JACC: HEART FAILURE
VOL. 5, NO. 8, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.05.001

Atrial Fibrillation in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

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ABSTRACT

OBJECTIVES The study sought to assess the independent risk factors for, consequences of, and outcomes with atrial fibrillation (AF) compared with sinus rhythm (SR) in heart failure (HF) with preserved ejection fraction (HFpEF) versus HF with mid-range ejection fraction (HFmrEF) versus HF with reduced ejection fraction (HFrEF).

BACKGROUND AF is common in HF, but most data are from HFrEF. The importance of AF in HFpEF and HFmrEF is less well known.

METHODS In patients from 2000 to 2012 in the SwedeHF (Swedish Heart Failure Registry) registry, enriched with patient-level data from national health care registries, the authors assessed prevalence of, associations with, and prognostic impact of AF in HFpEF versus HFmrEF versus HFrEF.

RESULTS Of 41,446 patients, 23% had HFpEF, 22% had HFmrEF, and 55% had HFrEF. The prevalence of AF was 65%, 60%, and 53% in HFpEF, HFmrEF, and HFrEF, respectively. Independent associations with AF were similar in HFpEF, HFmrEF, and HFrEF and included greater age, male, duration of HF, prior myocardial infarction, and prior stroke or transient ischemic attack (TIA). The adjusted hazard ratios for AF versus SR in HFpEF, HFmrEF, and HFrEF were the following: for death, 1.11 (95% confidence interval [CI]: 1.02 to 1.21), 1.22 (95% CI: 1.12 to 1.33), and 1.17 (95% CI: 1.11 to 1.23); for HF hospitalization or death, 1.17 (95% CI: 1.09 to 1.26), 1.29 (95% CI: 1.20 to 1.40), and 1.15 (95% CI: 1.10 to 1.20); and for stroke or TIA or death, 1.15 (95% CI: 1.07 to 1.25), 1.23 (95% CI: 1.13 to 1.34), and 1.19 (95% CI: 1.14 to 1.26).

CONCLUSIONS AF was progressively more common with increasing ejection fraction, but was associated with similar clinical characteristics in HFpEF, HFmrEF, and HFrEF. AF was associated with similarly increased risk of death, HF hospitalization, and stroke or TIA in all ejection fraction groups. In contrast, AF and SR populations were considerably different regarding associated patient characteristics and outcomes. (J Am Coll Cardiol HF 2017;5:565–74)

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Manuscript received April 5, 2017; revised manuscript received April 26, 2017, accepted May 1, 2017.

JACC: HEART FAILURE VOL. 5, NO. 8, 2017
AUGUST 2017:565–74

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

EF = ejection fraction

HF = heart failure

HFmrEF = heart failure with mid-range ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OR = odds ratio

SR = sinus rhythm

TIA = transient ischemic attack

Atrial fibrillation (AF) is common in heart failure (HF), and HF predisposes AF and vice versa (1,2), but most data are from HF with reduced ejection fraction (HFrEF). HF with preserved ejection fraction (HFpEF) is heterogeneous and remains poorly understood, but affects one-half of the HF population and is associated with mortality as high as in HFrEF (3). An ejection fraction (EF) of 40% to 49% is neither normal nor preserved, but there is no evidence-based therapy. This category was recently designated a separate HF with mid-range EF (HFmrEF) category, where characteristics and potential for therapy are unknown (1).

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In HFrEF, the prevalence of AF has been assessed mainly from trial data and ranges from <10% to 50% (4,5). In HFpEF, the prevalence of AF appears generally higher, at 21% to 65% (3,6–11). However, within-cohort comparisons are scarce (12–14). Whether the independent determinants of AF are similar or different in HFpEF versus HFmrEF versus HFrEF is unknown. Although conflicting, most data suggest that AF is associated with increased mortality in both HFpEF and HFrEF (9,15–21). However, these analyses suffer from low sample size, poor comparability, or insufficient multivariable adjustment.

