, (n%))	91 (24.33%)	23 (19.82%)	68 (26.35%)	0.148
	Long standing persistent AF (n, (n%))	84 (22.45%)	28 (24.13%)	56 (21.70%)	0.002
	Permanent AF (n, (n%))	76 (20.32%)	25 (21.55%)	51 (19.76%)	0.001
Comorbidities	Stroke (n, (n%))	45 (12.03%)	12 (10.34%)	33 (12.79%)	0.156
	Congestive HF(n, (n%))	253 (67.64%)	84 (72.41%)	169 (78.29%)	0.002
	Ischaemic heart disease (n, (n%))	205 (54.81%)	68 (58.62%)	137 (53.10%)	0.001
	Arterial hypertension (n, (n%))	274 (73.26%)	89 (76.72%)	185 (71.70%)	0.047
	Valvular heart disease (n, (n%))	118 (31.55%)	36 (31.03%)	82 (31.78%)	0.04
	Chronic obstructive pulmonary disease (n, (n%))	92 (24.59%)	27 (23.27%)	65 (25.19%)	0.015
	Diabetes mellitus (n, (n%))	127 (33.95%)	41 (35.34%)	86 (33.33%)	0.002
	Anaemia (n, (n%))	39 (10.42%)	13 (11.20%)	26 (10.07%)	0.31
	Chronic kidney disease (n, (n%))	98 (25.52%)	32 (27.58%)	66 (25.58%)	0.004
	Cardiomyopathy (n, (n%))	76 (20.32%)	22 (18.96%)	54 (20.93%)	0.053
	Endocrine diseases (n, (n%))	47 (12.56%)	15 (12.93%)	32 (12.40%)	0.06

**Table 1: Baseline Characteristics assessed in our study and compared between the 2 groups.; yo: years old; AF: Atrial fibrillation; HF: Heart failure**

on diuretics, 20.58% on aspirin, 22.45% statins, 18.44% antiarrhythmic agents. Approximately 9.89% of our patients had a prescription of antiplatelet agents and anticoagulant therapy.

Compared with VKAs, NOACs were more commonly recommended in patients with history of stroke and with higher thromboembolic risk ( $p < 0.001$ ).

A worse QoL was associated with comorbidities ( $p < 0.001$ ), polypharmacy ( $p = 0.001$ ), and previous treatment with VKA ( $p = 0.002$ ).

In patients with NOAC, EQ-5D-3L total score was  $75.6 \pm 20.9$  and the visual analogue scale ranked  $63.1 \pm 20.6$ . In comparison, the total score of this questionnaire in VKA patients was  $73.1 \pm 18.6$  and the visual analogue scale was  $58.7 \pm 19.2$ . The scores obtained from the QoL questionnaire are presented in figure 1. (Figure 1)

By comparing these two groups (NOAC vs VKA), we can appreciate a better QoL for patients from the first lot in accordance with better results obtained in the questionnaire, as presented in table 2. Patients from the both groups strongly expressed their desire for improving their QoL.

AF is also associated with increased mortality. The mortality rate after AF was 15.77% at 6 months, 22.39% in one year, 28.87% at 18 months and reached at 35.82% in 2 years.

## Discussions

The relationships between QoL and different disease states in clinical AF are largely unexplored. Some of the most common conditions associated with AF (stroke, cognitive disorder) are responsible for 10–40% of hospitalized AF patients each year. [19] *ORBIT-AF*, *ONTARGET* and *TRANSCEND* studies include decreased QoL as a deteriorating condition that increases the number of hospitalization [20,21].

It is estimated that more than half of the patients in selected populations have episodes of silent AF [22].

Most of the times, the patient does recall and can very well describe the episode of arrhythmia, even if these could not be validated throughout electrocardiogram (ECG). These repeated episodes are disturbing and frustrating for the patient and sometimes even have a negative impact on the patient's activities and social life. There are also times, when the patient does not have the memory of the episode. In patients with persistent or permanent AF symptoms can be conspicuous and patients can't describe having an arrhythmia.

Undiagnosed AF is common; but this condition may only be materialized when a critical and often difficult-to-reverse pathology occurs (e.g. stroke, decompensated heart failure), or throughout loop-recorder or newer devices that use tele-monitoring; nevertheless, these are for the future to approach. All of these only contribute to significantly reduce the patient's QoL.

Regarding the symptom assessment and severity in AF, EHRA suggested the EHRA symptom scale [23].

We should be able to quantify patients' perceptions of their disease and patients' reported outcomes by defining the efficacy of new treatments and determining the quality of health care.

