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Associations of symptoms and quality of life with outcomes in patients with atrial fibrillation

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Key questions

What is already known about this subject?

The associations of atrial fibrillation (AF)-related symptoms with cardiovascular outcomes was inconsistent in prior studies. Little data is available for the association of quality of life (QoL) with adverse outcomes.

What does this study add?

AF-related symptoms significantly changed over time and were not associated with adverse cardiovascular outcomes. Reduced QoL was strongly associated with a multitude of adverse clinical outcomes, including death. AF patients with a low QoL therefore represent a high-risk patient population.

How might this impact on clinical practice?

Decisions regarding oral anticoagulation should not be based on the presence or absence of AF-related symptoms. QoL may be an easily available and cost effective screening tool to identify AF patients at high risk for adverse outcomes, which need careful medical attention and might benefit from more intense treatment of risk factors and comorbidities.

Abstract

Objective

We aimed to investigate changes in atrial fibrillation (AF)-related symptoms and quality of life (QoL) over time, and their impact on prognosis.

Methods

We prospectively followed 3836 patients with known AF for a mean of 3.7 years. Information on AF-related symptoms and QoL was obtained yearly. The primary endpoint was a composite of stroke or systemic embolism. Main secondary endpoints included stroke subtypes, all-cause mortality, cardiovascular death, hospitalization for congestive heart failure (CHF), myocardial infarction and major bleeding. We assessed associations using multivariable, time-updated Cox proportional-hazards models.

Results

Mean age was 72 years, 72% were male. Patients with AF-related symptoms (66%) were younger (70 vs 74 years, p<0.0001), more often had paroxysmal AF (56 vs 37%, p<0.0001) and had lower QoL (71 vs 72 points, p=0.009). The incidence of the primary endpoint was 1.05 and 1.02 per 100 person-years in patients with and without symptoms, respectively. The multivariable adjusted hazard ratio (aHR) (95% confidence intervals) for the primary endpoint was 1.11 (0.77; 1.59; p=0.56) for AF-related symptoms. AF-related symptoms were not associated with any of the secondary endpoints. QoL was not significantly related to the primary endpoint [aHR per 5-point increase 0.98 (0.94; 1.03; p=0.37)], but was significantly related to CHF hospitalizations [0.92 (0.90; 0.94; p<0.0001)], cardiovascular death [0.90 (0.86; 0.95; p<0.0001)] and all-cause mortality [0.88 (0.86; 0.90; p<0.0001)].

Conclusions

AF-related symptoms were not associated with adverse outcomes and should therefore not be the basis for prognostic treatment decisions. QoL was strongly associated with CHF, cardiovascular death and all-cause mortality.

Key words: Atrial fibrillation; Symptoms; Quality of Life; Mortality; Stroke.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it is associated with an increased risk for death, stroke and congestive heart failure (CHF).[1–5] AF-related symptoms are a frequent cause for emergency visits and an impaired quality of life (QoL).[6–8] The presence of symptoms is an important hint for the presence of AF, especially in intermittent AF, and may identify a population with more severe AF and a higher cardiovascular risk.[9] The association of AF-related symptoms with adverse cardiovascular outcomes, especially stroke, is of special interest for AF screening. If asymptomatic AF is not associated with potentially preventable outcomes, the usefulness of AF screening would be questionable. Furthermore, the prognostic impact of QoL, a more direct measure of patient wellbeing, has not been studied in detail.[9,10]

Prior studies have shown inconsistent associations of AF-related symptoms with cardiovascular outcomes. In addition, they were somewhat limited by a short follow-up duration and assessment of AF-related symptoms and QoL only at study entry.[7,9–12] Both metrics may substantially change over time, either spontaneously or due to therapeutic interventions.[13,14] Thus, failure to update these variables over time may induce significant bias in the assessment of AF-related symptoms and QoL with adverse cardiovascular events.

In the current analysis, we therefore aimed to investigate the association of AF-related symptoms, QoL and their changes over time with incident stroke and other cardiovascular outcomes in a large, prospective sample of AF patients.