Therefore, we performed a comprehensive comparative assessment of the prevalence of, independent associations with, and independent prognostic role of AF versus sinus rhythm (SR) in HFpEF versus HFmrEF versus HFrEF.

METHODS

STUDY POPULATION AND DATA. The nationwide SwedeHF (Swedish Heart Failure Registry) registry has been previously described (22) and provided the study population and baseline clinical characteristics and medications. The inclusion criterion is clinician-judged HF. Approximately 80 variables are recorded at discharge from hospital or outpatient clinic visit and entered into a web-based database managed by the Uppsala Clinical Research Center. EF is characterized as <30%, 30% to 39%, 40% to 49%, and ≥50%. For this study, an EF of ≥50% was defined as HFpEF, an EF of 40% to 49% as HFmrEF, and an EF of ≤39% as HFrEF.

Information on AF is available from history in the SwedeHF registry (yes or no), electrocardiogram in the SwedeHF registry (sinus, AF, or other), and history in National Patient Registry (yes or no). For purposes of this analysis, AF was defined broadly, where AF in any of these 3 variables was considered AF = yes, which therefore includes paroxysmal AF. Patients were included if the index date was between May 11, 2000, and December 31, 2012. The index date was defined as the date of an outpatient visit or hospital discharge. Patients that died during the hospitalization were excluded. Follow-up was until December 31, 2012.

The Swedish Board of Health and Welfare maintains the National Population and Patient Registries. The Population Registry provided date of death. The Patient Registry provided additional baseline comorbidities and the pre-specified outcomes HF hospitalization and stroke or transient ischemic attack (TIA). It contains International Classification of Diseases-10th Revision codes (Online Table 1) for encounters as inpatients in any setting and as outpatients at specialty (but not primary care) clinics, and is updated and validated annually (last update and thus end of follow-up for this study, December 31, 2012). The positive predictive value for most diagnoses is between 85% and 95% (23); an HF diagnosis was verified in between 86% and 91% of cases (and used in this study for the HF hospitalization outcome but not used to include patients because all patients were included from the SwedeHF registry) (24). Comorbidities present at baseline were defined by corresponding International Classification of Diseases-10th Revision codes in any position between January 1, 1997, when use of International Classification of Diseases-10th Revision codes began, and up to and including the index date (except for cancer, counted only for a health care encounter in the 3 years preceding the index date). The outcomes HF hospitalization, stroke or TIA, and death were defined as between the day after the index date and end of follow-up (December 31, 2012), for which HF and stroke or TIA diagnoses was required as the primary diagnosis.

Statistics Sweden maintains socioeconomic data and provided additional baseline data. Establishment of the HF registry and this analysis with linking to the previous registries were approved by a multisite ethics committee. Individual patient consent was not required, but patients were informed of entry into national registries and allowed to opt out.

STATISTICAL ANALYSIS. To avoid bias due to data not missing at random, missing baseline covariate data were handled by multiple imputation by chained equations (25). The primary event (death) indicator, the Nelson-Aalen estimator of the cumulative baseline hazard, and 40 relevant clinical variables (**Table 1**) were included in the imputation model. We generated 10 multiply imputed datasets, and

estimates from these datasets were combined using Rubin's rules. All analyses except for descriptive statistics were performed using the imputed dataset. Patients with missing data on EF or AF were excluded, but clinical characteristics and outcome rates were assessed and compared to included patients to get a sense of the representativeness of our findings. Analyses were performed in the overall cohort and separately in HFpEF, HFmrEF, and HFrEF. Associations between baseline characteristics and baseline presence of AF were assessed with univariable and multivariable logistic regression.

The primary outcome was all-cause mortality and separate secondary outcomes were composite of all-cause death and HF hospitalization and composite of all-cause death and stroke or TIA. The Kaplan-Meier method was used to estimate survival and event-free survival comparing HFpEF, HFmrEF, and HFrEF, and AF and SR. Univariable and multivariable Cox regression was used to estimate the risk of outcomes, separately in HFpEF, HFmrEF, and HFrEF, according to presence of AF, with SR as reference category. Interaction analyses assessed whether any subgroups interacted with AF with regard to outcomes. All 40 variables listed in Table 1 were included as covariates in the final multivariable models. Because of the large sample size and large number of events, we did not perform statistical modeling to select covariates. All continuous variables were modeled using restricted cubic splines. The proportional hazards assumption was assessed graphically by using smoothed scaled Schoenfeld residual plots, and we found no important violations; p values were not corrected for multiple comparisons.

