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Characteristics of symptom burden in atrial fibrillation with concomitant heart failure

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Abstract

Background: Symptom burden is an important factor in determining the treatment of atrial fibrillation (AF). AF is frequently accompanied by heart failure (HF). This study investigated the characteristics of AF symptoms with concomitant HF.

Methods: A total of 4885 patients with AF were consecutively enrolled through a prospective observational registry (the Comparison Study of Drugs for Symptom Control and Complication Prevention of Atrial Fibrillation [CODE-AF] registry). Clinically diagnosed HF was divided into three categories (preserved, mid-range, and reduced ejection fraction [EF]). Symptom severity was assessed using the European Heart Rhythm Association (EHRA) classification.

Results: The presence of AF-related symptoms was comparable irrespective of concomitant HF. Patients with HF with reduced EF demonstrated severe (EHRA classes 3 and 4) and atypical symptoms. HF with preserved EF was also associated with atypical symptoms. Female sex and AF type were associated with the presence of symptoms in AF without HF, and non-maintenance of sinus rhythm and increased left atrial pressure ($E/e' \geq 15$) were factors related to the presence of symptoms in AF with HF.

Conclusion: AF with concomitant HF presented with more severe and atypical symptoms than AF without HF. Maintaining the sinus rhythm and reducing the *E*/*e*′ ratio are important factors for reducing symptoms in AF with concomitant HF.

Keywords: Symptom burden, Atrial fibrillation, Heart failure

Introduction

Atrial fibrillation (AF) is associated with various symptoms. Although palpitations are the most typical symptom of AF, atypical symptoms are frequently encountered in clinical situations [1]. Severe symptoms, such as dyspnea or palpitations, can decrease the quality of life and increase the risk of hospitalization [2]. Furthermore, the presenting symptoms have important prognostic implications. AF patients with non-palpitation symptoms have higher rates of stroke and mortality than those with a more typical presentation [1]. AF is often concomitant with heart failure (HF), with each condition predisposing the patient to the other [3]. Patients with HF also experience shortness of breath, dyspnea on exertion, and fatigue, all of which affect quality of life. AF is also commonly associated with dyspnea on exertion followed by palpitations [2]. Therefore, when AF is present

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in combination with HF, their symptoms can be mixed, confused, and affected by each other.

Rhythm control via antiarrhythmic medication can be used to treat AF patients, and catheter ablation is a well-established treatment for symptomatic AF [4]. Recently, catheter ablation for AF in patients with HF has been shown to be beneficial in reducing the burden of AF and improving the left ventricular (LV) ejection fraction (EF), and it is similarly effective regardless of the presence of systolic dysfunction [5, 6]. In clinical situations, the presence of symptoms plays a major role in determining the proper treatment strategy for AF, with catheter ablation recommended mainly for symptomatic patients [4]. Therefore, evaluating the symptoms in AF with concomitant HF is important for the management of AF patients. To the best of our knowledge, no large-scale data have yet been evaluated in that way. Therefore, we investigated the characteristic differences in symptom burden and related factors in AF with concomitant HF.

Methods

Database

The data we analyzed for this study were from the prospective Comparison Study of Drugs for Symptom Control and Complication Prevention of AF (CODE-AF) registry. The CODE-AF is a prospective, multicenter, observational study of patients older than 18 years with AF. Patients were enrolled in ten tertiary centers encompassing all geographical regions of Korea. The study design and centers have been described previously [7]. The study was approved by the ethics committee of each center, and all patients provided informed consent for their inclusion. This study was registered at ClinicalTrials.gov (NCT02786095). The CODE-AF registry is an ongoing enrollment database. The first database for analysis was released in May 2017 and included patients from June 2016 to April 2017. The data entered at each center were audited regularly, and the database used for this analysis had completed the data cleaning process. Patient data collection was performed according to the same criteria. The collected data were registered in the Web-based clinical research management system iCreat (Internet-based Clinical Research and Trial Management System, http://icreat.nih.go.kr) provided by the Korean government.

