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Symptoms and quality of life in patients with coexistent atrial fibrillation and atrial flutter

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ABSTRACT

Aims: Atrial fibrillation (AF) and atrial flutter (AFL) are two of the most common atrial arrhythmias and often coexist. Many patients with AF or AFL are symptomatic, which impacts their quality of life (QoL). The purpose of this study was to determine whether coexistent AFL represents an added burden for AF patients.

Methods: We combined baseline data from two large prospective, observational, multicenter cohort studies (BEAT-AF and Swiss-AF). All 3931 patients included in this analysis had documented AF. We obtained information on comorbidities, medication, and lifestyle factors. All participants had a clinical examination and a resting ECG. Symptom burden and QoL at the baseline examination were compared between patients with and without coexistent AFL using multivariable adjusted regression models.

Results: Overall, 809 (20.6%) patients had a history of AFL. Patients with coexistent AFL more often had history of heart failure (28% vs 23%, p = 0.01), coronary artery disease (30% vs 26%, p = 0.007), failed therapy with antiarrhythmic drugs (44% vs 29%, p < 0.001), and more often underwent AF-related interventions (36% vs 17%, p < 0.001). They were more often symptomatic (70% vs 66%, p = 0.04) and effort intolerant (OR: 1.14; 95% CI: 1.01–1.28; p = 0.04). Documented AFL on the baseline ECG was associated with more symptoms (OR: 2.30; 95% CI: 1.26–4.20; p = 0.007).

Conclusion: Our data indicates that patients with coexistent AF and AFL are more often symptomatic and report poorer quality of life compared to patients suffering from AF only.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is considered a public health epidemic [1,2]. Patients suffering from AF have an increased risk of stroke, heart failure, death, and cognitive decline [3,4]. Many patients with AF are symptomatic with untoward effects on their health-related quality of life (QoL) [5,6]. Patients with AF have a poorer QoL compared to healthy controls, the general population, or patients with coronary heart disease [7]. Typical AF related symptoms include palpitations, dyspnea, chest pain, effort intolerance, dizziness, and less commonly fatigue, syncope, and anxiety [8,9].

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While its prevalence and incidence have been less studied than for AF, atrial flutter (AFL) is considered as the second most common sustained atrial arrhythmia encountered in clinical practice [10–12]. AFL tends to be associated with a rapid ventricular rate responsible for many of its symptoms [13]. AF and AFL commonly coexist [14], but little is known on whether this coexistence leads to an additional symptoms- and QoL-related burden among patients suffering from both arrhythmias. Considering that arrhythmia-related symptoms and lower health perception are associated with a higher risk of hospitalization [4] and are important factors for the choice of therapeutic approach, the aim of our study was to determine whether the coexistence of AFL was a predictor for a poorer QoL and more symptoms among patients with AF, therefore potentially requiring a different therapy.

2. Materials and methods

2.1. Study population

For this analysis, data from the BEAT-AF (Basel Atrial Fibrillation Cohort) and Swiss-AF (Swiss Atrial Fibrillation Cohort) cohorts were combined. Both are large prospective, observational, multicenter cohort studies in Switzerland. Between 2010 and 2014, the BEAT-AF Study enrolled 1553 patients with documented AF across 7 centers in Switzerland, and 2415 patients with documented AF were enrolled in Swiss-AF between 2014 and 2017 across 13 swiss centers [15,16]. Inclusion criteria were very similar, rendering the two populations comparable. All patients had AF that was previously documented by either 12-lead ECG, rhythm strip, or device interrogation. Main exclusion criteria for both BEAT-AF and Swiss-AF were the inability to sign informed consent, the presence of exclusively short transient episodes of AF during a reversible condition (e.g., secondary after cardiac surgery or severe sepsis), as well as any acute illness within the last 4 weeks. For our analysis, we excluded 37 (0.9%) patients due to missing data regarding symptoms, quality of life or regarding a potential coexistent AFL at baseline, such that 3931 patients remained in the analysis. Both study protocols were approved by the local ethics committees, and informed written consent was obtained from each participant.