Methods

Patient population

The Basel Atrial Fibrillation (BEAT-AF) and Swiss Atrial Fibrillation (Swiss-AF) cohorts are two ongoing, prospective, multicentre studies in Switzerland. Details about the methodology of BEAT-AF and Swiss-AF have been published previously.[5,15,16] Main inclusion criteria for both studies were previously documented AF and an age ≥65 years. A limited, predefined subset of patients aged 45-65 years were enrolled in both cohorts in order to study the effects of AF in patients, who are still in the active workforce. Main exclusion criteria were inability to give informed consent, the presence of temporary forms of AF due to secondary causes, or any acute illness in the last 4 weeks. The latter group was eligible for enrolment after stabilization or resolution of the underlying condition. The study protocols of both cohorts were approved by the local ethics committees and informed written consent was obtained from each participant. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Of 3961 (Swiss-AF 2408; Beat-AF 1553) participants in the two cohorts, 58 (1.5%) were excluded due to missing information about AF-related symptoms at study enrolment and 67 (1.7%) due to missing follow-up, leaving 3836 (96.8%) subjects for the current analyses.

Assessment of study variables

During an in person baseline study visit, trained study personnel administered study questionnaires inquiring about subject demographics, AF-related symptoms, QoL, AF-type, interventional and medical treatment for AF, comorbidities and risk factors. AF-related symptoms assessed in this study included palpitations, dizziness, angina

pectoris, dyspnea, fatigue, syncope, exercise intolerance or other related symptoms. Multiple responses per patient were possible. AF-related symptoms were considered to be present if a patient responded yes to at least one symptom. In Swiss-AF, AF-related symptoms were also assessed using the European Heart Rhythm Association (EHRA) score. The EHRA score ranges from I-IV with I indicating no symptoms, II indicating mild symptoms, III indicating severe symptoms and IV indicating disabling symptoms.[17] For the assessment of QoL we used a visual analogue scale (VAS) ranging from 0-100, with higher values indicating a higher QoL.[18] AF was classified as paroxysmal (self-terminating AF lasting <7 days without cardioversion), persistent (AF sustained ≥7 days and/or requiring cardioversion) or permanent (acceptance of AF by the patient and physician without pursued rhythm control) according to guidelines at the time of study inception.[19] Weight and height were directly measured using calibrated devices. Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared.

Information on AF-related symptoms, QoL, comorbidities, risk factors and outcomes were updated annually. Annual follow-up visits were done by mail and phone calls in BEAT-AF and by in person study visits in Swiss-AF.

Outcome measurements

The primary outcome for this analysis was a composite of incident stroke and systemic arterial embolism. Secondary outcomes were the individual components of the primary endpoint, ischemic stroke, hemorrhagic stroke, all-cause mortality, cardiovascular death, hospitalization for CHF, myocardial infarction and major bleeding. Definitions of all outcomes are listed in the supplementary appendix. All outcomes were adjudicated by two independent physicians in a standardized manner

including all available information. In case of discordance, a third physician was consulted.

Statistical analysis

Baseline characteristics were stratified by symptom status at baseline. Categorical variables were presented as counts (percentages) and compared using Chi-square tests. The distribution of continuous variables was checked by visual inspection of the histogram and using skewness and kurtosis. All variables were normally distributed, and therefore presented as means (± standard deviations (SD)) and compared using Student's t-tests. We constructed separate Cox proportional hazards models to investigate the association of AF-related symptoms or QoL with adverse outcomes. In a first step, models were adjusted for age, sex and study cohort. In a second step, models were further adjusted for a prespecified list of risk factors, including history of CHF, hypertension, diabetes, stroke, myocardial infarction, vascular disease, history of renal failure, prior catheter ablation for AF, BMI, smoking status, education, use of beta-blockers, use of ACE-inhibitors or angiotensin II receptor blockers and use of oral anticoagulation and/or aspirin. All variables were time-updated at each available yearly follow-up visit, whenever appropriate. If a data point during follow-up was missing, parameter values were carried forward from the last follow-up visit. Medication variables were included as dichotomous variables (i.e. intake versus no intake). In order to reduce a possible alpha error introduced by multiple comparisons, we used the Benjamini-Hochberg procedure with a false discovery rate of 10% and provided corrected in addition to nominal p-values for the main analyses.

Analyses for the primary endpoint were then repeated in a combined model including both AF-related symptoms and QoL. In additional, exploratory analyses we assessed

the prognostic impact of the EHRA score, and evaluated the associations of individual symptoms present in at least 10% of patients at baseline in one combined model.

