Title

The influence of progression of atrial fibrillation on quality of life; a report from the Euro Heart Survey

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Structured Abstract

Aims

Progression of atrial fibrillation (AF) from paroxysmal to persistent forms is an active field of research. The influence of AF progression on health related quality of life (HRQoL) is currently unknown. We aimed to assess the influence of AF progression on HRQoL, and whether this association is mediated through symptoms, treatment and major adverse events.

Methods

In the Euro Heart Survey, 967 patients were included with paroxysmal AF who filled out EuroQoL-5D at baseline and at 1 year follow-up.

Results

Those who progressed (n=132, 13.6%) developed more problems during follow-up than those who did not, on all EuroQoL-5D domains (increase in problems on Mobility 20.5% vs 11.4%; Self-care 12.9% vs 6.2%; Usual activities 23.5% vs 14.0%; Pain / discomfort 20.5% vs 13.7%; and Anxiety / depression 22.7% vs 15.7%; all $p<0.05$), leading to a decrease in utility (baseline 0.744±0.26, follow-up 0.674±0.36; difference -0.07 (95%CI [-0.126,-0.013], p=0.02). Multivariate analysis showed that the effect of progression on utility is mediated by a large effect of adverse events (stroke (-0.27 (95%CI [-0.43,-0.11]); p=0.001), heart failure (-0.12 (95%CI [-0.20,-0.05]); p=0.001), malignancy (-0.31 (95%CI [-0.56,-0.05]); p=0.02) or implantation of an implantable cardiac defibrillator (-0.12 (95%CI [-0.23,-0.02]); p=0.03)), as well as symptomatic AF (-0.04 (95%CI [-0.08,-0.01]); p=0.008).

Conclusion

AF progression is associated with a decrease in HRQoL. However, multivariate analysis revealed that AF progression itself does not have a negative effect on HRQoL, but that this effect can be attributed to a minor effect of the associated symptoms and a major effect of associated adverse events.

Keywords

Atrial fibrillation; progression of atrial fibrillation; health related quality of life

Condensed abstract

In 967 patients with paroxysmal atrial fibrillation (AF), progression to persistent AF (n=132) was associated with a decrease in quality of life during 1 year (difference in utility -0.07 (95%CI [-0.013,-0.126],p=0.02)). This was mediated by a major effect of adverse events, and a minor effect of AF being symptomatic.

What's new

- AF progression is associated with a decrease in quality of life
- This decrease can be attributed to the associated occurrence of symptoms and adverse events, not to progression itself

Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia, has been demonstrated to lead to a considerable reduction in health-related quality of life (HRQoL).[1] While rarely life-threatening in itself, AF is associated with several arrhythmia-associated symptoms, such as palpitations, exercise intolerance, dizziness and dyspnoea, which can have substantial influence on the possibility to undertake daily activities.[2] In addition, AF is associated with an increased incidence of major adverse events, such as stroke and heart failure, which are associated with increased mortality, but also have detrimental effects on daily functioning and HRQoL.[3] The consequences of AF treatment, such as side effects of drugs, interventions, and especially hospitalization, may also have a negative impact on HRQoL. Lastly, the diagnosis of AF may be associated with considerable psychological distress.

AF is a progressive disease that clinically may progress from short-lasting self-terminating paroxysms towards more non-self-terminating sustained forms, such as persistent and permanent AF.[4] This progression is usually accompanied by electrical and structural changes of the left atrium.[5] Recent reports suggest that predictors of AF progression lie in factors that represent an impaired vascular status, leading to the observation that patients who progress from paroxysmal to more sustained forms of AF are those who will have adverse events.[6] As AF progression appears to correlate with adverse events, one may hypothesize that AF progression has a detrimental effect on HRQoL.