Data management and statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, Texas) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. Between May 11, 2000, and December 31, 2012, there were 80,772 registrations from 67 of Sweden's approximately 75 hospitals, and 94 of approximately 1,000 primary care outpatient clinics in Sweden, representing 51,051 unique patients. We excluded 1,597 patients due to missing information on AF and 8,008 due to missing information on EF, yielding 41,446 patients: 9,595 (23%) HFpEF (65% AF), 8,897 (22%) HFmrEF (60% AF), and 22,954 (55%) HFrEF (53% AF). AF was confirmed by electrocardiogram in 67.4% of all patients with AF. The excluded patients had higher age and more comorbidities compared with the study population, and survival was worse in excluded patients. The difference in survival was largely attenuated after accounting for baseline differences by multivariable regression analysis.

When comparing the 3 EF groups, some characteristics exhibited a continuous relationship with EF, whereas others were more similar in HFmrEF and HFrEF (Table 1). Patients with AF, compared with patients with SR, were older, with more hypertension, less ischemic heart disease, more TIA or stroke, longer duration of HF, more severe HF, lower creatinine clearance, and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP). These patterns were similar in HFpEF, HFmrEF, and HFrEF. The CHA_2DS_2VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65 to 74 years, and sex category) score was 4.9 ± 1.55, 4.6 ± 1.64, and 4.3 ± 1.72 in patients with AF and HFpEF, HFmrEF, and HFrEF, respectively.

AIM 1. PREVALENCE OF AF IN HFpEF VERSUS HFrEF. The prevalence of AF decreased with decreasing EF, HFpEF (65%), HFmrEF (60%), and HFrEF (53%), but in all 3 EF groups the prevalence of AF was higher in men, and increased with age. The prevalence ranged from a minimum of 21% in women <60 years of age with HFrEF and HFmrEF to a maximum of 77% in men >90 years of age with HFpEF (Figure 1).

AIM 2. ASSOCIATIONS BETWEEN BASELINE CHARACTERISTICS AND AF IN HFpEF, HFmrEF, AND HFrEF. The baseline characteristics between AF and SR differ in part because of differences in age, sex, and comorbidities (Table 1). Therefore, to assess unadjusted and adjusted (independent) associations with AF, we assessed odds ratios for the prevalence of AF (Table 2).

In both HFpEF and HFrEF, there were numerous risk markers and potential risk factors independently and significantly associated with AF, the strongest being age > median, with an odds ratio (OR) in HFpEF of 2.23 (95% confidence interval [CI]: 1.98 to 2.51), in HFmrEF of 2.28 (95% CI: 1.98 to 2.62), and in HFrEF of 2.34 (95% CI: 2.15 to 2.55). Others were inversely associated with AF (e.g., notably female sex and prior myocardial infarction) (Table 2).

There were also numerous potential consequences of AF, including previous stroke or TIA, heart rate > median, and use of digoxin, and oral anticoagulants, as shown in Table 2.

Finally, there were independent associations with AF where the cause-and-effect relationship was less clear, including New York Heart Association functional class III to IV versus I to II, and creatinine clearance less than median (Table 2).