2.2. Data collection

Baseline assessment was similar for both cohorts. All study participants were asked to complete detailed questionnaires about lifestyle, personal, nutritional and medical factors. Smoking status was categorized in current, past, or never smokers. We collected information on the current medication, medical history, comorbidities and history of arrhythmia-related interventions (defined as previous pulmonary vein isolation or cavotricuspid isthmus radiofrequency ablation). The diagnosis of heart failure (HF) was made on the basis of medical reports and only patients with a reported diagnosis of HF, a hospitalization for heart failure or echocardiographic signs of HF were classified as patients with a history of heart failure. AF was classified according to current guidelines as paroxysmal, persistent, or permanent AF [3]. During baseline examination, patients were asked whether or not they experienced any symptoms related with their arrhythmia. Symptoms potentially related to AF or AFL included palpitations, dyspnea, chest pain, effort intolerance, fatigue, dizziness, syncope, anxiety or any other symptom. The precise length of the recall period was not clearly defined, but patients who had suffered symptoms were asked about the length and frequency of symptomatic episodes. Patients reporting no symptoms at baseline visit were patients with asymptomatic AF. For QoL however, patients were asked to assess their overall health perception at the very day of baseline examination using a visual analogue scale (VAS) ranging from 0 (worst possible health status) to 100 (best possible health status), similar to the extensively validated Euro-Qol VAS [5]. Additionally, in Swiss-AF more detailed information on QoL was available through the European Heart Rhythm Association (EHRA) Score and the European Quality of life – 5 Dimensions Questionnaire (EQ-5D). The EQ-5D-3L is a standardized instrument to assess generic health-related QoL and contains questions on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each of the five dimensions, respondents are offered three response categories (no problems, some problems, extreme problems), leading to 243 possible health states. These health states are then converted into index-based values (utilities) ranging from 0 to 1 by applying a country-specific valuation algorithm. As no Swiss value set is available, we used the European Value set (VAS validated) to calculate utilities [17].

All participants also underwent clinical examination, including measurement of body height and weight, blood pressure, and heart rate. A resting ECG was obtained from every participant, using validated devices at the local study center. We also performed a thorough medical history research and collected available ECG for every patient with reported coexistent AFL and then performed manual ECG interpretation in order to confirm the diagnostic of coexistent AFL.

2.3. Statistical analysis

Baseline characteristics were stratified according to the presence or absence of coexistent AFL and presented as numbers (percentage) for categorical variables and means ± standard deviations for continuous variables. Among patients with coexistent AFL versus patients with AF only, data were compared using a Chi-squared test or *t*-test, as appropriate.

To investigate the relationship between coexistent AFL and the presence of symptoms, we performed logistic regression analyses to calculate the odds ratio (OR) with corresponding 95% confidence interval (95% CI) for the predictor coexistent AFL, using binary symptom-related variables as the outcome (any symptom, palpitations, dyspnea, fatigue, dizziness, effort intolerance, chest pain, syncope, anxiety). The predictor coexistent AFL was additionally classified in two groups: patients with and without cavotricuspid isthmus (CTI) ablation, and the same regression analyses were performed. Patients with CTI ablation constitute a subpopulation with clearly proven CTI-dependent AFL while some of the remainders may have had pseudonormalized AF or another regularized atrial arrhythmia. Both variables were included in the same logistic regression model. Linear regression analyses were performed to calculate ß coefficients (95% confidence interval) for the continuous outcome variables VAS (0–100) and EQ5D utilities in order to assess the relationship between coexistent AFL (again stratified by the presence or absence of CTI ablation) and health perception.

In a secondary analysis, we divided the study population according to the rhythm on the ECG performed at baseline (sinus rhythm, AF, or AFL). We excluded 82 patients due to missing ECG and 158 others because of a different rhythm presented on the ECG (e.g., atrial paced rhythm). The regression analyses were then repeated for all patients using the respective heart rhythm on the baseline ECG as the predictor and symptom-related variables and health perception as the outcome variable. Sinus rhythm was defined as the reference group.

All regression models were adjusted for a predefined set of covariates. The first model was adjusted for age and sex. The second model was additionally adjusted for body mass index, history of hypertension, diabetes mellitus, heart failure, coronary heart disease, and antiarrhythmic therapy. A two-sided p value < 0.05

was considered to indicate statistical significance. All statistical analyses were performed using SAS 9.4 (SAS Corporation Institute).