Study population

A total of 6265 patients enrolled between June 2016 and April 2017 were included in the initial analysis. Patients missing the following data were excluded from this study: symptom descriptions ($n=232$), recent echocardiography data ($n=968$), available clinical history about the presence of HF ($n=55$), or appropriate clinical data ($n=125$). The final study group included 4885 patients with AF. Among them, 563 (11.5%) were also diagnosed with HF by each clinician of tertiary centers according to HF guideline for the diagnosis [8].

Definition of AF-related symptoms

Patient symptoms were collected through questionnaires, and clinical research coordinators at each center checked the responses. When patients were enrolled, they were asked about symptoms such as chest pain, dizziness, fainting, irregular pulse, palpitations, shortness of breath, sweating, and tiredness. If the patient reported at least one symptom, he or she was considered to be symptomatic. Patients experiencing palpitations with or without other concomitant symptoms were considered to offer a "typical presentation." Patients with symptoms but without palpitations were considered to offer an "atypical presentation" using the same method as previous study [1]. Symptoms related to AF were classified into three grades according to their degree of influence on daily activity, based on the European Heart Rhythm Association (EHRA) symptom scale [9]. EHRA class 1 indicates no symptoms; class 2 includes mild or moderate symptoms that leave normal daily activities unaffected; and classes 3–4 include severe to disabling symptoms, with normal daily activities affected or discontinued.

Echocardiography

Transthoracic echocardiography (2D, M-mode, pulsed-wave, continuous-wave, and color tissue Doppler) was performed before the enrollment of each patient. Echocardiographic data were obtained by trained research echocardiographers at each center and measured according to published guidelines [10]. The left ventricular EF was reported as a percentage. HF patients were categorized as having reduced (< 40%), mid-range (40–49%), or preserved (≥ 50%) EF (HFrEF, HFmrEF, and HFpEF, respectively). The left atrial diameter was measured from the parasternal view. The ratio between the early mitral inflow velocity and mitral annular early diastolic velocity (E/e') was obtained. An E/e' of 15 or more was considered to indicate increased left atrial (LA) pressure.

Statistical analysis

Baseline characteristics were compared according to the presence of HF. Continuous variables are presented as the mean ± standard deviation and were compared using independent t-tests. Categorical variables were compared by Fisher's exact test or the χ^2 test. A multivariate binary logistic regression analysis was used to determine the effect of HF on AF symptoms. The covariates were age, sex, CHADS-VASc score ≥ 2, stage of chronic kidney disease ≥ 3, smoking status, alcohol consumption,

AF pattern, blood pressure (BP), and heart rate (HR). Additionally, a multivariate analysis with a forward variable selection process was performed to document factors associated with the presence of AF symptoms in AF patients with and without concomitant HF. We included parameters of electrocardiography (presence of sinus rhythm, QRS duration, and QT interval) and echocardiography (EF, size of the left atrium, and E/e' ratio) as covariates. Two-tailed tests were used to determine significance. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS Statistics 21.0 software package (IBM SPSS, New York, USA).

Results

General characteristics of AF patients with HF

Table 1 lists the general characteristics of patients with AF according to the presence or absence of HF. AF patients with HF were older and had greater ratios of CHADS-VASc score ≥ 2 and HAS-BLED score ≥ 3. These patients were more likely to have diabetes mellitus, a history of myocardial infarction, peripheral artery disease, or chronic kidney disease. Current alcohol consumption was less frequent. However, patients with AF and HFrEF were male dominant, and current alcohol consumption or smoking was more frequent than those without HF (Additional file 1: Table S1). They had lower systolic and diastolic BP and higher HR.