Current treatment of AF has HRQoL as a major focus, and aims to preserve or improve HRQoL by two strategies[4]: on one hand, to prevent serious adverse events through life style changes, anticoagulation upon indication and adequate vascular protective therapy, and on the other hand to

alleviate symptoms associated with AF if necessary. In addition to this, prevention of AF progression has recently been proposed as a treatment goal in itself.[7] The influence of AF progression on HRQoL, and whether this is mediated by adverse events and symptoms, is however currently unknown.

In this report, we used the data from the Euro Heart Survey (EHS) on Atrial Fibrillation to assess the influence of AF progression on HRQoL, and whether this association is mediated through symptoms or concomitant vascular disease and major cardiac events.

Methods

A description of the methods and data collection of the EHS on AF has been given in detail earlier.[8] In 2003 and 2004, 5,333 consecutive patients with AF on an ECG or Holter recording in the previous 12 months were included in the Euro Heart Survey, a large-scale registry, at cardiology departments of 182 hospitals in 35 countries. The study protocol was submitted to the institutional review board or ethical committee of all participating centres and approved or waived for the requirement of formal approval being an observational survey.

Only patients with paroxysmal AF at baseline were included: patients with known paroxysmal AF (spontaneous conversion to sinus rhythm <7 days; 1,517 patients) and patients with first detected AF that converted to sinus rhythm spontaneously or through pharmacological cardioversion during the index visit (238 patients). Out of these, rhythm status at follow-up was available in 1,219 patients, and amongst these, complete EuroQoL-5D data at both baseline and follow-up was available for 967 patients. The definition of AF-progression by de Vos et al[6] was used: paroxysmal AF at baseline becoming persistent or permanent AF at 1-year follow-up, or first detected AF at baseline with spontaneous or pharmacological cardioversion to sinus rhythm during admission becoming persistent or permanent AF at 1-year follow-up.

Quality of life measurements

The EuroQol-5D consists of five domains (mobility, self-care, usual activities, pain / discomfort, and anxiety / depression) with three possible answers for each domain (no problems, moderate problems, or severe problems), generating 3^5=243 possible health states. These health states, at baseline and follow-up, were translated into a single index – the utility score– using the United Kingdom time trade-off value set.[9] No problems on each of the EuroQol-5D domains corresponds to a utility of 1.0 (best possible health), with deductions for reporting problems on any of the EuroQol-5D. A utility score of 0 is equivalent to death, while negative values are possible (indicating a health status worse than death).

Statistical analysis

Data analysis was performed with IBM SPSS for Windows statistical software (version 23.0, IBM Corp., Armonk, NY, USA) and regression analysis using Stata Statistical Software Release 10.0 (StataCorp LP, College Station, TX, USA). Baseline characteristics for the groups with and without AF progression are presented as mean±SD for continuous variables, or number (percentage) for categorical variables. Baseline characteristics of the groups were compared using an independent *t*-test for continuous variables and a χ^2–test for categorical variables. Increase in problems experienced at each of the EuroQoL-5D domains was defined as 'no problems' at baseline and 'some problems' or 'severe problems' at 1-year follow-up, or 'some problems' at baseline and 'severe problems' at follow-up. The fractions showing an increase were compared for the group with and without AF progression using χ^2–tests. Utility scores at baseline and follow-up were compared using paired-samples *t*-testing.

Regression analyses

Apart from AF progression, the following parameters were tested for a significant relation with the change in utility over 1 year ($p<0.1$) in univariate ordinary least squares regression using robust

standard errors: age at inclusion, sex, domestic status, body mass index, level of physical activity, medical history (hypertension, diabetes, coronary artery disease, myocardial infarction, valvular heart disease, congestive heart failure, hyperthyroidism or hypothyroidism, chronic obstructive pulmonary disease, malignancy, peripheral vascular disease, renal failure, transient ischemic attack (TIA), stroke), AF symptoms (palpitations, chest pain, dyspnoea, syncope, dizziness, fatigue), events during follow-up (stable angina, acute coronary syndrome, TIA, ischemic or haemorrhagic stroke, peripheral embolism, pulmonary embolism, syncope, asystole, malignancy, heart failure), AF related parameters (AF recurrence, number of pharmacological cardioversions, number of electrical cardioversions, use of beta-blockers, calcium channel blocker, anti-arrhythmic drugs (Vaughan-Williams class 1a, 1c, 3)) and cardiac treatment during follow-up (catheter ablation, AF surgery, pacemaker or ICD implantation, percutaneous coronary intervention, coronary artery bypass surgery, valvular surgery).