3. Results

3.1. Baseline characteristics

We included 3931 patients with documented AF in this study. Of these, 809 (20.6%) had known coexistent AFL. Baseline characteristics stratified by the presence of coexistent AFL are presented in Table 1. Mean age of all patients was 71 (±10) years and mean BMI was 27.5 (±4.8). The proportion of women was significantly lower in patients with coexistent AFL (22.7%) than in those with AF only (29.6%). Patients with a concomitant history of AFL less often had permanent AF (17% versus 26%, p < 0.001) and were more likely to have a history of heart failure (28% versus 23%, p = 0.01), coronary artery disease (30% versus 26%, p = 0.007), and renal failure (22% versus 18%, p = 0.02). Additionally, they had a higher prevalence of unsuccessful therapy with antiarrhythmic drugs in the past (44% versus 29%, p < 0.001) and more frequently underwent a pulmonary vein isolation before enrollment (36% versus 17%, p < 0.001). Baseline characteristics of patients with coexistent AFL stratified by their history of CTI ablation are shown in the Supplementary Table 1.

3.2. Symptoms and quality of life

Prevalence of various symptom categories and health perception are shown in Table 2. Overall, two thirds of our population presented symptoms related to atrial arrhythmias. Patients with coexisting AFL had more often any symptoms than patients with AF only (70% versus 66%, p = 0.04). When comparing the different symptom categories separately, effort intolerance was more prevalent in patients suffering from both arrhythmias (22% versus 17%, p = 0.003), whereas no significant differences were observed across other symptom categories, or health perception. The prevalence of any symptoms (75% versus 65%, p = 0.002) and palpitations (51% versus 40%, p = 0.003) was significantly higher in AFL patients with a history of CTI ablation compared to those without. In contrast,

Table 1
Baseline characteristics stratified by the presence of coexistent AFL.

	All patients (n = 3931)	AF only (n = 3122, 79.4%)	AF/AFL (n = 809, 20.6%)	p-value*
Age (years)	71 ± 10	72 ± 10	70 ± 9	0.0001
Sex (% women)	1108 (28.2)	924 (29.6)	184 (22.7)	0.0001
Body mass index (kg/m^2)	27.5 ± 4.8	27.4 ± 4.8	27.6 ± 4.7	0.25
Heart rate (beats/min)	70 ± 17	70 ± 17	70 ± 18	0.83
Blood Pressure (mm Hg)				
– Systolic	134 ± 19	134 ± 19	133 ± 18	0.15
– Diastolic	78 ± 12	78 ± 12	78 ± 12	0.95
AF Type, %				<0.0001
– Paroxysmal	1928 (49.1)	1529 (49.0)	399 (49.3)	
– Persistent	932 (23.7)	796 (25.5)	273 (33.8)	
– Permanent	1069 (27.2)	796 (25.5)	136 (16.8)	
Time since diagnosis, years**	3.2 (0.8; 7.6)	3.1 (0.8; 7.4)	3.6 (1.0; 7.8)	0.98
– <1 year	963 (24.5)	778 (24.9)	185 (22.9)	0.005
– 1–2 years	416 (10.6)	334 (10.7)	82 (10.1)	
– 2–5 years	762 (19.4)	593 (19.0)	169 (20.9)	
– 5–10 years	629 (16.0)	471 (15.1)	158 (19.5)	
– ≥10 years	625 (15.9)	497 (15.9)	128 (15.8)	
Smoking Status, %				0.66
– Current	310 (7.9)	245 (7.9)	65 (8.0)	
– History	1889 (48.0)	1486 (47.6)	403 (49.8)	
– Never	1728 (44.0)	1388 (44.5)	340 (42.0)	
Education, %				0.02
– Basic	477 (12.2)	400 (12.8)	77 (9.5)	
– Middle	1925 (49.0)	1533 (49.1)	392 (48.5)	
– Advanced	1515 (38.5)	1176 (37.7)	339 (41.9)	
Regular physical activity, %	1899 (48.3)	1458 (46.7)	441 (54.5)	< 0.0001
CHA2DS2-VASc Score	3.2 ± 1.8	3.2 ± 1.8	3.1 ± 1.7	0.01
Hypertension, %	2707 (68.9)	2160 (69.2)	547 (67.7)	0.39
Diabetes mellitus, %	616 (15.7)	482 (15.4)	134 (16.6)	0.43
History of Heart Failure, %	937 (23.8)	714 (22.9)	223 (27.6)	0.01
History of Myocardial Infarction, %	578 (14.7)	462 (14.8)	116 (14.3)	0.74
History of Stroke/TIA, %	672 (17.1)	562 (18.0)	110 (13.6)	0.009
History of CAD, %	1048 (26.7)	802 (25.7)	246 (30.4)	0.007
History of Renal Failure, %	733 (18.6)	557 (17.8)	176 (21.8)	0.02
Implanted device, %	690 (17.6)	510 (16.3)	180 (22.2)	<0.0001
History of failed AAD, %	1257 (32.0)	905 (29.0)	352 (43.5)	< 0.0001
Antiarrhythmic drugs, %				
– Class Ic	202 (5.1)	151 (4.8)	51 (6.3)	0.09
– Class II (Beta-blockers)	2707 (69.9)	2145 (68.7)	562 (69.5)	0.68
– Class III	711 (18.1)	546 (17.5)	156 (19.2)	0.06
History of Intervention, %				
– PVI	822 (20.9)	534 (17.1)	288 (35.6)	< 0.0001
– CTI ablation	473 (12.0)	97 (3.1)	376 (46.5)	< 0.0001