In AF patients with HF, paroxysmal AF was less frequent than in AF patients without HF (47.1 vs. 66.0%, $p < 0.001$). The average EF was 47.7 ± 13.6% and the ratio of HFrEF, HFmrEF, and HFpEF was 29.0%, 27.0%, and 44.0%, respectively. Patients with both AF and HF demonstrated a larger LA and increased E/e' ratio. They showed less frequent sinus rhythm maintenance and a longer QRS duration and QT interval than AF patients without HF.

Treatment strategies according to presence of HF

The prescription pattern differed significantly between the groups with and without HF (Table 2). Angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, beta blockers, and digoxin were prescribed more frequently to AF patients with HF than to patients without HF. However, the use of non-dihydropyridine calcium channel blockers was less frequent in patients with HF. Regarding the AF treatment strategy, rhythm control strategies were used less frequently in patients with HF than in patients without. Among the non-pharmacological AF treatments, ablation was less frequent in the HF group, but electrical cardioversion was more

Table 1 General characteristics according to the presence of heart failure in atrial fibrillation

No. of patients $n = 4885$	No HF $n = 4322$	HF $n = 563$	p value
Age, years	67.2 ± 10.7	69.3 ± 11.0	< 0.001
Age ≥ 65	2686 (62.1%)	388 (68.9%)	0.002
Sex			0.603
Female	1579 (36.5%)	212 (37.7%)	
Male	2743 (63.5%)	351 (62.3%)	
BMI (kg/m^2)	24.7 ± 3.4	24.6 ± 3.7	0.503
CHA_2DS_2-VASc score ≥ 2	3141 (72.7%)	525 (93.3%)	< 0.001
HAS-BLED score ≥ 3	1046 (24.2%)	161 (28.6%)	0.025
Hypertension	2964 (68.6%)	401 (71.2%)	0.209
Diabetes mellitus	1089 (25.2%)	171 (30.4%)	0.009
Dyslipidemia	1590 (36.8%)	205 (36.4%)	0.553
Myocardial infarction	93 (2.2%)	44 (7.8%)	< 0.001*
Stroke history	719 (16.6%)	109 (19.4%)	0.107
Cancer	490 (11.3%)	54 (9.6%)	0.227
PAD	212 (4.9%)	53 (9.4%)	0.002
CKD (eGFR < 60)	434 (10.0%)	85 (15.1%)	< 0.001
ESRD on dialysis	75 (1.6%)	6 (1.1%)	0.294*
Permanent pacemaker	278 (6.4%)	48 (8.5%)	0.072
ICD	17 (0.4%)	33 (5.9%)	< 0.001*
Alcohol drinking			0.045
Current	945 (22.0%)	106 (18.9%)	
Social	340 (7.9%)	34 (6.0%)	
Never	3014 (70.1%)	422 (75.1%)	
Smoking			0.027
Current	363 (8.4%)	64 (11.4%)	
Former	1002 (23.2%)	140 (24.9%)	
Never	2957 (68.4%)	359 (63.8%)	
Systolic blood pressure (mmHg)	122.2 ± 14.7	120.2 ± 16.6	0.002
Diastolic blood pressure (mmHg)	74.6 ± 11.1	73.0 ± 12.6	0.002
Heart rate (bpm)	74.7 ± 15.6	78.5 ± 17.9	< 0.001
AF pattern			< 0.001
Paroxysmal	2851 (66.0%)	265 (47.1%)	
Persistent	1290 (29.8%)	240 (42.6%)	
Permanent	181 (4.2%)	58 (10.3%)	
AF documentation			0.840
Newly diagnosed	206 (4.8%)	26 (4.6%)	
Within 3 months	353 (8.2%)	50 (8.9%)	
Above 3 months	3763 (87.1%)	487 (86.5%)	
Echocardiography			
EF (%)	63.6 ± 6.2	47.7 ± 13.6	< 0.001
< 40	–	163 (29.0%)	
40–50	–	152 (27.0%)	
> 50	4322 (100%)	248 (44.0%)	
LA size (mm)	43.3 ± 7.7	47.3 ± 8.8	< 0.001
E/e' ratio	11.4 ± 5.0	14.2 ± 6.6	< 0.001
Electrocardiography			
Sinus rhythm	2236 (51.8%)	187 (33.2%)	< 0.001
QRS duration (ms)	98.6 ± 19.3	103.6 ± 24.7	< 0.001