TABLE 1 Baseline Characteristics According to Heart Rhythm in 41,446 Patients With HFpEF, HFmrEF, and HFrEF

	HFpEF EF ≥50% (n = 9,595) (23.1%)		HFmrEF EF 40%–49% (n = 8,897) (21.5%)		HFrEF EF ≤39% (n = 22,954) (55.4%)	
	Sinus Rhythm (n = 3,345) (35%)	Atrial Fibrillation (n = 6,250) (65%)	Sinus Rhythm (n = 3,585) (40%)	Atrial Fibrillation (n = 5,312) (60%)	Sinus Rhythm (n = 10,767) (47%)	Atrial Fibrillation (n = 12,187) (53%)
Characteristics						
Age, yrs	74.4 ± 12.5	79.1 ± 9.0	70.7 ± 13.1	76.8 ± 9.9	68.8 ± 13.4	74.3 ± 10.7
Sex						
Male	1,481 (44)	2,861 (46)	2,189 (61)	3,198 (60)	7,345 (68)	8,933 (73)
Female	1,864 (56)	3,389 (54)	1,396 (39)	2,114 (40)	3,422 (32)	3,254 (27)
Civil status						
Other	1,935 (58)	3,618 (58)	1,791 (50)	2,738 (52)	5,379 (50)	5,896 (48)
Married	1,410 (42)	2,632 (42)	1,794 (50)	2,574 (48)	5,384 (50)	6,288 (52)
Education						
Compulsory school	1,720 (52)	3,345 (54)	1,647 (46)	2,635 (50)	4,935 (46)	5,967 (50)
Secondary school	1,122 (34)	2,010 (33)	1,378 (39)	1,858 (35)	4,240 (40)	4,328 (36)
University	451 (14)	819 (13)	517 (15)	772 (15)	1,468 (14)	1,757 (15)
Disposable income						
Below median	1,882 (56)	3,562 (57)	1,801 (50)	2,628 (50)	5,107 (48)	5,703 (47)
Above median	1,457 (44)	2,682 (43)	1,779 (50)	2,681 (50)	5,628 (52)	6,452 (53)
Clinic						
Medicine/geriatrics	1,481 (50)	2,888 (50)	1,638 (49)	2,305 (46)	4,497 (43)	5,215 (44)
Cardiology	1,466 (50)	2,847 (50)	1,706 (51)	2,664 (54)	5,966 (57)	6,631 (56)
Location						
Inpatient	2,093 (63)	4,428 (71)	1,715 (48)	3,159 (59)	5,519 (51)	7,210 (59)
Outpatient	1,252 (37)	1,822 (29)	1,870 (52)	2,153 (41)	5,248 (49)	4,977 (41)
Follow-up referral specialty						
Cardiology or Internal medicine	1,477 (48)	2,493 (44)	2,182 (65)	2,778 (56)	7,379 (73)	7,437 (66)
Primary care	1,613 (52)	3,133 (56)	1,184 (35)	2,151 (44)	2,692 (27)	3,767 (34)
Follow-up referral to outpatient heart failure nurse clinic	840 (27)	1,386 (25)	1,322 (39)	1,701 (34)	5,034 (50)	4,892 (44)
Medical history						
Duration of heart failure						
<6 months	1,865 (56)	2,789 (45)	2,045 (57)	2,400 (45)	6,364 (60)	5,533 (46)
>6 months	1,447 (44)	3,414 (55)	1,525 (43)	2,882 (55)	4,329 (40)	6,576 (54)
NYHA functional class						
I–II	1,366 (65)	2,282 (58)	1,966 (75)	2,396 (63)	4,874 (59)	4,558 (50)
III–IV	728 (35)	1,647 (42)	660 (25)	1,402 (37)	3,398 (41)	4,623 (50)
Smoking						
Never	1,153 (46)	2,336 (53)	1,167 (40)	1,906 (48)	3,299 (37)	3,947 (42)
Former	1,021 (41)	1,732 (39)	1,299 (45)	1,707 (43)	3,978 (44)	4,199 (45)
Current	345 (14)	347 (8)	443 (15)	385 (10)	1,692 (19)	1,168 (13)
Diabetes mellitus	1,031 (31)	1,666 (27)	987 (28)	1,385 (26)	2,944 (27)	3,232 (27)
Peripheral artery disease	357 (11)	623 (10)	375 (10)	542 (10)	989 (9)	1,274 (10)
Hypertension	2,379 (71)	4,405 (70)	2,160 (60)	3,446 (65)	5,526 (51)	6,912 (57)
Prior myocardial infarction	1,180 (35)	1,622 (26)	1,903 (53)	1,750 (33)	5,014 (47)	4,811 (39)
Prior stroke/TIA	559 (17)	1,348 (22)	471 (13)	1,024 (19)	1,336 (12)	2,281 (19)
Ischemic heart disease	1,837 (55)	2,998 (48)	2,436 (68)	2,814 (53)	6,535 (61)	6,787 (56)
Alcohol dependency	130 (4)	182 (3)	117 (3)	195 (4)	480 (4)	500 (4)
Cancer (within 3 yrs)	471 (14)	999 (16)	445 (12)	762 (14)	1,206 (11)	1,638 (13)
Valve disease	812 (25)	1,861 (31)	551 (16)	1,302 (25)	1,826 (17)	2,782 (24)
Pulmonary disease	1,199 (36)	2,128 (34)	1,000 (28)	1,615 (30)	2,858 (27)	3,354 (28)
History of valve surgery	152 (5)	595 (10)	137 (4)	486 (9)	330 (3)	889 (7)
Prior revascularization	904 (27)	1,212 (19)	1,475 (41)	1,418 (27)	3,668 (34)	3,693 (30)