All parameters that showed a significant relation were included in multivariate linear regression using robust standard errors. No significant correlations between predictors were found. Backward variable elimination ($p>0.05$) was applied, not forcing any specific variable to be retained.

All tests were performed 2-sided. Overall, a p value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the patients with complete EuroQoL-5D at baseline and follow-up (n=967) were comparable to those with incomplete EuroQoL-5D (n=252), with only differences in regular physical activity (36.8% vs 27.6%; p=0.008) and history of stroke (2.4% vs 6.5%; p = 0.001).

In the 967 patients included, progression of AF occurred in 132 patients (13.7%). Baseline characteristics of patients with and without AF progression are shown in Table 1. Patients with AF progression were on average older (66.1±11.2 vs. 62.8±13.1 years; p=0.007) and had larger left atria (LA diameter 45.9±8.8 vs 42.9±7.6 mm; p < 0.001). Hypertension (71.2% vs 59.8%), left ventricular hypertrophy (50.4% vs 29.8%) coronary artery disease (36.0% vs 23.2%), heart failure (31.5% vs

15.5%), chronic obstructive pulmonary disease (18.3% vs 9.6%) and history of TIA (10.7% vs 5.2%; all p<0.01) were more prevalent in the AF progression group, leading to a higher mean CHA_2DS_2VASc-score of 3.2±1.9 vs 2.4±1.7 (p<0.01) and HATCH-score of 2.2±1.5 vs 1.3±1.3 (p<0.01). Medication use, further medical history and event rates in both groups were reported previously. [6]

At baseline, patients that will progress experienced more problems (some problems or severe problems) on each domain of the EuroQoL-5D than those who did not progress (Table 2). Furthermore, in the patients that progressed, the percentage of patients that experienced more problems on each of the domains at 1-year follow-up than at baseline was significantly higher than in the patients that did not progress (Figure 1; Mobility 20.5% vs 11.4%; Self-care 12.9% vs 6.2%; Usual activities 23.5% vs 14.0%; Pain / discomfort 20.5% vs 13.7%; and Anxiety / depression 22.7% vs 15.7%; all p<0.05).

While the calculated utility for the group without AF progression increases during 1 year (baseline 0.796±0.23, 1 year 0.814±0.23; p= 0.04; difference +0.018 (95% CI [0.008,0.033])), the utility decreased significantly in the group with AF progression (baseline 0.744±0.26, follow-up 0.674±0.36; p=0.02; difference -0.07 (95% CI [-0.126,-0.013])) (Figure 2).

Multivariate analysis showed that stroke (-0.27 (95% CI [-0.43,-0.11]); p=0.001), heart failure (-0.12 (95% CI [-0.20,-0.05]); p=0.001), malignancy (-0.31 (95% CI [-0.56,-0.05]); p=0.017) or implantation of an implantable cardiac defibrillator (-0.12 (95% CI [-0.23,-0.02]); p=0.03) during follow-up had the largest negative effect on the change in utility during this year. Patients with symptomatic AF had a reduction in utility of -0.04 (95% CI [-0.08,-0.01]; p=0.008), except when this symptom was dizziness (+0.06 (95% CI [0.02,0.10]); p=0.004). Patients with diabetes mellitus experienced an increase of utility during follow-up of 0.04 (95% CI [0.01,0.07]; p=0.006) (Table 3). Notably, in multivariate regression analysis, progression of AF is not a determinant of change in utility.