Data are presented as means (±standard deviation) or as counts (percentages), as appropriate. Data may not sum to the given number due to missing data. AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; AFL, atrial flutter; CAD, coronary artery disease; CTI, cavotricuspid isthmus ablation; PVI, pulmonary vein isolation; TIA, transient ischemic attack. AAD were classified according to the Vaughan Williams classification.

* P-values were based on Student *t* tests or χ^2 tests, as appropriate.

** n = 536 missings.

Table 2
Symptom status and health perception according to the presence of coexistent AFL.

	All patients (n = 3931)	AF only (n = 3122, 79.4%)	AF/AFL (n = 809, 20.6%)	p-value*	AF/AFL only		p-value†
					Hx of CTI (n = 376)	No CTI (n = 433)	
Any symptom, %	2608 (66.3)	2046 (65.5)	562 (69.5)	0.04	282 (75.0)	280 (64.8)	0.002
Palpitations, %	1661 (42.3)	1297 (41.5)	364 (45.0)	0.08	190 (50.5)	174 (40.2)	0.003
Dyspnea, %	987 (25.1)	768 (24.6)	219 (27.1)	0.16	95 (25.3)	124 (28.6)	0.28
Chest pain, %	455 (11.6)	359 (11.5)	96 (11.9)	0.77	52 (13.8)	44 (10.2)	0.11
Effort intolerance, %	712 (18.1)	536 (17.2)	176 (21.8)	0.003	91 (24.2)	85 (19.6)	0.12
Fatigue, %	702 (17.9)	549 (17.6)	153 (18.9)	0.38	81 (21.5)	72 (16.6)	0.08
Dizziness, %	598 (15.2)	463 (14.8)	135 (16.7)	0.19	67 (17.8)	68 (15.7)	0.42
Syncope, %	123 (3.1)	97 (3.1)	26 (3.2)	0.88	10 (2.7)	16 (3.7)	0.41
Anxiety, %	163 (4.1)	125 (4.0)	38 (4.7)	0.38	18 (4.8)	20 (4.6)	0.91
Health perception VAS (mean ±SD)	71.5 ±18.2	71.6 ±18.2	71.3 ±18.3	0.65	72.8 ±18.4	69.9 ±18.2	0.02

Data are shown as numbers (percentages) or as means (±standard deviation), as appropriate. The group "Hx of CTI" represents patients reporting of AFL-related cavotricuspid isthmus ablation, whereas "No CTI" indicates no reported ablation. AF indicates atrial fibrillation; AFL, atrial flutter; VAS, Visual Analog Scale.

* P-values are based on Student *t* tests or χ^2 tests, as appropriate, and indicate differences in symptoms and health perception according to the presence or absence of coexistent atrial flutter.

† P values are based on Student *t* tests or χ^2 tests, as appropriate, and indicate differences in symptoms and health perception within patients with coexistent atrial flutter according to whether they underwent AFL-related cavotricuspid isthmus ablation or not.

Table 3
Relationship of coexistent AF and AFL with symptom status and health perception.