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TABLE 1 Continued

	HFpEF EF ≥50% (n = 9,595) (23.1%)		HFmrEF EF 40%–49% (n = 8,897) (21.5%)		HFrEF EF ≤39% (n = 22,954) (55.4%)	
	Sinus Rhythm (n = 3,345) (35%)	Atrial Fibrillation (n = 6,250) (65%)	Sinus Rhythm (n = 3,585) (40%)	Atrial Fibrillation (n = 5,312) (60%)	Sinus Rhythm (n = 10,767) (47%)	Atrial Fibrillation (n = 12,187) (53%)
Laboratory examinations						
Potassium, mmol/l	4.1 ± 0.4	4.1 ± 0.5	4.2 ± 0.4	4.1 ± 0.5	4.2 ± 0.4	4.2 ± 0.5
Hemoglobin, g/l	127.7 ± 17.5	127.7 ± 16.8	131.9 ± 17.1	131.4 ± 17.5	134.1 ± 17.0	134.5 ± 17.6
Creatinine clearance, ml/min	64.3 ± 34.2	57.2 ± 29.0	71.8 ± 35.2	61.4 ± 30.7	72.1 ± 35.1	63.5 ± 31.5
NT-proBNP, ng/l	1,148 (450–3,010)	2,547 (1,306–4,880)	1,360 (485–4,183)	2,710 (1,342–5,340)	2,599 (1,030–6,510)	3,627 (1,732–7,550)
Medications						
RAS antagonist	2,379 (72)	4,362 (71)	3,068 (86)	4,271 (81)	9,755 (91)	10,693 (88)
Beta-blocker	2,402 (72)	5,042 (81)	2,972 (83)	4,587 (87)	9,625 (90)	10,930 (90)
Diuretic	2,602 (78)	5,482 (88)	2,244 (63)	4,313 (82)	7,960 (74)	10,182 (84)
Statin	1,545 (46)	2,101 (34)	2,093 (59)	2,140 (40)	5,660 (53)	5,163 (43)
Aldosterone antagonist	687 (21)	1,792 (29)	677 (19)	1,401 (27)	3,327 (31)	4,030 (33)
Digoxin	75 (2)	1,683 (27)	73 (2)	1,367 (26)	460 (4)	3,617 (30)
Nitrate	648 (20)	1,086 (18)	578 (16)	877 (17)	1,647 (15)	1,877 (16)
Platelet inhibitor	2,065 (62)	2,333 (38)	2,588 (73)	2,019 (38)	7,218 (67)	4,596 (38)
Anticoagulant	261 (8)	3,438 (55)	272 (8)	3,138 (59)	1,535 (14)	7,489 (62)
Examinations						
Mean arterial pressure, mm Hg	94.1 ± 13.9	92.5 ± 13.5	92.5 ± 13.2	92.7 ± 13.2	90.4 ± 13.8	90.3 ± 13.2
Heart rate, beats/min	71.7 ± 13.8	75.7 ± 16.6	69.2 ± 13.2	75.5 ± 16.4	71.9 ± 14.1	77.0 ± 17.1
Body mass index, kg/m^2	27.8 ± 6.4	27.3 ± 5.9	27.3 ± 5.4	27.1 ± 5.5	26.5 ± 5.3	26.4 ± 5.2