Discussion

This report is the first to show the association between AF progression and HRQoL. From this report, it can be concluded that AF progression is associated with a decrease in quality of life (HRQoL) during the year in which progression occurs, indicated by an increase in problems reported on each of the EuroQoL-5D domains, leading to a change in utility of -0.07 (95% CI [-0.126,-0.013]) which appears clinically significant.[10] Upon correcting for major adverse events and symptoms during follow-up, this association disappears. This suggests that the decrease of HRQoL associated with AF progression is mediated by adverse events and symptoms: there is a significant relationship between AF progression and adverse events and symptoms,[6] a significant relation between utility and both adverse events and symptoms and progression, and the relationship between progression and utility becomes non-significant upon correction for adverse events and symptoms.

The main determinants of a reduction in utility in this population of patients with paroxysmal AF were the occurrence of stroke, heart failure, malignancy and ICD implantation during follow-up, which was already known for AF patients in general[3]. Already, one of the cornerstones of current treatment is focusing on the reduction of the incidence of cardiac adverse events,[4] but the fact that these events still occur indicates that our current treatment strategies are not sufficient yet. Although the percentage of patients that will experience such an event is low, the effect on HRQoL is large. This report emphasizes that strategies focused on the prevention of adverse events may ultimately have a major influence on HRQoL, irrespective of their influence on AF progression.

Next to adverse events, symptomatic AF is a determinant of the change in utility during one year. The utility of patients that remain symptomatic is reduced modestly (-0.04 (95% CI [-0.08,-0.01]; p=0.008)). This effect is cancelled out if the symptom is dizziness, as this symptom is usually readily treatable by reducing the dose of negative chronotropic drugs or implanting a pacemaker in case of sinus arrest. If patients remain symptomatic, despite the efforts of patient and physician, it is only to be expected that this has a detrimental effect on the quality of life. [3] Furthermore, this underlines

the need to continue focusing on reducing AF symptoms through more modern rhythm control strategies, with pharmacological as well as interventional measures.

Patients in this cohort who suffered from diabetes experienced an increase in quality of life during one year. This may be explained by the correction for events in the multivariate analysis, as diabetes without complications may have little influence on the perceived HRQoL. The increase in HRQoL may be explained by the fact that these patients visit a doctor more frequently than patients without diabetes, which may have a beneficial effect, or they get more comfortable living with their diabetes as time passes since their diagnosis.

On one hand, one may hypothesize that AF progression in itself is a cause for adverse events. Based on this hypothesis, preventing AF progression may be instrumental in preventing the associated events and the associated decrease in HRQoL. Although trials have never shown benefit of rhythm over rate control in the long term on clinical endpoints,[11, 12] more recent reports have shown signals that there is an association between the duration of AF episodes and stroke risk,[13, 14] and that rhythm control may reduce the number of strokes[15] and mortality.[16] Furthermore, our current strategy of rhythm control has not been shown to improve HRQoL to a clinically significant extent.[17, 18] This led to the design of the EAST trial, that aims to inhibit AF progression through modern and early rhythm control, in which HRQoL will be a key secondary outcome.[7] Results from this trial should show whether early rhythm control could limit progression – and thereby retain HRQoL more effectively than a rate control strategy. Our current study suggests that preventing AF progression may only influence HRQoL if indeed this focus on inhibition of rhythm deterioration prevents major adverse cardiac and cerebrovascular events. As rhythm control generally encompasses intensive treatment, including potentially hazardous anti-arrhythmic drug use and invasive therapy, the net effect of inhibition of progression of AF on the quality of life remains to be determined.

On the other hand, based on the association between the occurrence of major adverse events and AF progression, it may be hypothesized that both AF progression and adverse events are the result of

an underlying common mechanism. One of the proposed underlying mechanisms is an early state of hypercoagulability leading to both an atrial substrate for more persistent forms of AF and adverse events.[19] Early intervention in this hypercoagulable state may thus improve both progression rates and incidence of adverse events. Furthermore, this hypothesis implicate a less stringent need for rhythm control, as events do not relate to the rhythm status, such that side effects of intensive treatment associated with aggressive rhythm control can be averted.[20]

Lastly, the results reported here support the notion that – also from the perspective of HRQoL – the current daily practice of classifying AF by the duration of the episodes - ie paroxysmal and persistent AF - rather than the underlying pathology may need reconsideration,[21] as the results indicate that HRQoL is not so much determined by the duration of the episodes of the arrhythmia, but more by the associated events and symptoms.

