Prevalence and Incidence of Atrial Fibrillation in Ambulatory Patients With Heart Failure

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Heart failure (HF) and atrial fibrillation (AF) commonly co-exist. We aimed to determine the prevalence and incidence of AF in ambulatory patients with HF. HF was defined by the presence of symptoms or signs supported by objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) ≤45% (HF and a reduced ejection fraction, HFrEF), or LVEF >45% and a raised plasma concentration of amino-terminal pro-B type natriuretic peptide (NT-proBNP >220 ng/L; HFpEF). Of 3,570 patients with HF, 1,164 were in AF at baseline (33%), with a higher prevalence among patients with HFpEF compared with HFrEF (40% vs 26%, respectively, p <0.001). Compared with patients with HF in sinus rhythm, those in AF were older, had more severe symptoms and higher NT-proBNP, worse renal function, and were more likely to receive loop diuretics, despite having a higher LVEF. Of those in sinus rhythm, 1,372 patients had HFrEF and 1,034 had HFpEF. The incidence of AF at 1 year (3.0%) was similar for each phenotype (p = 0.73). Increasing age, male gender, history of paroxysmal AF, and higher plasma concentrations of NT-proBNP were independent predictors of incident AF during a median follow-up of 1,574 (interquartile range: 749 to 2,821) days; the predictors were similar for each phenotype. In conclusion, the prevalence of AF is high, especially in patients with HFpEF, but its incidence is modest. This may be because their onset is near simultaneous with the development of AF precipitating the onset of HF. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:1554−1560)**

Background

Heart failure (HF) and atrial fibrillation (AF) are common, both associated with an increase in morbidity and mortality,[1,2] and share many of the same predisposing conditions, such as increasing age, hypertension, diabetes, and ischemic heart disease.[3,4] Pathophysiologically, HF and AF are closely intertwined. A constant and prolonged increase in atrial pressure might increase atrial wall fibrosis, impair atrial contraction, and provoke AF in patients with, or predisposed to, HF. In turn, the onset of AF may cause a fast ventricular rate, or a decrease in the atrial contribution to ventricular filling, with a subsequent decrease in cardiac output, leading to worsening of pre-existing, subclinical, ventricular dysfunction and, ultimately, the new-onset or clinical worsening of HF.[5] The prevalence of AF in patients with heart failure and a reduced ejection fraction (HFrEF) enrolled in registries or clinical trials is high, ranging from 15% to 40%.[6−12] It may be even higher[13−15] in patients with HF and preserved left ventricular ejection fraction (HFpEF), perhaps reflecting their older age. However, there are few data on the *incidence* of new-onset AF in patients with HF, which may be no higher than 5%/year.[4,16] Our aim was to determine the prevalence and incidence of AF in ambulatory patients with HF and the clinical predictors of new-onset AF.

Methods

From 2001 to 2014, a large, epidemiologically representative cohort of patients with suspected HF has been enrolled at a single National Health Service (NHS) community HF clinic serving a local population of about 600,000 people (The Hull LifeLab). Referrals to the HF clinic include a broad range of patients from both primary and secondary care physicians. Patients are consented for the use of medical information before investigation. Some patients had no previous diagnosis of HF and were treatment naive, therefore requiring initiation of guideline-recommended treatment, or might have a pre-existing diagnosis of HF and already have been initiated on treatment that might require optimization.

Patients are reviewed by HF specialist nurses and doctors and are followed up at regular intervals, usually at 4 months, 12 months, and then yearly unless a clinical appointment is requested sooner by the patient, other physicians or a specialist nurse. Patients who develop new, or worsening symptoms, are encouraged to contact the department and are followed more closely if needed. Information on demography, symptoms and signs, hematology and

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See page 1559 for disclosure information.

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biochemistry profiles (including amino-terminal pro-brain natriuretic peptide [NT-proBNP]), and echocardiograms are systematically recorded at each time point in a dedicated electronic health record stored on a secure NHS server.