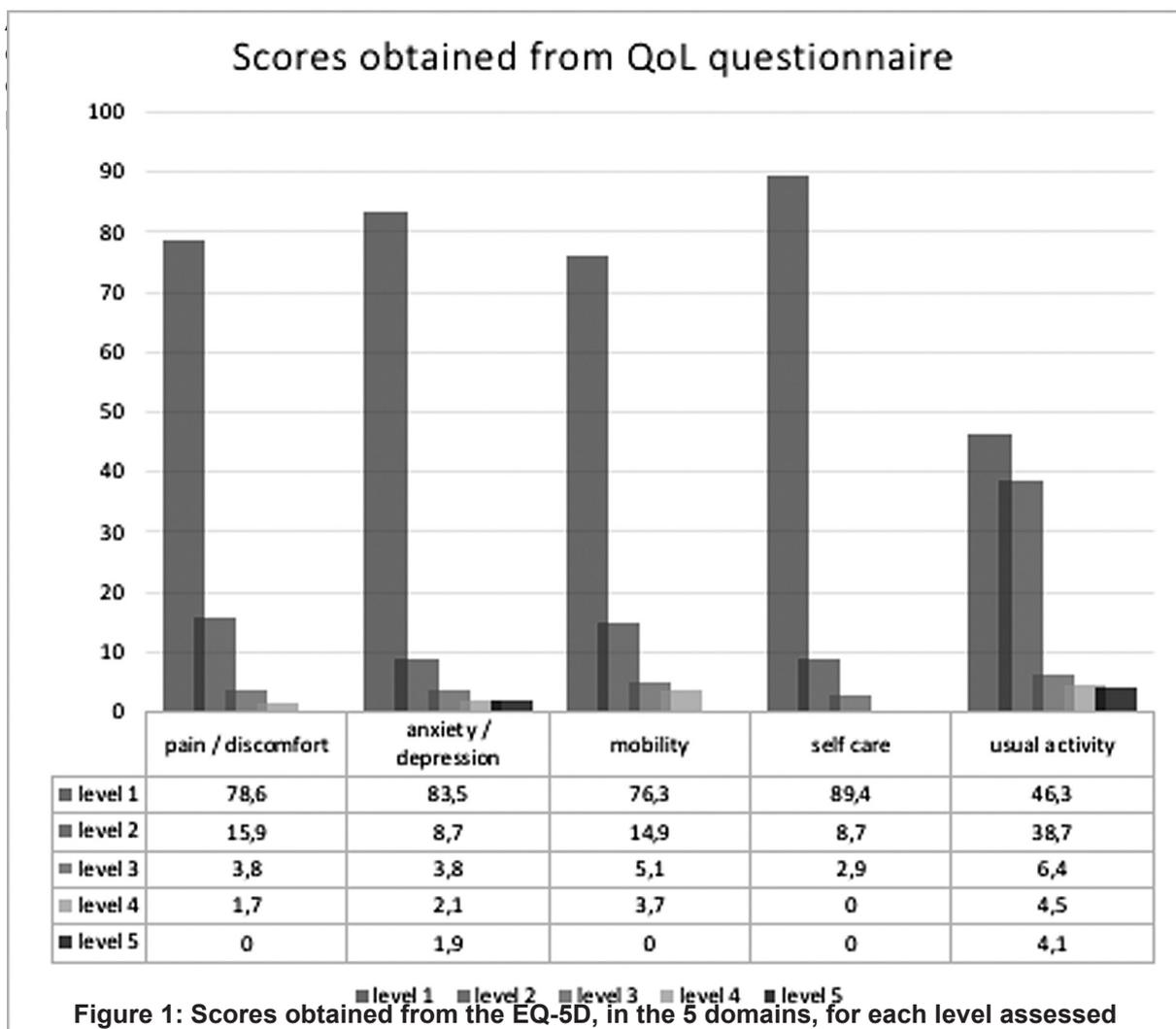
There are generic and symptoms assessing scales developed for measuring this pathology.

EQ-5D is an easy-to-use, extensively validated scale for most languages, benefitting from a long track record of use in a variety of medical conditions, a well-accepted method for transforming raw scores to preference-based utility weights and generalizability; these are just some of its advantages, but there are extensive data on AF already collected using this method. Maybe one of the most suitable examples is the EURObservational Research Programme, with the acronym EORP registry, which uses EQ-5D questionnaire to assess the patient QoL.

Although it may not be sensitive to health-related QoL aspects correlated to AF not covered by the five generic dimensions, the questionnaire, by design, reflects general health and functioning. The scores among AF patients are strongly influenced by patient demographics and comorbid conditions, but less sensitive to change in older AF patients with multiple health problems [15].