Pre-specified subgroup analyses stratified by sex (men vs women), age (<65 vs ≥65 years), AF-type (paroxysmal vs non-paroxysmal) and prior catheter ablation (yes vs no) were performed for the primary outcome. P values for interaction were calculated by adding multiplicative interaction terms in the non-stratified models. Due to low numbers of events in individual strata, analyses for individual symptoms and subgroup analyses were adjusted for age, sex and study cohort only. Due to the exploratory nature of these analyses, the interaction p values were not adjusted for multiple testing. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Corporation, Cary, North Carolina, USA).

Results

Baseline characteristics stratified by the presence or absence of AF-related symptoms are shown in Table 1. Symptomatic patients (66%) were less often male (67 vs 82%, p<0.0001), younger (70 vs 74 years, p<0.0001), had more often paroxysmal AF (56 vs 37%, p<0.0001) and a lower burden of comorbidities compared to asymptomatic patients (all p <0.0002). Furthermore, they were more often treated with medical (p=0.02) and interventional (p<0.0001) rhythm control, but less often anticoagulated (p<0.0001). The most frequent symptoms at baseline were palpitations (43%), dyspnea (25%) and fatigue (18%). The change in prevalence of AF-related symptoms over time is shown in Figure 1. Among Swiss-AF participants, the EHRA score was <II in 12% and 60% of patients with and without symptoms (p<0.0001).

Over a mean (SD) follow-up of 3.7 (1.9) years, 140 (3.6%) participants reached the primary endpoint. The incidence per 100 person years was 1.05 and 1.02 for patients with and without AF-related symptoms, respectively. Time-updated, multivariable Cox models found no significant associations of AF-related symptoms with the primary or any of the secondary endpoints (Table 2).

The presence of palpitations was associated with a lower risk of hospitalization for CHF (HR (95% CI) 0.75 (0.60; 0.93)), all-cause mortality (HR (95% CI) 0.80 (0.65; 0.99)) and cardiovascular death (HR (95% CI) 0.64 (0.43; 0.97)). The presence of dyspnea was associated with increased risks of hospitalization for CHF (HR (95% CI) 1.42 (1.14; 1.78)) and cardiovascular death (HR (95% CI) 1.67 (1.12; 2.51)). Fatigue was associated with increased risks for the primary endpoint (HR (95% CI) 1.59 (1.06; 2.38)) and any stroke (HR (95% CI) 1.59 (1.05; 2.41)). Exercise intolerance was associated with a decreased risk for hospitalizations for CHF (HR (95% CI) 0.66

(0.45; 0.95)). No associations were found for angina pectoris or dizziness with any of the endpoints (Table 3). We observed very similar results when the EHRA score was used as the main predictor variable instead of AF-related symptoms among Swiss-AF participants (Table S1). Subgroup analyses did not reveal any significant interactions for AF-related symptoms and the primary endpoint (Table S2).

Mean (SD) QoL was 71.0 (18.2) at baseline and was lower in patients with AF-related symptoms (70.5 vs 72.1 points, p=0.009). Over the first four years mean (SD) QoL scores remained stable (73.1 (18.0), 73.6 (18.0), 73.1 (17.9) and 73.4 (18.0) points; p=0.06) in all patients. Baseline characteristics stratified by quartiles of increasing QoL at baseline are shown in Table S3. Patients with higher QoL were more often male (78.4 % in the highest vs 65.6% in the lowest quartile, p<0.0001), were younger (68.8 vs 73.2 years, p<0.0001), had more often paroxysmal AF (58.3 vs 43.1%, p<0.0001) and a lower burden of comorbidities. Patients with higher QoL also tended to have less symptoms (Figure 2). Patients with lower QoL more often had dyspnea (p<0.0001), fatigue (p<0.0001), angina pectoris (p=0.007) and dizziness (p=0.02).

In time-updated, multivariable Cox models there was no significant association of QoL with stroke or systemic arterial embolism. There were significant associations between QoL and risk of CHF hospitalizations (HR (95% CI) 0.92 (0.90; 0.94)), cardiovascular death (HR (95% CI) 0.90 (0.86; 0.94)), all-cause mortality (HR (95% CI) 0.88 (0.86; 0.90)) (all p <0.0001) and major bleeding (HR (95% CI) 0.95 (0.92; 0.99); p=0.005) (Table 2). Correction for multiple comparisons provided similar results (Table S4). Subgroup analyses showed no significant interactions for the primary endpoint (Table S2).

Including both AF-related symptoms and QoL in one multivariable model did not change the association of AF-related symptoms (HR (95% CI) 1.10 (0.76; 1.57);

p=0.62) or QoL (HR (95% CI) 0.98 (0.94; 1.03); p=0.40) with stroke or systemic arterial embolism.