Table 1 (continued)

No. of patients $n=4885$	No HF $n=4322$	HF $n=563$	*p* value
Corrected QT interval (ms)	439.7 ± 32.9	452.0 ± 40.0	< 0.001

Numerical variables are expressed as mean ± standard deviation, and categorical variables are represented as the absolute value with the percentage in parentheses

Fisher's exact test (*)

AF atrial fibrillation, *BMI* body mass index, *CKD* chronic kidney disease, *EF* ejection fraction, *ESRD* end-stage renal disease, *ICD* implantable cardiac defibrillator, *LA* left atrium, *PAD* peripheral artery disease

Table 2 Treatment strategies according to the presence of heart failure

No. of patients $n=4885$	No HF $n=4322$	HF $n=563$	*p* value
Pharmacologic treatment			
ARB or ACEi	1627 (37.7%)	389 (69.5%)	< 0.001
Beta blocker	2163 (50.1%)	378 (67.5%)	< 0.001
Non-DHP CCB	1322 (30.6%)	136 (24.3%)	0.002
Digoxin	235 (5.4%)	104 (18.6%)	< 0.001
Statin	1501 (34.7%)	241 (43.0%)	< 0.001
AF treatment strategy			< 0.001
Rhythm control	2129 (49.3%)	201 (35.7%)	
Rate control only	1564 (36.2%)	317 (56.3%)	
None	629 (14.6%)	45 (8.0%)	
Non-pharmacological AF treatment			
Catheter ablation	809 (18.7%)	83 (14.8%)	0.023
Electrical cardioversion	748 (17.3%)	131 (23.3%)	0.001
Stroke prevention			
CHA_2DS_2-VASc ≤ 1			0.095*
None	797 (67.5%)	20 (52.6%)	
Anti-platelet agents	22 (1.0%)	0 (0.0%)	
Oral anticoagulants	362 (30.7%)	18 (47.4%)	
CHA_2DS_2-VASc ≥ 2			0.030*
None	550 (17.5%)	72 (13.7%)	
Anti-platelet agents	13 (0.4%)	0 (0.0%)	
Oral anticoagulants	2578 (82.1%)	453 (86.3%)	

ACEi angiotensin-converting enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin receptor blocker, *Non-DHP CCB* non-dihydropyridine calcium channel blocker

Categorical variables are represented as the absolute value with the percentage in parentheses. Fisher's exact test (*)

frequent. Stroke prevention was relatively well undertaken in AF patients with HF (86.3 vs. 82.1%, $p=0.030$).

Symptom burden in AF with concomitant HF

Among AF patients with HF, 220 (39.1%, Additional file 1: Table S2) were symptomatic (EHRA class 2–4). The frequency of symptomatic AF was highest in AF patients with HFrEF (47.8%), but the difference was not significant after adjustment (Fig. 1a). AF patients with HFmrEF and HFrEF had a significantly higher frequency of severe symptoms (EHRA class 3 or 4, Fig. 1b) compared with AF patients without HF, but the presence of HF was not associated with the number of symptoms (Fig. 1c). In symptomatic AF cases, atypical symptoms were more frequently reported by AF patients with HFpEF and HFrEF (Fig. 1d). Among the types of symptoms observed (Additional file 1: Table S2), palpitations were the most common symptom in AF without HF, and shortness of breath was the most common symptom in AF with HF.