Electrocardiography was systematically performed at each clinic visit to document heart rate and rhythm, and QRS duration. If clinically indicated, we investigated for symptoms of palpitations using ambulatory cardiac monitoring. Titration of treatment is coordinated by the clinic but often implemented by community HF nurses or general practitioners.

For the purpose of the present analysis, HF was defined by the presence of symptoms or signs of HF supported by objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) ≤45% or equal to, or worse than mild to moderate left ventricular systolic dysfunction (LVSD) on visual assessment at echocardiography (HFrEF), or raised plasma concentration of amino-terminal pro-B type natriuretic peptide (NT-proBNP) >220 ng/L consistent with the European Society of Cardiology (ESC) consensus statement for diagnosis of HFpEF at the time of initiation of the study.[17] Patients who did not fulfil criteria for cardiac dysfunction (those with LVEF >45% or equal to, or better than, mild LVSD at visual assessment at echocardiography who had an NT-proBNP below or equal to 220 ng/L) were used as a control group.

In 2016, the ESC-HF guidelines changed the definition for HF,[18] after our analysis plan was developed. The new guidance suggested taking a cutoff of LVEF <40% as the upper limit for making a diagnosis of HFrEF; and reduced the NT-proBNP cutoff in excluding HF to 125 ng/L. Therefore, we partially repeated our analysis applying the newer ESC-HF 2016 criteria, defining HF by the presence of symptoms or signs supported by objective evidence of cardiac dysfunction: either LVEF <40% or equal to, or worse than moderate LVSD on visual assessment on echocardiography (HFrEF), or raised plasma concentration of NT-proBNP (>125 ng/L; HFpEF, without further distinguishing between those with mid-range (HFmrEF) or preserved ejection fraction).

Patients whose echocardiography, electrocardiogram (ECG) or NT-proBNP (in the presence of normal or mildly reduced LVEF) were not available at baseline have been excluded from this analysis (n = 511; Supplementary Figure 1).

For patients in sinus rhythm at baseline, information regarding previous episodes of paroxysmal AF was retrieved from the electronic hospital records and hospital or General Practitioner (GP) notes before their baseline visit. We did not attempt to distinguish between persistent and permanent AF.

Ischemic heart disease was defined as a previous documented history of myocardial infarction. Diabetes mellitus (DM) was defined as previous medical history of DM based on GP or hospital records or on the prescription of treatment for DM. Hypertension was defined as previous medical history of hypertension based on GP or hospital records, or systolic blood pressure ≥160 mm Hg or diastolic ≥100 mm Hg at the baseline clinical visit, despite the use of medications that might decrease systolic or diastolic blood pressure (including β blockers, ACE-inhibitors or sartans, thiazide-like diuretics, and calcium-antagonists). Valvular heart disease was defined as a significant valvular abnormality identified as one of the causes for the referral or by baseline echocardiography, or a previous history of aortic or mitral valve replacement. Peripheral vascular disease was defined as previous documented history of peripheral vascular disease, including abdominal aortic aneurysm, from GP or hospital records.

Our hospital is the only hospital providing acute medical care for the region and is notified of all acute clinical events. It is unusual, although possible, for a patient with HF followed up in our region to be admitted elsewhere. For patients who move out of the region, other clinical information, in particular death, can be tracked through hospital health records.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All participants gave their written informed consent.

Categorical data are presented as numbers and percentages; normally distributed continuous data as mean ± SD and non-normally distributed continuous variables as median and interquartile range. One-way analysis of variance and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-square test for categorical variables. Cox proportional hazard regression models were used to investigate the relation of variables and incident AF in the overall population, and separately in patients with HFrEF and HFpEF. Models were constructed including and excluding left atrial diameter, available in <90% of patients. Treatment variables were not included in either model as these might be confounded by indication and might vary over time. Assumptions of the models, such as multicollinearity and proportional hazards, were tested. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. All analyses were performed using SPSS (v.22) and Stata software. A 2-sided p value <0.05 was considered statistically significant.