Discussion

This is one of the largest cohort studies to prospectively assess the associations of time-updated AF-related symptoms and QoL with cardiovascular outcomes in patients with AF. Importantly, AF-related symptoms were not significantly associated with any of the cardiovascular outcomes assessed. While a lower QoL was not significantly related to the primary endpoint of stroke and systemic embolism, we found a strong association between QoL and all-cause mortality, cardiovascular death, hospitalizations for CHF and major bleeding.

AF-related symptoms significantly changed over time and were frequent in our study population. In order to obtain unbiased estimates, our analyses took these changes into account. In the context of prior evidence on this topic,[7,9,11,12] our study provides several new features. First, it included time-updated symptom status. Second, we used a comprehensive set of AF-related symptoms both by patient self-reporting and by EHRA class. Third, follow-up of our study was longer than in most prior studies. A secondary analysis from the AFFIRM trial was limited by the small proportion of asymptomatic patients (12%) available.[7] Results of AF registries were limited by short follow-up and limited availability of symptom assessments.[9,11,12] In line with prior evidence, we found that time-updated AF-related symptom status was not associated with stroke, systemic arterial embolism, or any other endpoint assessed. Taken together, these results suggest that preventative treatment decisions, mainly oral anticoagulation, should not be based on the presence or absence of AF-related symptoms. In other words, our data indicate that incidentally detected AF should be treated the same way as symptomatic AF. However, the minimal temporal burden for AF, especially of subclinical AF detected by cardiac devices, to justify oral anticoagulation is currently not known. [20,21]

Palpitations were associated with a lower risk of hospitalizations for CHF and mortality. Prior evidence showed that palpitations are more prevalent in younger patients with less comorbidities.[13,22] The observed associations are therefore probably due to residual confounding, although we can't exclude the possibility that these patients get more intense medical treatment as they come to medical attention early. On the other end of the spectrum, dyspnea was significantly more prevalent in patients with low QoL and was associated with increased risks for hospitalizations for CHF and cardiovascular death. Dyspnea most likely is a marker of underlying structural heart disease or significant lung disease, both of which are associated with adverse outcomes, especially CHF.[23] Heart failure is a common and one of the most important adverse outcome as the leading cause of death in patients with AF.[24,25] Although AF-related symptoms should not be used for decision making in stroke prevention, they should be used to identify patients for intensified management and prevention of heart failure.

Lower QoL was common in patients with AF and not associated with the risk of stroke or systemic embolism, confirming the results obtained with AF-related symptoms. By contrast, lower QoL was strongly associated with an increased risk for other adverse outcomes, including all-cause mortality, cardiovascular death, hospitalizations for CHF, and major bleeding. In addition, QoL did not significantly change over time, suggesting that it may be less amenable to treatment compared with symptom status. In this context, our results suggest that QoL is determined by the overall burden of comorbidities and risk factors, and less by AF itself.

Nevertheless, QoL might be a more robust and comprehensive patient reported metric than symptom status, and may provide incremental information about the individual health status beyond symptoms. Consequently, QoL may be an easily

available and cost-effective screening tool to identify AF patients at high risk for adverse outcomes. These patients need careful medical attention and might benefit from more intense treatment of risk factors and comorbidities, although such an approach should ideally be tested in a randomized trial.

Strengths of our study include the large number of well-characterized patients available, and the use of time-updated analyses with a very small number of missing data. Some potential limitations have to be taken into account when interpreting our results. First, this is an observational study, and by design this type of study does not allow for causal inferences given the possibility of residual confounding or bias. Second, our participants were mainly white, and generalizability to other populations is uncertain.

In conclusion, AF-related symptoms significantly changed over time and were not associated with adverse cardiovascular outcomes. Decisions regarding oral anticoagulation should therefore not be based on the presence or absence of AF-related symptoms. On the other hand, reduced QoL was strongly associated with a multitude of adverse clinical outcomes, including death. AF patients with a low QoL therefore represent a high-risk patient population.

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Conflicts of interest

Michael Kühne received grants from the Swiss National Science Foundation and the Swiss Heart Foundation, and lecture/consulting fees from Daiichi-Sankyo, Boehringer Ingelheim, Bayer, Pfizer-BMS, AstraZeneca, Sanofi-Aventis, Novartis, MSD, Medtronic, Boston Scientific, St. Jude Medical, Biotronik, Sorin, Zoll and Biosense Webster. Jeff S Healey reports research grants and speaking fees from BMS/Pfizer and Servier.