Table 3 shows the different factors related to the presence of symptoms in AF according to the presence of HF. Increased HR (≥ 100 bpm) was significantly associated with the presence of symptoms in both groups. However, whereas female sex and AF pattern were determinant factors in AF without HF, non-maintenance of sinus rhythm and increased E/e' ratio (≥ 15) were more strongly correlated factors in AF with HF.

Discussion

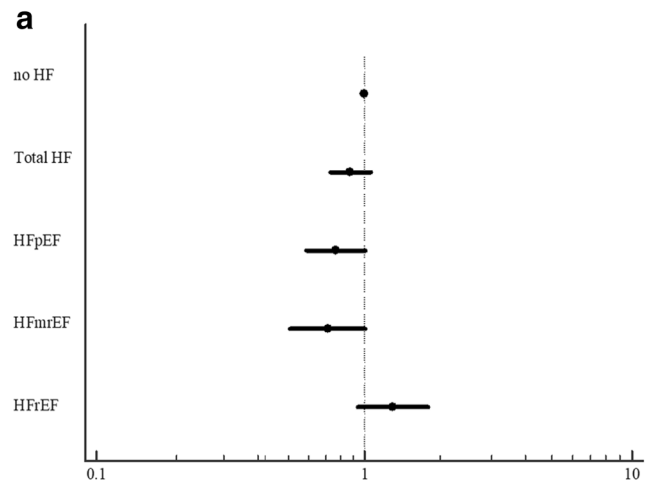
Our study demonstrates that AF patients with HF had a frequency of symptoms similar to that of AF patients without HF. However, symptom presentation was more severe and more commonly atypical in patients with HF than in those without it. Factors related to the presence of symptoms also differed according to the presence or absence of HF. Female sex and the type of AF were associated with the presence of symptoms in AF patients without HF. In AF patients with HF, maintenance of the sinus rhythm and a low E/e' ratio were closely correlated with the absence of symptoms.

In this study, the presence of HF did not influence the frequency of symptoms. It seems that AF patients with HF had factors associated with asymptomatic presentations, such as a history of diabetes and myocardial infarction [11, 12]. In addition, more than half the subjects in the present study were asymptomatic, regardless of their degree of LV dysfunction, perhaps because our study population had a relatively high ratio of males. In systematic reviews, the percentage of males was higher among patients with asymptomatic AF than among those with symptomatic AF [13].

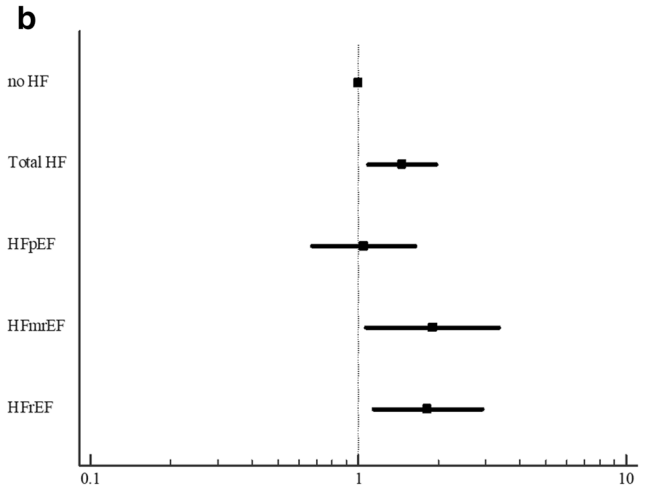
Atypical symptoms in AF patients could not be differentiated from the symptoms of other cardiovascular diseases. Most notably, AF and HF frequently coexisted [3]. Therefore, when evaluating the symptoms of AF patients with HF, it is difficult to discriminate whether their symptoms result from AF, HF, or both. Based on our results, the presence of HF appears to be associated with atypical presentation of AF, regardless of the degree of LV dysfunction. Among the various atypical symptoms,