Results

Of the 5,211 patients with available data, 511 were excluded due to missing information (Figure 1 Supplementary), leaving a total of 4,700 patients in the study. Of these, 3,570 met the definition of HF and 1,130 did not (Table 1 Supplementary).

Of those with HF, 1,164 (33%) had AF on their baseline electrocardiogram. AF was more common in patients with HFpEF than HFrEF (40% vs 26%, respectively, p <0.001). Compared with patients in SR, those with AF and HF were older, had more severe symptoms, lower systolic blood pressure, and more commonly had a clinical history of transient ischemic attack (TIA)/stroke and valvular heart disease. They also had higher plasma concentrations of NT-proBNP, worse renal function, and were receiving more loop diuretics; on echocardiography, they had larger left atrial diameters, despite having a higher LVEF (Table 1).

Compared with those with HFrEF and AF, those with HFpEF and AF were older and more likely to be women, had higher body mass index and systolic blood pressure, better renal function, but lower hemoglobin. They also had fewer symptoms, a smaller left atrium, were less likely to

Table 1
Baseline characteristics of patients with HF, by diagnostic category and by heart rhythm. *Left ventricular ejection fraction was measured (n = 2,013) or visually estimated. # Medications recorded at baseline before changes subsequent to initial referral

Variable	Missing	Heart failure and atrial fibrillation (1,164)	Heart failure and sinus rhythm (2,406)	p	HFrEF in sinus rhythm (1,372)	HFpEF in sinus rhythm (1,034)	p
Demographics							
Age (Years)	0	76 (70-82)	73 (65-79)	<0.001	71 (63-77)	76 (70-82)	<0.001
Men	0	774 (67%)	1483 (62%)	0.005	1002 (73%)	481 (47%)	<0.001
Body Mass index (kg/m^2)	11	28 (25-32)	28 (25-32)	0.07	28 (24-31)	28 (25-32)	<0.001
Systolic blood pressure (mmHg)	11	136 (25)	139 (26)	<0.001	132 (24)	149 (26)	<0.001
Diastolic blood pressure (mmHg)	10	80 (16)	77 (14)	<0.001	76 (13)	78 (14)	<0.001
Heart rate (bpm)	10	81 (20)	71 (15)	<0.001	72 (15)	70 (15)	<0.001
Diabetes mellitus	0	278 (24%)	603 (25%)	0.444	326 (24%)	277 (27%)	0.090
Hypertension	0	629 (54%)	1238 (52%)	0.147	563 (41%)	675 (65%)	<0.001
Valvular disease	0	192 (17%)	181 (8%)	<0.001	75 (6%)	106 (10%)	<0.001
Ischemic heart disease	0	483 (42%)	1425 (59%)	<0.001	956 (70%)	469 (45%)	<0.001
Previous TIA/Stroke	0	144 (12%)	163 (7%)	<0.001	103 (8%)	60 (6%)	0.100
Peripheral vascular disease	0	76 (7%)	179 (7%)	0.322	113 (8%)	66 (6%)	0.086
Paroxysmal atrial fibrillation	0	Not applicable	190 (8%)	Not applicable	116 (9%)	74 (7%)	0.242
NYHA Class I	0	174 (15%)	583 (24%)	<0.001	268 (20%)	315 (31%)	<0.001
NYHA Class II		571 (49%)	1156 (48%)		682 (50%)	474 (46%)	
NYHA Class III		399 (34%)	618 (26%)		386 (28%)	232 (22%)	