Contributorship statement

Conception and design: PK, SB, SA, MK, SO, DC.

Analysis and interpretation of the data: PK, SB, SA, MK, DC.

Drafting of the manuscript: PK, DC.

Critical revision for important intellectual content: All authors.

Final approval of the manuscript: All authors.

Responsible for the overall content as the guarantors: PK, DC.

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Figure legends

Figure 1 Presence of atrial fibrillation-related symptoms over time. FU = follow up.

Figure 2 Presence of atrial fibrillation-related symptoms stratified by quartiles of quality of life

Table 1 Baseline characteristics stratified by presence or absence of AF-related symptoms at the baseline study visit

AF-related symptoms	***Yes*** ***n=2534***	***No*** ***n=1302***	***P value*** †
Sex (male)	1687 (66.6%)	1068 (82.0%)	<0.0001
Age, years	69.9 (10.5)	74.3 (8.3)	<0.0001
BMI, kg/m^2	27.4 (4.8)	27.6 (4.6)	0.18
Paroxysmal AF, n	1408 (55.6%)	475 (36.6%)	<0.0001
History of stroke/TIA, n	394 (15.6%)	265 (20.4%)	0.0002
History of CHF, n	526 (20.8%)	388 (29.8%)	<0.0001
Arterial hypertension, n	1661 (65.6%)	984 (75.6%)	<0.0001
Diabetes, n	335 (13.2%)	267 (20.5%)	<0.0001
Prior myocardial infarction, n	322 (12.7%)	247 (19.0%)	<0.0001
Peripheral artery disease, n	153 (6.0%)	125 (9.6%)	<0.0001
History of renal disease, n	391 (15.4%)	322 (24.7%)	<0.0001
Previous electrocardioversion, n	884 (34.9%)	446 (34.3%)	0.69
Previous catheter ablation for AF, n	640 (25.3%)	169 (13.0%)	<0.0001
Systolic blood pressure, mmHg	133.8 (18.6)	134.6 (19.4)	0.21

Medication			
Beta-blocker, n	1734 (68.6%)	847 (65.1%)	0.03
ACE-inhibitor/ARB, n	1382 (54.5%)	856 (65.7%)	<0.0001
Amiodarone, n	461 (18.2%)	199 (15.3%)	0.02
Oral anticoagulation, n	2077 (82.0%)	1150 (88.3%)	<0.0001
Aspirin, n	468 (18.5%)	262 (20.1%)	0.22

Data are mean (standard deviation) or numbers (percentages).

† P values were obtained from Student's t-tests or Chi-square tests, as appropriate.

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = Angiotensin II receptor blocker; BMI = body mass index; CHF = congestive heart failure; TIA = transient ischemic attack.

Table 2 Separate Cox proportional hazards models for the relationships of AF-related symptoms and quality of life with adverse clinical outcomes.

		AF-related symptoms				Quality of life†			
		Model 1		**Model 2**		**Model 1**		**Model 2**	
	n	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Stroke/systemic embolism	140	1.09 (0.76; 1.55)	0.63	1.11 (0.77; 1.59)	0.56	0.96 (0.92; 1.01)	0.08	0.98 (0.94; 1.03)	0.37
Stroke	133	1.06 (0.74; 1.52)	0.77	1.07 (0.74; 1.55)	0.70	0.96 (0.92; 1.00)	0.05	0.97 (0.93; 1.02)	0.22
Ischemic	104	1.15 (0.76; 1.74)	0.49	1.16 (0.77; 1.76)	0.48	0.97 (0.92; 1.02)	0.20	0.98 (0.93; 1.04)	0.49
Hemorrhagic	30	0.78 (0.36; 1.68)	0.52	0.80 (0.37; 1.73)	0.56	0.93 (0.85; 1.02)	0.11	0.95 (0.86; 1.04)	0.24
Systemic embolism	10	2.01 (0.46; 8.79)	0.36	2.17 (0.48; 9.72)	0.31	0.98 (0.83; 1.17)	0.85	1.05 (0.88; 1.27)	0.58
Hospitalization for CHF	405	0.81 (0.66; 0.99)	0.04	0.90 (0.73; 1.10)	0.30	0.88 (0.86; 0.90)	<0.0001	0.92 (0.90; 0.94)	<0.0001
All-cause mortality	422	0.85 (0.69; 1.04)	0.11	0.93 (0.76; 1.14)	0.50	0.85 (0.83; 0.87)	<0.0001	0.88 (0.86; 0.90)	<0.0001