Values are mean ± SD, n (%), or median (first quartile to third quartile)

EF = ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RAS = renin-angiotensin system; TIA = transient ischemic attack.

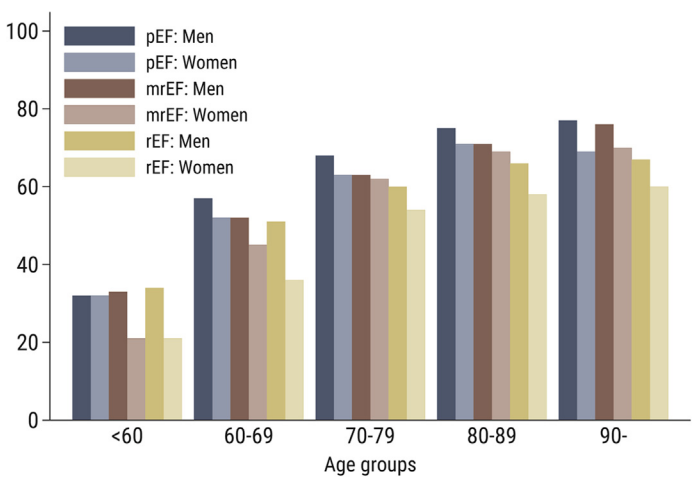
There were fewer associations that were present in HFpEF but not in HFrEF: diabetes mellitus appeared paradoxically protective in HFpEF against AF (OR: 0.88; 95% CI: 0.78 to 0.99) but not in HFrEF; NT-proBNP > median was associated with AF in HFpEF (OR: 1.25; 95% CI: 1.07 to 1.47) but not in HFrEF.

AIM 3. ASSOCIATION BETWEEN AF AND OUTCOMES IN HFpEF AND HFrEF. Over a median follow-up of 2.20 (interquartile range: 0.84 to 4.08) years overall, HFpEF had slightly higher all-cause Kaplan-Meier (unadjusted) mortality than HFmrEF or HFrEF. In contrast, AF had considerably higher mortality than SR in all 3 EF groups (Figure 2).

Table 3 shows event rates and 1-year survival, which was 83% in HFpEF SR, 78% in HFpEF AF, 88% in HFmrEF SR, 81% in HFmrEF AF, 86% in HFrEF SR, and 80% in HFrEF AF.

There was a statistically significant association between AF and the 3 different outcomes of all-cause mortality, HF hospitalization or death, and stroke or TIA or death, in HFpEF, HFmrEF, and HFrEF, respectively, in both crude and adjusted analyses. The multivariable adjusted association between AF and all-cause mortality according to EF is shown in Figure 2. The multivariable adjusted

FIGURE 1 Prevalence of Atrial Fibrillation



Prevalence of atrial fibrillation in heart failure with preserved ejection fraction (pEF), mid-range ejection fraction (mrEF), and reduced ejection fraction (rEF) according to age and sex. SR = sinus rhythm; AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction.

TABLE 2 Association Between Baseline Characteristics and Atrial Fibrillation in HFpEF, HFmrEF, and HFrEF