		AF/AFL (all, n = 809)		AF/AFL with CTI (n = 376)		AF/AFL no CTI (n = 433)	
	Adjustment	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Any symptom	Age and sex	1.07 (0.96–1.18)	0.23	1.39 (1.08–1.80)	0.01	1.04 (0.84–1.30)	0.70
	Multivariate*	1.06 (0.96–1.18)	0.27	1.34 (1.04–1.74)	0.03	1.05 (0.85–1.31)	0.66
Palpitations	Age and sex	1.06 (0.96–1.17)	0.26	1.31 (1.05–1.64)	0.02	1.04 (0.84–1.29)	0.72
	Multivariate*	1.07 (0.97–1.19)	0.19	1.32 (1.05–1.66)	0.02	1.07 (0.86–1.33)	0.56
Dyspnea	Age and sex	1.12 (1.01–1.25)	0.04	1.08 (0.84–1.39)	0.54	1.27 (1.01–1.59)	0.04
	Multivariate*	1.10 (0.99–1.22)	0.09	1.02 (0.79–1.32)	0.86	1.23 (0.98–1.55)	0.07
Chest pain	Age and sex	1.00 (0.86–1.16)	0.96	1.25 (0.91–1.72)	0.17	0.90 (0.65–1.26)	0.55
	Multivariate*	0.99 (0.85–1.15)	0.87	1.22 (0.88–1.69)	0.22	0.90 (0.64–1.25)	0.53
Effort intolerance	Age and sex	1.14 (1.02–1.29)	0.03	1.38 (1.07–1.78)	0.01	1.22 (0.94–1.58)	0.13
	Multivariate*	1.14 (1.01–1.28)	0.04	1.35 (1.04–1.75)	0.03	1.22 (0.94–1.58)	0.14
Fatigue	Age and sex	1.03 (0.91–1.17)	0.65	1.22 (0.93–1.59)	0.15	0.99 (0.76–1.30)	0.95
	Multivariate*	1.02 (0.90–1.15)	0.81	1.18 (0.90–1.54)	0.24	0.98 (0.74–1.28)	0.86
Dizziness	Age and sex	1.09 (0.95–1.24)	0.21	1.22 (0.91– 1.62)	0.18	1.14 (0.86–1.50)	0.38
	Multivariate*	1.09 (0.95–1.24)	0.23	1.21 (0.90–1.61)	0.20	1.13 (0.86–1.50)	0.38
Syncope	Age and sex	1.07 (0.82–1.40)	0.61	0.83 (0.43–1.61)	0.58	1.24 (0.72–2.12)	0.44
	Multivariate*	1.10 (0.84–1.44)	0.48	0.88 (0.45–1.71)	0.70	1.29 (0.75–2.22)	0.36
Anxiety	Age and sex	1.12 (0.89–1.41)	0.33	1.16 (0.70–1.94)	0.57	1.24 (0.76–2.02)	0.39
	Multivariate*	1.14 (0.91–1.44)	0.26	1.17 (0.70–1.97)	0.54	1.29 (0.79–2.10)	0.31
		β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value
Health perception VAS 0-100	Age and sex	−0.70 (−1.55 to 0.16)	0.11	−0.05 (−1.99 to 1.89)	0.96	−1.62 (−3.43 to 0.19)	0.08
	Multivariate	−0.26 (−1.09 to 0.57)	0.54	0.80 (−1.10 to 2.69)	0.41	−0.87 (−2.63 to 0.88)	0.41
		β-coefficient (95% CI) n = 516	p-value	β-coefficient (95% CI) n = 232	p-value	β-coefficient (95% CI) n = 284	p-value
EQ5D Utilities	Age and sex	−0.00 (−0.009; 0.008)	0.87	−0.005 (−0.02; 0.02)	0.64	−0.00 (−0.02; 0.02)	0.98
	Multivariate*	0.00 (−0.008; 0.009)	0.95	−0.005 (−0.03; 0.014)	0.59	0.002 (−0.015; 0.02)	0.80

ORs (95% CIs) and β-coefficient (95% CIs) are for patients with coexistent atrial flutter compared with patients with atrial fibrillation only. The group "AF/AFL with CTI" represents AF patients with coexistent AFL reporting of an AFL-related cavotricuspid isthmus ablation, whereas "No CTI" indicates no reported ablation. AF indicates atrial fibrillation; AFL, atrial flutter; CI, confidence interval; CTI, cavotricuspid isthmus ablation; OR, odds ratio; VAS, Visual Analog Scale.
EQ5D utilities are available in patients of the Swiss-AF study (n = 2415).
n = 3923

* Multivariable models were adjusted for age, sex, body mass index, hypertension, heart failure, diabetes mellitus, coronary heart disease (myocardial infarction, percutaneous transluminal coronary angioplasty, or aortocoronary bypass) and antiarrhythmic drugs.

the health perception was significantly higher in these patients (73 ± 18 versus 70 ± 18, p = 0.02).