shortness of breath was the most common in AF patients with HF. Shortness of breath was also frequently present in patients with only HF, but that could not be considered separately from AF. Kaye et al. [14] showed that AF influences the central hemodynamic and peripheral oxygen kinetics in HF. They explained that HF patients with AF had increased filling pressures and lower cardiac output indices despite having similar resting HR and that such patients exhibited a reduced capacity to increase their oxygen consumption and had relatively impaired cardiac indices during exercise compared with HF patients with sinus rhythm. Therefore, although shortness of breath can originate from HF itself, it can also be caused or aggravated by AF, regardless of the degree of LV dysfunction. Palpitations are considered to be the hallmark AF symptom, but the typical presentation including palpitations might be less common than the asymptomatic or atypical presentation in clinical situations [1]. In this study, palpitations were the most frequent symptom, but they occurred in only one-fifth of patients (Additional file 1: Table S2). However, palpitations were the most common symptom in AF patients without HF. Although atypical symptoms are characteristic of AF patients with HF, palpitations were still the next most common symptom in this study.

A previous study showed that patients with atypical symptoms had higher rates of stroke and mortality than patients with typical symptom presentation [1]. Patients with atypical symptoms had significantly higher CHA_2DS_2-VASc scores and lower estimated glomerular filtration rates, and they were more likely to have a prior history of diabetes and congestive HF [1]. Our study also shows that AF patients with HF had atypical symptoms more frequently than AF patients without HF, which

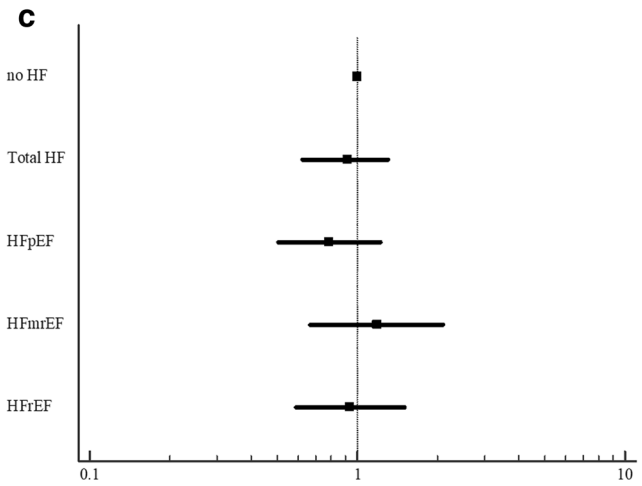


	Adjusted OR	95% CI	P value
Total HF vs. no HF	0.880	0.730-1.061	0.180
HFpEF vs. no HF	0.767	0.584-1.006	0.055
HFmrEF vs. no HF	0.713	0.502-1.013	0.059
HFrEF vs. no HF	1.297	0.940-1.789	0.113

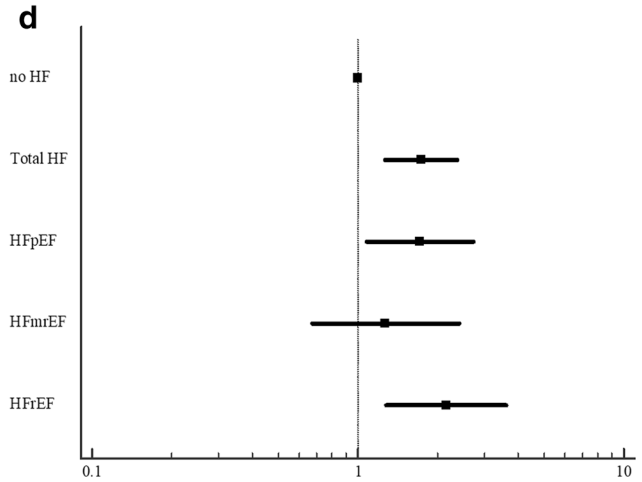


	Adjusted OR	95% CI	P value
Total HF vs. no HF	1.461	1.088-1.963	0.012
HFpEF vs. no HF	1.050	0.673-1.640	0.829
HFmrEF vs. no HF	1.894	1.068-3.361	0.029
HFrEF vs. no HF	1.820	1.138-2.912	0.013