	HFpEF EF ≥50%		HFmrEF EF 40%–49%		HFrEF EF ≤39%	
	Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age > median (76 yrs)	2.23 (1.98–2.51)	<0.001	2.28 (1.98–2.62)	<0.001	2.34 (2.15–2.55)	<0.001
Female	0.70 (0.63–0.78)	<0.001	0.74 (0.66–0.84)	<0.001	0.69 (0.64–0.75)	<0.001
Disposable income above median			1.13 (1.00–1.27)	0.044		
Clinic is cardiology (ref: medicine/geriatrics)			1.16 (1.03–1.30)	0.012		
Outpatient (ref: inpatient)	0.73 (0.64–0.82)	<0.001	0.71 (0.63–0.80)	<0.001	0.78 (0.72–0.83)	<0.001
Follow-up referral specialty is primary care (ref: cardiology/internal medicine)					1.17 (1.07–1.28)	0.001
Follow-up referral to outpatient heart failure nurse clinic					0.92 (0.86–1.00)	0.037
Duration of heart failure >6 months	1.50 (1.34–1.66)	<0.001	1.38 (1.23–1.55)	<0.001	1.54 (1.44–1.65)	<0.001
Diabetes mellitus	0.88 (0.78–0.99)	0.039				
Hypertension			1.14 (1.01–1.28)	0.031	1.28 (1.19–1.37)	<0.001
Prior myocardial infarction	0.79 (0.70–0.90)	<0.001	0.64 (0.56–0.72)	<0.001	0.86 (0.78–0.95)	0.004
Prior stroke/TIA	1.30 (1.14–1.49)	<0.001	1.29 (1.11–1.50)	0.001	1.24 (1.13–1.36)	<0.001
Ischemic heart disease					0.88 (0.79–0.98)	0.017
Alcohol dependency			1.64 (1.22–2.20)	0.001	1.37 (1.17–1.61)	<0.001
Cancer (within 3 yrs)					1.15 (1.04–1.27)	0.006
History of valve surgery	1.36 (1.09–1.71)	0.008			1.33 (1.14–1.56)	<0.001
Prior revascularization					1.28 (1.17–1.40)	<0.001
Creatinine clearance < median (59 ml/min)			1.32 (1.14–1.52)	<0.001	1.28 (1.17–1.40)	<0.001
NT-proBNP > median (2,622 ng/l)	1.25 (1.07–1.47)	0.007				
RAS antagonist					0.81 (0.73–0.90)	<0.001
Beta-blocker	1.55 (1.37–1.76)	<0.001	1.45 (1.24–1.69)	<0.001		
Diuretic	1.35 (1.16–1.57)	<0.001	1.46 (1.27–1.67)	<0.001	1.23 (1.13–1.34)	<0.001
Statin	0.61 (0.54–0.68)	<0.001	0.61 (0.54–0.69)	<0.001	0.75 (0.70–0.81)	<0.001
Aldosterone antagonist	1.21 (1.07–1.37)	0.003	1.16 (1.01–1.33)	0.033	0.87 (0.81–0.93)	<0.001
Digoxin	10.7 (8.35–13.7)	<0.001	8.88 (6.85–11.5)	<0.001	6.42 (5.74–7.19)	<0.001
Nitrate					0.89 (0.81–0.98)	0.019
Platelet inhibitor	1.30 (1.15–1.48)	<0.001				
Anticoagulant	16.7 (14.1–19.6)	<0.001	16.9 (14.5–19.5)	<0.001	10.3 (9.51–11.1)	<0.001
Mean arterial pressure < median (90 mm Hg)	1.12 (1.01–1.25)	0.033			0.88 (0.82–0.94)	<0.001
Heart rate > median (72 beats/min)	1.25 (1.12–1.40)	<0.001	1.43 (1.27–1.61)	<0.001	1.41 (1.32–1.51)	<0.001
Body mass index < median (26.1 kg/m^2)					0.89 (0.81–0.98)	0.018

CI = confidence interval; OR = odds ratio; ref = reference; other abbreviations as in Table 1.