Cardiovascular death	119	0.61 (0.41; 0.90)	0.01	0.70 (0.48; 1.04)	0.07	0.85 (0.82; 0.89)	<0.0001	0.90 (0.86; 0.95)	<0.0001
Myocardial infarction	99	1.10 (0.72; 1.67)	0.66	1.20 (0.79; 1.83)	0.40	0.91 (0.87; 0.96)	0.0002	0.95 (0.90; 1.01)	0.08
Major bleeding	259	0.91 (0.71; 1.18)	0.46	0.96 (0.74; 1.25)	0.78	0.94 (0.91; 0.97)	0.0002	0.95 (0.92; 0.99)	0.005

† Data are by 5-point increase in quality of life score

Model 1 was adjusted for age, sex and study cohort.

Model 2 was additionally adjusted for history of heart failure, hypertension, diabetes, stroke, myocardial infarction, vascular disease, history of renal failure, prior catheter ablation for atrial fibrillation, body mass index, smoking status, education, use of beta-blockers, use of ACE-inhibitors or angiotensin II receptor blockers and use of oral anticoagulation and/or aspirin

Presence/absence of AF-related symptoms and 5-point increase in QoL were used as the predictor variables.

AF = atrial fibrillation; CHF = congestive heart failure; QoL = quality of life.

Table 3 Cox proportional hazards model for the associations of individual AF-related symptoms with adverse clinical outcomes.

Outcome	Palpitations	Dizziness	Angina pectoris	Dyspnea	Fatigue	Exercice intolerance
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Stroke/systemic embolism	0.98 (0.68; 1.42)	0.97 (0.62; 1.50)	0.87 (0.52; 1.46)	1.00 (0.68; 1.47)	1.59 (1.06; 2.38)	0.60 (0.31; 1.17)
Stroke	0.98 (0.68; 1.45)	1.04 (0.67; 1.62)	0.93 (0.55; 1.55)	0.96 (0.64; 1.43)	1.59 (1.05; 2.41)	0.58 (0.29; 1.17)
Ischemic	1.10 (0.72; 1.68)	1.26 (0.78; 2.03)	0.77 (0.42; 1.41)	1.11 (0.71; 1.72)	1.49 (0.93; 2.37)	0.61 (0.28; 1.33)
Hemorrhagic	0.66 (0.30; 1.48)	0.39 (0.11; 1.34)	1.58 (0.58; 4.31)	0.61 (0.25; 1.52)	2.34 (0.99; 5.54)	0.48 (0.11; 2.23)
Systemic embolism	0.83 (0.22; 3.15)	0.32 (0.04; 2.62)	-	2.46 (0.64; 9.47)	2.04 (0.50; 8.33)	0.49 (0.05; 4.57)
Hospitalization for CHF	0.75 (0.60; 0.93)	1.06 (0.81; 1.38)	0.87 (0.64; 1.18)	1.42 (1.14; 1.78)	1.00 (0.77; 1.31)	0.66 (0.45; 0.95)
All-cause mortality	0.80 (0.65; 0.99)	0.89 (0.68; 1.16)	1.09 (0.82; 1.45)	1.19 (0.96; 1.49)	1.15 (0.90; 1.48)	0.72 (0.48; 1.07)
Cardiovascular death	0.64 (0.43; 0.97)	0.92 (0.56; 1.52)	1.02 (0.60; 1.74)	1.67 (1.12; 2.51)	0.99 (0.61; 1.60)	0.53 (0.23; 1.18)
Myocardial infarction	0.96 (0.62; 1.49)	1.00 (0.59; 1.67)	1.32 (0.77; 2.26)	1.05 (0.66; 1.65)	1.36 (0.83; 2.23)	0.59 (0.27; 1.28)

Major bleeding	1.07 (0.82; 1.40)	1.01 (0.73; 1.40)	1.02 (0.71; 1.47)	0.89 (0.67; 1.19)	1.20 (0.87; 1.64)	0.87 (0.57; 1.35)

Models were adjusted for all individual symptoms, age, sex and study cohort.

Individual AF-related symptoms were used as predictor variables in a combined model.

AF = atrial fibrillation, CHF = congestive heart failure.