Fig. 1 Difference of symptom burden according to presence or type of heart failure in atrial fibrillation. **a** Presence of symptoms, **b** severity of symptoms (EHRA class ≥ 3), **c** multiple symptom (number of symptoms ≥ 2), **d** atypical symptom. Covariates were age, sex, CHADS-VASc ≥ 2, renal function, AF pattern, smoking status, alcohol consumption, blood pressure, and heart rate



	Adjusted OR	95% CI	P value
Total HF vs. no HF	0.920	0.623-1.307	0.587
HFpEF vs. no HF	0.786	0.506-1.222	0.286
HFmrEF vs. no HF	1.181	0.667-2.092	0.568
HFrEF vs. no HF	0.940	0.588-1.502	0.795



	Adjusted OR	95% CI	P value
Total HF vs. no HF	1.732	1.266-2.369	0.001
HFpEF vs. no HF	1.716	1.080-2.727	0.022
HFmrEF vs. no HF	1.270	0.670-2.406	0.464
HFrEF vs. no HF	2.142	1.273-3.605	0.003

Fig. 1 continued

suggests that the presence of HF might influence the likelihood of unfavorable cardiovascular outcomes in AF patients with atypical symptoms. In a previous study, AF patients with typical symptoms had a generally lower-risk profile, but patients with atypical symptoms were not significantly more likely to suffer cardiovascular mortality after adjustment for CHA_2DS_2-VASc scores [1].

Treatment of AF consists of reducing the arrhythmia-associated symptoms and preventing ischemic stroke. To reduce arrhythmia-associated symptoms, more than 50% of AF patients with HF were treated only with rate control medication. In addition to rhythm control, rate control might be important in reducing the symptoms in patients with AF. In data from the EORP-AF Pilot Registry, the HR of asymptomatic patients was about 20 beats/min lower than that in symptomatic patients [15]. In our study, a HR of more than 100 bpm was a significant factor for the presence of symptoms in AF patients both with and without HF. However, rate control had a limited ability to reduce AF symptoms. Standard guidelines recommend a rhythm control strategy for patients with symptomatic AF [9], and radiofrequency catheter ablation is effective in reducing symptom burden and improving quality of life [15]. A meta-analysis suggested that a rhythm control strategy was superior to rate control in AF combined with HF and that catheter ablation was more effective in reversing cardiac remodeling than antiarrhythmic medication [16]. The presence of LV systolic dysfunction caused no significant differences in arrhythmia-free recurrence and symptom improvement [6]. However, a rhythm control strategy seems not to have been appropriately applied to AF patients with HF in our cohort. Compared with the degree of symptom burden, AF patients with concomitant HF were less likely than those without HF to be treated with antiarrhythmic drugs or catheter ablation. A previous study using

Table 3 Deterministic factors related to symptoms according to the presence of heart failure in atrial fibrillation

	No HF		HF	
	Adjusted OR (95% CI)	***p* value**	**Adjusted OR (95% CI)**	***p* value**
Age ≥ 65 years	Not selected		Not selected	
Female	1.52 (1.33–1.73)	< 0.001	Not selected	
BMI ≥ 25 kg/m^2	Not selected		Not selected	
CHADS-VASc ≥ 2	Not selected		Not selected	
PAF versus PmAF	2.18 (1.42–3.35)	< 0.001	Not selected	
PeAF versus PmAF	1.75 (1.13–2.72)	0.013	Not selected	
Heart rate ≥ 100 bpm	1.54 (1.18–2.01)	0.001	1.92 (1.07–3.43)	0.028
Sinus rhythm at ECG	Not selected		0.64 (0.43–0.97)	0.033
QRS duration ≥ 120 ms	Not selected		Not selected	
QTc interval ≥ 480 ms	Not selected		Not selected	
HFmrEF versus HFpEF	Not applicable		Not selected	
HFrEF versus HFpEF	Not applicable		Not selected	
LA size ≥ 40 mm	Not selected		Not selected	
E/*e*′ ratio ≥ 15	Not selected		1.47 (1.01–2.16)	0.047