*Short Form Heart Survey: SF-36* measures the limitations in physical activities caused by health problems, general mental health (psychological distress and well-being), limitations in usual role activities due to emotional problems, vitality (energy and fatigue), general health perceptions.

AF-specific questionnaires, like *AFEQT*, allow patients to quantify their limitations and the extent to which they are attributable to a specific disease. Initially it was developed as a 42-item questionnaire to assess the impact of AF and its treatment on patients' symptoms, behaving, and daily activities through six domains: symptoms, social functioning, physical functioning, emotional running, treatment concerns, and treatment satisfaction. Later, it was renewed as



EQ-5D-3L index value for the whole cohort

EQ index	Whole cohort	
	NOAC subgroup	VKA subgroup
Mean	0.45	0.55
Standard error	0.013	0.015
Median	0.40	0.55
25th	0.30	0.50
75th	0.50	0.60
N	114	260

**Table 2: Index value from the questionnaire**

Other AF specific questionnaires (QLAF, AF-QoL, AFQLQ), or symptom specific scales (*Atrial Fibrillation Severity Scale: AFSS*) are relatively time-consuming and have uncertain generalizability. EHRA AF symptom scale has limited clinical data, and future studies are required to validate it [15].

The assessment of QoL is still not standardized, and many assessment tools have shortcomings.

Integrated care includes a multidisciplinary approach with the help of nurses specialising in AF, primary care physicians, cardiologists, stroke specialists, allied health practitioners and informed patients. For complex and difficult decisions, particularly for patients after failed rhythm control, an AF Heart Team should advise future management, consisting of a cardiologist, interventional electrophysiologist and cardiac surgeon, all with experience in managing AF.

There are on-going trials about measuring the effect of nurse practitioner (NP)-led care on health-related quality of life in adult patients with atrial fibrillation. The study wants to determine the effect of NP-led AF care on health-related quality of life in patients with AF, as well as to measure its impact on relevant outcomes such as death, hospitalization, and emergency department visits. Future findings may have implications for delivery of care to patients with AF [24].

In the *SAFE-T study* (n = 1180), patients with persistent AF, restoration and maintenance of sinus rhythm was associated with improvements in QoL scores.

Several patient-operated devices [25] and extended continuous ECG monitoring using skin patch recorders have been validated for the detection of paroxysmal AF [26].

The detection of asymptomatic AF by new technologies, such as smartphone cases with ECG electrodes, smartwatches, and blood pressure devices with AF detection algorithms, has not yet been formally evaluated against an established arrhythmia detection method [27].

### Future research

Integrated AF management, and lifestyle modifications are clearly developing the required evidence, while areas such as rate control needs better studies to be included in future guidelines. Integrated care models that provide patient-centred care in while maintaining access to all specialist treatment options, emerge as the best approach to achieve consistent delivery of these chronic treatments to

all patients with atrial fibrillation [28]. These should include: a comprehensive treatment approach including AF risk factor management; a patient-centred approach with active patient involvement in the care process; well prepared, proactive, multidisciplinary treatment teams; and dedicated smart software to guide decision making in the treatment team. It is mandatory to integrate the evidence in AF specific and risk factor management and to extend the integrated care approach to AF management [29].

### Limitations of the study

This is a small single-centre retrospective non-randomized study, without a control group. This makes interpretation of data difficult and we could not determine the appropriateness of EQ-5D. The data shown in this study represent the clinical practice in our centre, so they cannot be generalized. However, compared with the data in the literature the prevalence of AF comorbidities is quite similar with the general data, except for the stroke, but this could be explained throughout the stroke unit available in our hospital. There are many lost-to-follow up patients compared to the total number of patients. We did not perform echocardiographic assessments in the follow-up period, neither echocardiographic assessment of the left atrial strain and of the left atrial functions.

### Conclusions

AF has a major impact on patients' quality-of-life, but measuring this outcome it has proven to be challenging. Thus far, there are limited data assessing QoL in a general AF patient population. A simple and easy-to-use scale, a comprehensive, validated, symptom-specific questionnaire to measure the QoL for patients with AF and its treatment is not yet available. It is mandatory to have a measurement tool to accurately and reliably quantify the effect of AF on patients' QoL, for both clinical and research purposes.

Quality of life is impaired in the majority of patients with AF, thus it should become the keystone for care management. Patients strongly expressed their desire to improve their QoL.

Satisfaction and QoL with with NOACs are higher compared with those with VKAs. A worse QoL was associated with comorbidities, polypragmasy, and previous treatment with VKA.

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