NYHA Class IV		20 (2%)	49 (2%)		36 (2%)	13 (1%)	
Blood results							
NT-proBNP (ng/L)	11	1936 (1057-3607)	833 (372-2119)	<0.001	1165 (474-3012)	587 (326-1288)	<0.001
Albumin (g/L)	233	37 (4)	38 (4)	0.001	38 (4)	37 (4)	0.002
Bilirubin (μmol/L)	243	16 (13-21)	13 (11-17)	<0.001	14 (12-18)	13 (10-15)	<0.001
Creatinine (μmol/L)	153	104 (86-130)	100 (82-128)	0.002	102 (86-128)	96 (79-125)	<0.001
Hemoglobin (g/**dL**)	157	13.4 (1.9)	13.1 (1.7)	<0.001	13.4 (1.7)	12.8 (1.7)	<0.001
K (mmol/L)	171	4.3 (4.0-4.6)	4.4 (4.1-4.7)	<0.001	4.4 (4.1-4.7)	4.3 (4.1-4.7)	0.001
Na (mmol/L)	151	138 (3)	138 (3)	0.894	138 (3)	138 (3)	0.584
Urea (mmol/L)	151	7.1 (5.4-9.8)	6.8 (5.2-9.2)	0.003	6.8 (5.3-9.2)	6.8 (5.2-9.2)	0.640
Thyroid-stimulating hormone (mU/L)	408	1.8 (1.2-2.8)	1.7 (1.1-2.5)	0.002	1.6 (1.0-2.5)	1.7 (1.1-2.6)	0.151
Medications#							
Loop diuretic	0	860 (74%)	1505 (63%)	<0.001	959 (70%)	546 (53%)	<0.001
Mineralocorticoid receptor antagonist	0	227 (20%)	525 (22%)	0.111	417 (30%)	108 (10%)	<0.001
ACE-I or ARB	0	812 (70%)	1743 (72%)	0.096	1115 (81%)	628 (61%)	<0.001
Beta-blockers	0	660 (57%)	1429 (59%)	0.126	906 (66%)	523 (51%)	<0.001
Echocardiography*							
Left ventricular ejection fraction ≥55%	0	403 (35%)	618 (26%)	<0.001	0	618 (60%)	Not applicable
Left ventricular Ejection fraction: 46-54%		283 (24%)	416 (17%)		0	416 (40%)	
Left ventricular ejection fraction: 36-45%		242 (21%)	658 (27%)		658 (48%)	0	
Left ventricular ejection fraction: ≤35%		236 (20%)	714 (30%)		714 (52%)	0	
Left atrial diameter (cm)	431	4.7 (0.8)	4.0 (0.7)	<0.001	4.2 (1.7)	3.9 (0.7)	<0.001
Events							
Incident atrial fibrillation	0	Not applicable	291 (12%)	Not applicable	205 (15%)	86 (8%)	Not applicable
Incident atrial fibrillation at 1 year	0	Not applicable	62 (3%)	Not applicable	34 (3%)	28 (3%)	0.73

be taking loop diuretics, and had lower plasma NT-proBNP (Supplementary Table 2).

During a median follow-up of 1,624 (784 to 3,054) days, 1,962 (42%) patients with HF died. The presence of AF was associated with higher mortality (hazard ratio [HR] vs those in sinus rhythm: 1.33, 95% confidence interval [CI] 1.20 to 1.47, p <0.001). Patients with HFrEF and AF had the worst outcome (HR 1.19, 95% CI 1.02 to 1.41, p = 0.026 vs those with HFpEF and AF, Figure 1 unadjusted; adjusted for age and gender, Figure 2 Supplementary).

Compared with patients with HFrEF in SR (n = 1,372), those with HFpEF in SR (n = 1,034) were older, had less severe symptoms, were more likely to be women, to have hypertension or valvular disease, but less likely to have ischemic heart disease (Table 1). They had lower NT-proBNP and hemoglobin concentrations, smaller left atria, better renal function, and were less frequently treated with loop diuretics.