Results of the regression models on the relationship between coexistent AFL and symptom prevalence are presented in Table 3. For patients with coexistent AFL, we observed a significant association with effort intolerance that persisted after multivariable adjustment (OR: 1.14; 95% CI: 1.01–1.28; p = 0.04). In the subgroup including AFL patients who had prior CTI ablation, associations were significant for overall symptoms (adjusted OR: 1.34; 95% CI: 1.04–1.74; p = 0.03), palpitations (adjusted OR: 1.32; 95% CI:

Table 4
Relationship of heart rhythm on ECG with symptom status and health perception.

		AF Rhythm (n = 1610, 41.0%)		AFL Rhythm (n = 80, 2.0%)	
	Adjustment	OR (95% CI)	p-value	OR (95% CI)	p-value
Any symptom	Age and sex	0.56 (0.49–0.66)	<0.0001	2.11 (1.16–3.84)	0.01
	Multivariate*	0.60 (0.51–0.70)	<0.0001	2.30 (1.26–4.20)	0.007
Palpitations	Age and sex	0.50 (0.43–0.57)	<0.0001	1.88 (1.17–3.03)	0.009
	Multivariate*	0.55 (0.47–0.64)	<0.0001	2.09 (1.30–3.39)	0.003
Dyspnea	Age and sex	1.14 (0.97–1.33)	0.12	3.40 (2.16–5.35)	<0.0001
	Multivariate*	1.05 (0.90–1.25)	0.53	3.38 (2.13–5.35)	<0.0001
Chest pain	Age and sex	0.77 (0.62–0.96)	0.02	1.92 (1.09–3.38)	0.02
	Multivariate*	0.75 (0.60–0.95)	0.02	1.95 (1.10–3.46)	0.02
Effort intolerance	Age and sex	0.71 (0.59–0.85)	0.0002	1.23 (0.72–2.08)	0.45
	Multivariate*	0.71 (0.59–0.85)	0.0003	1.29 (0.76–2.20)	0.36
Fatigue	Age and sex	1.03 (0.86–1.24)	0.73	1.55 (0.91–2.65)	0.11
	Multivariate*	1.02 (0.84–1.22)	0.86	1.60 (0.93–2.74)	0.09
Dizziness	Age and sex	0.66 (0.54–0.80)	<0.0001	0.73 (0.37–1.43)	0.36
	Multivariate*	0.65 (0.53–0.80)	<0.0001	0.72 (0.37–1.43)	0.35
Syncope	Age and sex	0.41 (0.26–0.65)	0.0001	0.64 (0.16–2.66)	0.54
	Multivariate*	0.43 (0.27–0.69)	0.0004	0.64 (0.15–2.67)	0.54
Anxiety	Age and sex	0.46 (0.32–0.67)	<0.0001	0.23 (0.03–1.65)	0.14
	Multivariate*	0.50 (0.34–0.73)	0.0004	0.26 (0.04–1.91)	0.19
		β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value
Health perception VAS 0-100	Age and sex	−5.37 (−6.57 to −4.17)	<0.0001	−11.66 (−15.61 to 7.71)	<0.0001
	Multivariate*	−3.69 (−4.89 to 2.49)	<0.0001	−9.70 (−13.56 to −5.84)	<0.0001

ORs (95% CIs) and β –coefficient (95% CIs) are for patients in AF-, respectively AFL-rhythm, compared with patients in Sinus rhythm.
AF indicates atrial fibrillation; AFL, atrial flutter; CI, confidence interval; OR, odds ratio; VAS, Visual Analog Scale.
n = 3684.
* Multivariable models were adjusted for age, sex, body mass index, hypertension, heart failure, diabetes mellitus, coronary heart disease (myocardial infarction, percutaneous transluminal coronary angioplasty, or aortocoronary bypass) and antiarrhythmic drugs.

1.05–1.66; p = 0.02), and effort intolerance (adjusted OR: 1.35; 95% CI: 1.04–1.75; p = 0.03). No significant associations were observed for AFL patients without a history of CTI.