Strengths and Limitations

The major strength of this report lies in the fact that the Euro Heart Survey provided longitudinal data on a large group of real life patients across Europe, which represent the daily clinical population better than results acquired in clinical trials.

For this report, only those patients who filled out the HRQoL questionnaires both at baseline and follow-up were used, which may have led to excluding those patients that were too sick or frail to fill out the questionnaires, or who died during follow-up. This may have influenced HRQoL measures, especially since from a previous report on the study population from which this cohort is selected, it is known that responders differed from non-responders on both demographic and disease-related characteristics.[3] Furthermore, HRQoL was measured using EuroQoL-5D as disease specific HRQoL questionnaires were not yet available. We corrected for treatments chosen, but were not able to assess the effectiveness of these treatments. The data from this study were acquired in 2003-2004, yet the outcomes we describe have remained relevant over the past decade, as AF progression is still a clinically identifiable problem, as well as the importance of stroke, heart failure, malignancy, ICD

implantation and symptomatic AF with respect to HRQoL remain relevant. We were not able to determine whether AF progression preceded events. Lastly, assessment of personality was not included in the EHS, which did not allow us to correct the user reported quality of life for differences in personality and thus coping strategies to deal with adverse events.

Conclusion

To conclude, quality of life in patients with AF progression decreases, which is largely caused by adverse events and to a smaller extent by AF symptoms. An effect of inhibition of AF progression on HRQoL is thus mainly to be expected if future studies show that inhibiting AF progression leads to fewer adverse events.

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Table 1. Baseline characteristics, grouped by the presence of AF progression.

n=	All patients 967	No AF progression 835	AF Progression 132	p-value
Age (years)	63.3 ± 12.9	62.8 ± 13.1	66.1 ± 11.2	**0.007**
Female	417 (43.1)	353 (42.3)	64 (48.5)	0.18
Body Mass Index (km/m^2)	27.4 ± 4.2	27.4 ± 4.1	27.9 ± 4.9	0.18
Regular physical activity	356 (36.8)	320 (40.7)	36 (30.0)	0.13
Echocardiogram				
Left atrial diameter (mm)	43.3 ± 7.8	42.9 ± 7.6	45.9 ± 8.8	**< 0.001**
Left ventricular hypertrophy	262 (32.7)	205 (29.8)	57 (50.4)	**< 0.001**
Type of AF				
First detected	149 (15.3)	127 (15.1)	22 (16.7)	0.64
Paroxysmal	825 (84.7)	715 (84.9)	110 (83.3)	
Underlying disease				
Hypertension	593 (61.3)	499 (59.8)	94 (71.2)	**0.01**
Coronary artery disease	205 (25.0)	164 (23.2)	41 (36.0)	**0.003**
Diabetes mellitus	127 (13.1)	102 (12.2)	25 (18.9)	0.06
Valvular disease	180 (18.8)	149 (18.0)	31 (24.2)	0.09
Heart failure	169 (17.7)	128 (15.5)	41 (31.5)	**< 0.001**
Chronic obstructive pulmonary disease	103 (10.8)	79 (9.6)	24 (18.3)	**0.003**
Hyperthyroidism	50 (5.4)	42 (5.3)	8 (6.2)	0.67
History of stroke	23 (2.4)	17 (2.1)	6 (4.6)	0.08
History of TIA	57 (5.9)	43 (5.2)	14 (10.7)	**0.01**
Malignancy	41 (4.4)	38 (4.7)	3 (2.4)	0.24
Peripheral vascular disease	57 (6.0)	46 (5.6)	11 (8.5)	0.19
Renal failure	41 (4.2)	33 (4.0)	8 (6.1)	0.26
CHA_2DS_2-VASc score	2.5 ± 1.8	2.4 ± 1.7	3.2 ± 1.9	**< 0.001**
HATCH score	1.5 ± 1.4	1.3 ± 1.3	2.2 ± 1.5	**< 0.001**