For those who had a minimum of 1-year follow-up, there was no difference in the incidence of persistent AF at

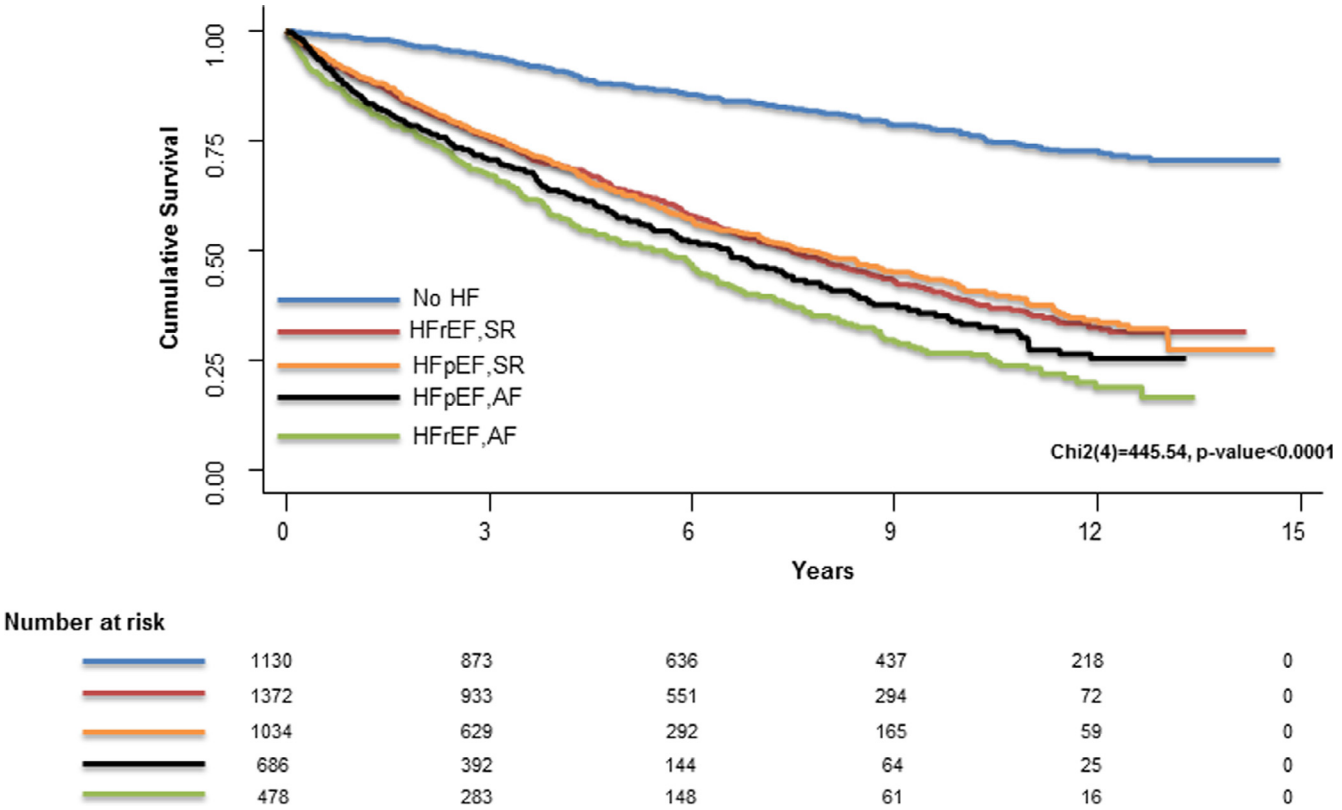

Figure 1. Kaplan-Meier curve for death from all causes. Patients with HFrEF and AF had the worst outcome (HR 1.19, 95% CI 1.02 to 1.41, p = 0.026 vs those with HFpEF and AF).

1 year between patients with HFrEF (n = 34 of 1,195; 2.8%) and those with HFpEF (n = 28 of 901; 3.1%; p = 0.73).