Table 4 shows the results of the secondary analysis, for which we divided the study population according to the rhythm on the ECG performed at baseline. Sinus rhythm was observed in 2001 patients (52.0%), AF in 1610 (41.8%) and AFL in 80 (2.1%). Symptom status and health perception stratified by these three groups, as well as their respective baseline characteristics, are presented in Supplementary Tables 2 and 3. Patients who had sinus rhythm and patients with AFL on the ECG had a significant higher symptom burden compared to patients with AF (75% and 83% vs 57%, p < 0.001). When comparing the individual symptoms, patients in AFL had more palpitations, dyspnea, chest pain and effort intolerance, compared to patients in AF or sinus rhythm. Using patients in sinus rhythm as the reference group, we observed a significant association between AFL rhythm and prevalence of any symptom (adjusted OR: 2.30; 95% CI: 1.26–4.20; p = 0.007). AFL rhythm was also associated with palpitations (adjusted OR: 2.09; 95% CI: 1.30–3.39; p = 0.003), dyspnea (adjusted OR: 3.38; 95% CI: 2.13–5.35; p < 0.001) and chest pain (adjusted OR: 1.95; 95% CI: 1.10–3.46; p = 0.02). On the other hand, AF was inversely associated with presence of any symptoms (adjusted OR: 0.60; 95% CI: 0.51–0.70; p < 0.001), as well as for most individual symptom categories. AFL rhythm (β-coefficient −9.70, 95% CI: −13.56 to −5.84; p < 0.001) and AF rhythm (β-coefficient −3.69, 95% CI: −4.89 to −2.49; p < 0.001) were both associated with a lower health perception.

4. Discussion

The main results of our study are as follows: 1) One fifth of the patients in our AF cohorts also suffered from coexistent AFL, 2) Patients with AF and coexistent AFL are more often symptomatic than patients with AF only, 3) Coexistent AFL is associated with more effort intolerance and 4) Patients with AFL on their baseline ECG reported a lower quality of life than AF patients in sinus rhythm.

4.1. Prevalence of coexistent AFL in AF patients

The coexistence of AF and AFL is common in clinical practice [14]. Recent studies have suggested that the prevalence of coexistent AF among AFL patients ranged between 24% and 62% [18,19]. Both arrhythmias may be different manifestations of the same electrical heart disease [20] and some hypothesize that without preceding AF resulting in rate dependent intraatrial block, AFL could not develop [21]. Of our 3931 patients with documented AF, 809 (20.6%) reported concurrent AFL. We could confirm the diagnostic of AFL through manual ECG interpretation and medical history research in the vast majority of patients with reported AFL and therefore concluded that our reported prevalence of 20.6% was not an overestimate of the true prevalence of coexistent AFL in our cohort. It may even be an underestimate considering that AFL has not been systematically documented in our cohorts and was elicited by medical history, and that patients who did not reported AFL and did not present with AFL rhythm on the ECG performed at baseline were classified as patients with AF only. To our knowledge we are the first to report the prevalence of AFL in a large population-based cohort of AF patients.

4.2. Symptoms and quality of life in patients with AF only and coexistent AFL

Earlier studies indicated that patients with both AF and AFL had less improvement in their QoL and frequency of symptoms following AFL ablation than patients with AFL only [22,23], generating the hypothesis that coexistence of both arrhythmias could have a greater impact on symptom status and QoL. However, the evidence on the impact of coexistent AF and AFL on the patients' wellbeing is sparse. When assessing symptom status in our population, we found an overall prevalence of symptoms of 66.3%, confirming

the high prevalence of symptoms among patients with AF [5]. When we compared patients with coexistent AF and AFL to patients with AF only, a higher symptom burden was found for patients with coexistence of both arrhythmias. This difference was observed even though the proportion of women, who are known to have substantially more symptoms than men when suffering from AF [8], was significantly higher in patients with AF only (as shown in Table 1).

The higher symptom burden for patients with coexistent AFL was particularly evident when our AF population was stratified according to the rhythm present on the ECG performed during the baseline visit. AFL rhythm emerged as a strong predictor for overall symptoms, more palpitations, more dyspnea and more chest pain, a finding that remained statistically significant after multivariable adjustment. Our results also showed that coexistence of AF and AFL was an independent predictor for more effort intolerance in our population. A possible explanation for this association between coexistence of AFL and effort intolerance might be that patients suffering from AFL more often received antiarrhythmic drugs (see Table 1), considering AFL does typically not respond well to antiarrhythmic drugs, treatment which predisposes them to develop adverse effects, including effort intolerance. Patients with coexistent AFL also reported more often a history of heart failure. This may in part be explained by poorer ventricular rate control among these patients, causing myocardial and electromechanical remodeling, potentially resulting in tachycardiomyopathy [13]. Patients in AFL rhythm at baseline had a significantly higher heart rate than both patients in AF or sinus rhythm, as well as a more frequent use of antiarrhythmic drugs (as shown on Supplementary Table 3), which could indicate poorer rate control. When comparing patients according to the rhythm on the ECG performed at baseline, we found that patients presenting in AFL had a significantly higher symptom burden and poorer QoL compared to patients who were either in sinus rhythm or in AF.