Data are expressed as the mean±SD or number (percentage) of patients. AF = atrial fibrillation; TIA = transient ischemic attack; CHA_2DS_2-VASc-score = Congestive heart failure (1 point), Hypertension (1 point), Age >75 years (2 points), Diabetes mellitus (1 point), Prior Stroke or TIA (2 points), Vascular disease (1 point), Age 65 - 74 years (1 point), Sex category (female = 1 point); HATCH-score = Hypertension (1 point), Age >75 years (1 point), Stroke or transient ischemic attack (2 points), Chronic obstructive pulmonary disease (1 point), and Heart failure (2 points).

Table 2. Percentage of patients that report no, some and severe problems on the five domains of EuroQoL-5D at baseline and after 1 year, in those that will not progress (n=835) versus those that will (n=132). P-values are derived from the comparison between non-progressors and progressors, a p-value <0.05 is considered significant.

	Baseline							Follow-up						
	Non-progressors			Progressors			p	Non-progressors			Progressors			p
Problems:	No	Some	Severe	No	Some	Severe		No	Some	Severe	No	Some	Severe	
Mobility	67.2	32.1	0.7	57.6	40.9	1.5	0.09	68.9	30.5	0.6	51.5	42.4	6.1	**<0.001**
Self-care	89.3	10.3	0.4	80.3	19.7	0.0	**0.006**	88.5	11.3	0.2	78.8	15.9	5.3	**<0.001**
Usual activities	72.9	25.9	1.2	56.8	42.4	0.8	**<0.001**	70.4	28.0	1.6	50.0	41.7	8.3	**<0.001**
Pain / discomfort	61.7	35.9	2.4	53.8	43.9	2.3	0.21	65.7	32.3	1.9	53.8	40.2	6.1	**0.002**
Anxiety / depression	62.9	32.5	4.7	50.0	43.9	6.1	**0.02**	64.1	32.5	3.5	47.7	43.2	9.1	**<0.001**

Table 3. Determinants of the change in utility during one year of follow-up. Notably, progression of atrial fibrillation (AF) is not a determinant of change in utility.

	Coefficient	p
Diabetes mellitus	0.04 [0.01,0.07]	**0.006**
Symptomatic AF	-0.04 [-0.08,-0.01]	**0.008**
Dizziness	0.06 [0.02,0.10]	**0.004**
Stroke during FU	-0.27 [-0.43,-0.11]	**0.001**
Heart failure during FU	-0.12 [-0.20,-0.05]	**0.001**
Malignancy during FU	-0.31 [-0.56,-0.05]	**0.017**
ICD during FU	-0.12 [-0.23,-0.02]	**0.030**

Shown are the coefficient [95% CI] and p-value of multivariate ordinary least squares regression. CI=Confidence Interval; FU=Follow-up; ICD=Implantable Cardiac Defibrillator.