In univariable analysis, ischemic heart disease, lower systolic and diastolic blood pressure, and higher creatinine and bilirubin were associated with incident AF (Table 2). In a multivariable analysis that did not include left atrial diameter, only greater age, male gender, history of paroxysmal AF, and higher NT-proBNP were independent predictors of incident AF. When LA diameter was entered into the model, the diagnosis of HFrEF rather than HFpEF and LA diameter were also independently associated with incident AF (Table 2).

For patients with HFrEF, increasing age, male gender, greater LogNT-proBNP, and history of paroxysmal AF independently predicted incident AF (Supplementary Table 3).

In multivariable models for patients with HFpEF, greater Log NT-proBNP, male gender, and history of paroxysmal AF predicted incident AF. When LA diameter was added, it competed with male gender for the association with incident AF (Supplementary Table 4).

Compared with the patients in the lowest quintile of NT-proBNP, those in the highest quintiles had three- to fourfold greater risk of developing AF during follow-up (Table 3).

Applying newer ESC-HF criteria, the number of patients with HF increased from 3,570 to 3,890, of whom 1,372 had HFrEF and 2,518 had HFpEF. Compared with patients with HFpEF, those with HFrEF were younger (71 (63 to 78) vs 75 (69 to 81) years; p <0.001), had higher plasma NT-proBNP (1819 (787 to 4,028) vs 750 (296 to 1,757) ng/L; p <0.001) and creatinine (105 (88 to 131) vs 96 (80 to 122) μmol/L: p <0.001), and a larger left atrial diameter (4.4 (3.9 to 4.9) vs 4.1 (3.6 to 4.6) cm, p <0.001).

Of 1,166 patients with HF and AF at baseline (30%), the prevalence was greater among patients with HFpEF (33%) compared with HFrEF (25%; p <0.001).

Of those in SR (n = 2,724), 2,467 had at least 1-year follow-up. The incidence of persistent AF at 1 year was 2.6% and was similar in patients with HFrEF (23 of 928 patients; 2.5%) and HFpEF (40 of 1,539 patients; 2.6%; p = 0.85). Changing the definition of HF did not change predictors of incident AF (Supplementary Table 5).

Discussion

We previously reported the low incidence of AF in a cohort of 623 patients with HFrEF and sinus rhythm. Here, we expand the numbers of patients and include many more with HFpEF on echocardiography.[19] Our results show that in ambulatory patients with HF, the prevalence of AF is high, particularly in those with HFpEF, but its incidence is fairly low, which is most readily explained by concurrent onset of HF and AF. Similar observations have been made both from the Framingham study[4,20] and Olmsted County residents.[15] AF may often be the precipitating cause of clinically overt HF but pre-existing ventricular dysfunction is likely to contribute both to the development AF and to a reduction in cardiac reserve, making the patient more vulnerable to the onset of HF.

Our findings confirm the association between well-known risk factors and incident AF, which maintain their

Table 2
Univariable and multivariable analysis for the incidence of atrial fibrillation in the overall population with heart failure. Two models were constructed, one including and one excluding left atrial diameter (available for 2,085 patients, 87%). Variable included in the multivariable models were age, gender, systolic blood pressure, diastolic blood pressure, ischemic heart disease, paroxysmal atrial fibrillation, LogNT-proBNP, albumin, bilirubin, hemoglobin, urea, diagnostic category (HFrEF vs HFpEF), and left atrial diameter