Covariates were age ≥ 65 years, sex, body mass index (BMI) ≥ 25 kg/m^2, CHADS-VASc ≥ 2, AF pattern, heart rate ≥ 100 bpm, and parameters of echocardiography and electrocardiography

BMI body mass index, *CI* confidence interval, *ECG* electrocardiography, *EF* ejection fraction, *HF* heart failure, *LA* left atrium, *OR* odds ratio, *QTc* corrected QT, *PAF* paroxysmal atrial fibrillation, *PeAF* persistent atrial fibrillation, *PmAF* permanent atrial fibrillation

registry data for AF showed that only palpitations predicted the use of interventions to restore sinus rhythm [17]. Because atypical symptoms are more common in AF patients with HF and severe symptoms are associated with cardiovascular outcomes [18], rhythm control strategies need to be encouraged. Our study shows that sinus rhythm is an important factor among the less frequent symptoms.

Study limitations

This study has several limitations. Because all patients were enrolled from tertiary centers, asymptomatic patients with AF might have been less likely to be included in our cohort. Thus, the current registry is not free of referral bias, and the clinical picture shown by these patients might not be generalizable to the whole population. Additionally, symptom status was assessed at the time of enrollment rather than the time of AF diagnosis. Questionnaires about symptom burden and echocardiographic data were not collected simultaneously. However, we analyzed the most recent echocardiographic data based on the time of enrollment to reduce bias. Antiarrhythmic medication and catheter ablation that patients had already undergone could have influenced the presence or degree of symptoms. A few HF patients with preserved EF who had not yet been diagnosed might have been included in the group without HF.

Conclusion

AF with concomitant HF has a significantly different characteristic symptom burden than AF without HF. The presence of HF mainly affected the severity of symptoms and atypical presentation rather than the mere existence of symptoms. Modifiable factors, such as maintaining the sinus rhythm and a low *E*/*e*′ ratio, were strongly associated with the asymptomatic AF in patients with concomitant HF. These findings could encourage physicians to choose an appropriate treatment strategy for AF patients with HF.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s42444-019-0009-9.

Additional file 1. Table S1. General characteristics according to the type of heart failure in atrial fibrillation. **Table S2.** EHRA score and rank of symptoms in atrial fibrillation with and without heart failure.

Abbreviations

ACEi: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; CODE-AF: Comparison Study of Drugs for Symptom Control and Complication Prevention of AF; ECG: electrocardiography; EF: ejection fraction; EHRA: European Heart Rhythm Association; ESRD: end-stage renal disease; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; ICD: implantable cardiac defibrillator; LA: left atrium; LV: left ventricle; Non-DHP CCB: non-dihydropyridine calcium channel blocker; PAD: peripheral artery disease; PAF: paroxysmal

atrial fibrillation; PeAF: persistent atrial fibrillation; PmAF: permanent atrial fibrillation.

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Authors' contributions
J-KP contributed to the idea and design of this study; J-KP and RH prepared and checked clinical coding and undertook the data analysis; RH, M-JC, and J-KP wrote the draft; T-HK, JML, JP, HWP, K-WK, JS, J-SU, JK, J-BK, CK, YSL, and E-KC contributed to data collection and analysis; and J-KP and BJ revised the manuscript; all authors have seen and approved the final version of the report.

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Availability of supporting data
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate
The study was approved by the ethics committee of each center, and all patients provided informed consent for their inclusion.

Consent for publication
Applicable.

Competing interests
The authors declare no conflicts of interest.

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