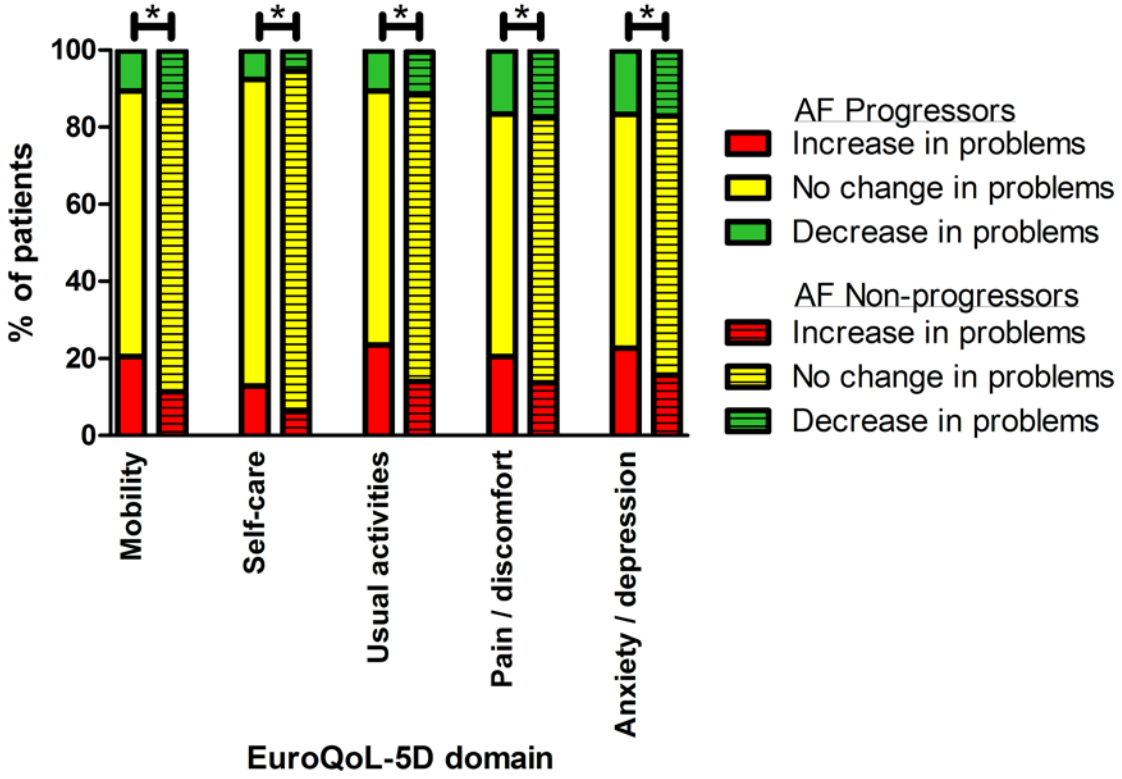

*Figure 1. Percentage of patients reporting an increase, no change and a decrease problems on the EuroQoL-5D domain at 1 year than at baseline, for the groups without and with AF-progression. * indicates $p < 0.05$.*

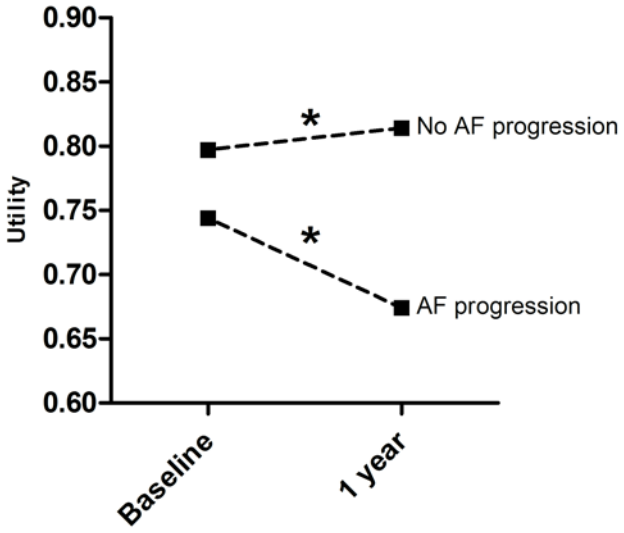

*Figure 2. In patients without progression of atrial fibrillation (AF), the utility increases from 0.796±0.23 at baseline to 0.814±0.23 at 1 year (p=0.04), while in patients with AF progression it decreases from 0.744±0.26 to 0.674±0.36 (p=0.02). Utility scores range from 0 (health state equivalent to death) to 1.0 (best possible health), negative values are possible. * indicates p < 0.05.*