Variable	Univariable analysis			Multivariable analysis LA included LA excluded		
	HR (95% CI)	Chi-square	p-value	HR (95% CI)	Chi-square	p-value
Age (1 Year increase)	1.03 (1.01-1.05)	17.69	<0.001	1.04 (1.02-1.05)	17.75	<0.001
				1.03 (1.02-1.05)	16.90	<0.001
Male sex (vs female)	1.70 (1.31-2.21)	15.59	<0.001	1.64 (1.17-2.30)	8.29	0.004
				1.98 (1.45-2.70)	18.75	<0.001
Body Mass Index (kg/m^2)	0.99 (0.98-1.02)	0.014	0.91			
Systolic Blood Pressure (mmHg)	0.99 (0.99-1.00)	6.34	0.012			
Diastolic Blood Pressure (mmHg)	0.99 (0.98-1.00)	6.23	0.013			
Heart Rate (bpm)	1.00 (1.00-1.01)	0.19	0.66			
Diabetes Mellitus (yes vs not)	1.12 (0.85-1.48)	0.68	0.41			
Hypertension (yes vs not)	0.89 (0.71-1.12)	0.99	0.32			
Valvular Disease (yes vs not)	1.13 (0.73-1.76)	0.29	0.59			
Ischemic Heart Disease (yes vs not)	1.40 (1.10-1.80)	7.16	0.007			
Previous TIA/Stroke (yes vs not)	0.95 (0.59-1.53)	0.05	0.95			
Peripheral Vascular Disease (yes vs not)	1.11 (0.71-1.75)	0.21	0.65			
Paroxysmal Atrial Fibrillation (yes vs not)	3.06 (2.26-4.13)	53.20	<0.001	2.52 (1.78-3.57)	27.18	<0.001
				2.62 (1.89-3.64)	33.28	<0.001
NYHA class (III/IV vs I/II)	1.40 (1.08-1.81)	6.54	0.010			
LogNT-proBNP (ng/L)	2.39 (1.94-2.96)	64.69	<0.001	1.80 (1.34-2.42)	15.19	<0.001
				1.91 (1.46-2.50)	22.04	<0.001
Albumin (g/l)	0.97 (0.94-1.00)	3.58	0.057			
Bilirubin (mol/L)	1.03 (1.01-1.05)	13.53	<0.001			
Creatinine (mol/L)	1.01 (1.00-1.01)	7.32	0.007			
Haemoglobin (g/dL)	0.94 (0.87-1.00)	3.28	0.070			
K (mmol/L)	1.03 (0.81-1.31)	0.06	0.81			
Na (mmol/L)	1.01 (0.97-1.05)	0.11	0.74			
Urea (mmol/L)	1.04 (1.02-1.06)	15.67	<0.001			
Thyroid-Stimulating Hormone (mU/L)	1.02 (0.99-1.04)	1.83	0.18			
HFrEF vs HFpEF	1.63 (1.27-2.09)	14.33	<0.001	1.44 (1.02-2.04)	4.36	0.037
				-	-	-
Left Atrial Diameter (cm)	1.78 (1.50-2.12)	42.86	<0.001	1.56 (1.28-1.89)	20.17	<0.001
				-	-	-

clinical importance regardless of left ventricular phenotype. We found that incident AF is more common in older subjects and men, perhaps reflecting an association with ischemic heart disease.

Raised plasma concentrations of natriuretic peptides are associated with an increasing risk of developing AF in the general population and in subjects at increased cardiovascular risk, but little is known about the association of

Table 3
Risk of developing AF during follow-up according to NTproBNP quintiles in patients with HFrEF and HFpEF

Quintile of NT-proBNP (range, ng/L)	Patients with HFrEF with incident AF (per 1000 person-years), n	Hazard ratio (95% CI), p (vs Q1)
Q1 (9-363)	14.44	1
Q2 (364-832)	25.51	1.80 (1.12-2.92); 0.016
Q3 (835-1652)	39.85	2.89 (1.82-4.58); <0.001
Q4 (1667-3780)	41.94	3.11 (1.93-4.99); <0.001
Q5 (3781-61888)	42.53	3.18 (1.93-5.25); <0.001
Quintile of NT-proBNP (range, ng/L)	**Patients with HFpEF with incident AF (per 1000 person-years), n**	**Hazard ratio (95% CI), p (vs Q1)**
Q1 (221-309)	8.95	1
Q2 (310-448)	9.22	1.03 (0.44-2.42); 0.948
Q3 (449-762)	15.28	1.64 (0.74-3.62); 0.223
Q4 (763-1573)	30.71	3.26 (1.59-6.69); 0.001
Q5 (1575-35000)	41.57	4.29 (2.12-8.70); <0.001

natriuretic peptides with incident AF in ambulatory patients with HF, particularly in those with HFpEF. We found a linear increase in the risk of developing AF with increasing plasma concentrations of NT-proBNP regardless of left ventricular phenotype.