4.3. Differences between patients with and without cavotricuspid isthmus ablation

Cavotricuspid isthmus (CTI) ablation is the treatment of choice for recurrent and symptomatic AFL, with a high procedural success rate [24] and significant QoL improvement [25]. However, coexistent AF is frequently unmasked after CTI ablation for AFL [14,26]. In a meta-analysis, Pérez et al. report an overall incidence of AF after AFL ablation of 33.6%, increasing up to 56.6% after a 3-year follow-up [24]. Several studies now even suggest that a prophylactic pulmonary vein isolation in AF should be performed in conjunction with AFL ablation, in order to improve long-term freedom from atrial arrhythmias [27,28]. Furthermore, it has been demonstrated that stand-alone pulmonary vein isolation prevents recurrence of AFL, even without CTI ablation [29]. Considering the strong impact of CTI ablation on the arrhythmia recurrence and that symptoms are usually linked to the arrhythmia burden [30], as well as the fact that an improvement in quality of life could be demonstrated for patients after CTI ablation [25], we subdivided the group of patients with coexistent AF and AFL in those with and without a history of CTI ablation. We observed that patients who underwent CTI ablation had significantly more symptoms, and particularly more palpitations, than patients without CTI ablation and patients with AF only. This seemingly surprising result is probably due to the fact that symptoms were assessed for the period (possibly before the CTI ablation had been performed) preceding the baseline visit and therefore might not reflect the symptom status on that very day. Furthermore, it is likely that a higher symptom burden was the reason to undergo CTI ablation. Since we did not follow this subgroup, we are not able to confirm that patients who underwent CTI ablation experience a decrease of symptom burden and improvement in quality of life over the years following the ablation, as suggested by previous studies [22,25]. Finally, it is conceivable that patients with renewed AFL after CTI ablation suffer from CTI-independent AFL which may be more symptomatic.

4.4. Differences in quality of life in relation to the baseline ECG rhythm

Quality of life perception depends on the rhythm at the time of the baseline visit. AF strongly impacts on QoL and Steg et al. demonstrated that among AF patients, those in sinus rhythm had less QoL impairment than those in AF rhythm [5]. This is in line with our findings, showing that patients in AF had an observed difference of 6 points in the VAS (see Supplementary Table 2), when compared with AF patients in sinus rhythm. However, we observed that AF rhythm was associated with a lower symptom burden. We explain this result by the fact that a majority (83%) of patients presenting AF on the baseline ECG had persistent or permanent type AF, both AF types known to generate less symptoms than paroxysmal AF [8]. Additionally, we found that AF patients who presented AFL on the ECG had a significantly poorer QoL than both patients in sinus rhythm and in AF, further underscoring the additional impact of coexistent AFL among our AF population.

4.5. Strengths and limitations

A major strength of this study is the availability of two large, well-characterized populations of unselected AF patients. Given the thorough assessment of a large number of study variables for each study participant and the little exclusion rate due to missing data, the findings of this study are of relevance.

However, several limitations need to be taken into account. First, the cross-sectional observational study design does not allow us to draw causal conclusions and residual confounders may be present despite multivariable adjustment. Nevertheless, our study suggests that differences in symptoms and QoL are not explained by the covariates added in the models. Second, we had a low prevalence of patients presenting with AFL rhythm on the baseline ECG, therefore the results obtained for this subgroup should be interpreted cautiously. Third, the success rates of the CTI ablations for the different centers were not available in our data. However, previous publications showed that CTI ablation was successful in over 90% of the procedures [24] and we therefore assumed that the vast majority of procedures succeeded. Finally, echocardiographic data was only available for a small proportion of patients and not systematically documented, therefore differences in type of underlying heart disease and severity of systolic dysfunction may impact the patients' QoL despite adjustment for heart failure and coronary artery disease.

5. Conclusion

Our data from two large prospective observational cohort studies of patients with AF showed that one fifth of the patients suffer from coexistent episodes of AFL which is associated with a significantly higher symptom burden and poorer quality of life. Furthermore, the presence of AFL on the baseline ECG was associated with lower quality of life and more symptoms. Our data therefore suggest that coexistent AFL represents an added burden for patients suffering from AF and further studies are needed to assess the best therapeutic approach for this specific population of patients.

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Appendix A. Supplementary material

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