In almost 4,000 participants in the Cardiovascular Health Study aged older than 65 years and free of AF, of whom only 3% had HF, those in the highest quintile of baseline NT-proBNP had a 5.2-fold greater risk of developing AF during follow-up compared with the lowest quintile.[21] In a report including more than 26,000 subjects enrolled from 5 distinct community-based cohort studies conducted in the United States and Europe, of whom fewer than 4% had HF, increasing plasma concentrations of natriuretic peptides were, along with increasing age, one of the strongest predictors of incident AF.[22] In a Swedish cohort of patients free of cardiovascular disease, natriuretic peptides, particularly MR-proANP, but not other biomarkers (including mid-regional pro-adrenomedullin, cystatin C, and copeptin), predicted incident AF.[23]

Other authors have shown that increasing plasma concentrations of natriuretic peptides are robust predictors of the recurrence of AF following ablation in patients with lone AF[24] or of recurrence in those with a history of paroxysmal AF.[25] In a retrospective analysis from the Valsartan Heart Failure Trial, in which >4,000 patients had HFrEF and sinus rhythm, a BNP at study entry above the median value (97 pg/ml) was the strongest predictor of AF occurrence (6.5% at 23 months).[12]

Although it is possible that raised levels of natriuretic peptides might promote atrial arrhythmias, it is more likely that higher plasma concentrations reflect advanced age and more advanced underlying cardiac and renal disease. In addition, higher natriuretic peptides are associated with atrial enlargement and dysfunction, often secondary to left ventricular dysfunction.[26] We found a similar incidence of AF regardless of LVEF, similar to other reports.[27] Our results also confirm that patients with HF and AF have a poorer outcome compared with those in sinus rhythm, regardless of LVEF.[28]

We defined "incident AF" as documented AF on a 12-lead ECG at a follow up visit. We did not systematically investigate patients for paroxysmal AF using cardiac monitoring because the clinical or therapeutic relevance of short, asymptomatic episodes of AF in patients with HF is not known and guidelines on HF do not recommend routine investigation.[29] Some incident AF might have occurred shortly before death and would thus not have been reported. Other potential confounders, such time-dependent changes in medications or compliance to HF medications have not been assessed. Some patients were treatment-naïve at the time of referral or required adjustment in HF medications, which might have affected the risk of developing AF during their first year of follow-up. We included patients with either reduced LVEF below 45% or raised natriuretic peptides (NT-proBNP >220 ng/L) in this analysis, in agreement with ESC recommendation that were contemporary when the study was conceived. However, there is no universal agreement on the optimal cutoff of NT-proBNP to be used to diagnose, or to rule out, HF in the presence of a normal, or mildly reduced LVEF. The use of a lower cutoff to rule out HF (125 ng/L), as suggested by the recent ESC-HF guidelines,[18] led to the inclusion of patients with less severe cardiac dysfunction and a lower prevalence of AF among patients with HFpEF, reflecting the uncertainty about the diagnostic criteria for HF. However, predictors and the 1-year incidence of AF remained similar for both HFrEF and HFpEF.

In conclusions, the prevalence of AF is high, especially in patients with HFpEF but its incidence is modest. This may be explained by a high concurrent onset of HF and AF. Greater age, a history of paroxysmal AF and increasing plasma concentrations of NT-proBNP, a marker of congestion, predict the risk of developing, or progressing to, persistent or permanent AF in patients with HF.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.018.

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