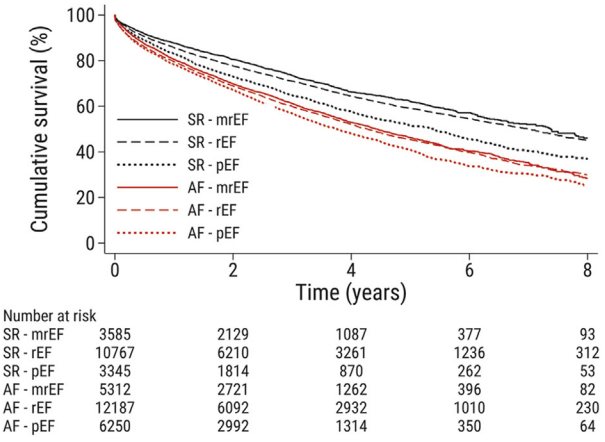
hazard ratio (HR) for the association between AF and HF hospitalization or death was 1.17 (95% CI: 1.09 to 1.26), 1.29 (95% CI: 1.20 to 1.40), and 1.15 (95% CI: 1.10 to 1.20) in patients with HFpEF, HFmrEF, and HFrEF, respectively. The multivariable adjusted HR for the association between AF and stroke or TIA or death was 1.15 (95% CI: 1.07 to 1.25), 1.23 (95% CI: 1.13 to 1.34), and 1.19 (95% CI: 1.14 to 1.26) in patients with HFpEF, HFmrEF, and HFrEF, respectively.

The reduction in risk after adjustment was primarily a result of adjustment for age, after which the HRs were similar to those after additional complete adjustment for the remainder of the 40 variables. The independent risk for the composite of death or stroke or TIA was not higher than the risk of death or the composite of death or HF hospitalization.

DISCUSSION

To our knowledge, this is the largest, most comprehensive, most covariate-adjusted, and most generalizable comparative assessment of AF versus SR in HFpEF versus HFrEF, and also the first specifically comparing them with the recently designated HFmrEF category. Our main findings were that: 1) AF was considerably more common in this population-wide setting than in clinical trials and, as expected, progressively more common with increasing EF; 2) there were numerous independent associations with AF, but despite clear differences among the HFpEF, HFmrEF, and HFrEF, the associations with AF were remarkably similar regardless of EF; and 3) death, HF hospitalization, and stroke or TIA rates were slightly greater in HFpEF versus HFmrEF and HFrEF, but considerably worse in AF versus SR, in all 3 EF groups.

FIGURE 2 Survival According to Rhythm and Ejection Fraction



Association between atrial fibrillation and all-cause mortality according to ejection fraction

	Multivariable adjusted hazard ratio (95% CI)
HFpEF *(n=9595)*	1.11 (1.02-1.21)
HFmrEF *(n=8897)*	1.22 (1.12-1.33)
HFrEF *(n=22954)*	1.17 (1.11-1.23)

Reference category: Sinus rhythm.

The graph displays the Kaplan-Meier estimated survival according to heart rhythm and ejection fraction, and the table shows the association between atrial fibrillation (AF) and all-cause mortality stratified by ejection fraction and expressed as multivariable adjusted hazard ratio and 95% confidence interval (CI). HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; mrEF = mid-range ejection fraction; pEF = preserved ejection fraction; rEF = reduced ejection fraction; SR = sinus rhythm.

AIM 1. PREVALENCE OF AF IN HFpEF VERSUS HFmrEF VERSUS HFrEF. The prevalence of AF in HFpEF versus HFrEF (but not HFmrEF) has been reported but is difficult to compare directly because of different settings (e.g., trials, cohorts, claims data) (3-10,26,27). In 3 within-cohort comparisons, the prevalence of AF was 19% in HFpEF and 17% in HFrEF in the CHARM (Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity) study (14); slightly over 20% in both HFpEF and HFrEF in the Framingham Heart Study (13), and 48% in HFpEF and 44% in HFrEF in a Medicare claims analysis (12). The prevalence of 65% in HFpEF, 60% in HFmrEF, and 53% in HFrEF in our study was much higher and is more reflective of a contemporary generalizable HF population than trials. Furthermore, the prevalence trends ranging from 21% to 76% according to age, sex, and EF in our study are novel data and highlight the very high burden of AF, particularly in HFpEF and in older patients, those with the highest risk of stroke but also the most frail and least likely to receive anticoagulation (28).

AIM 2. INDEPENDENT ASSOCIATIONS WITH AF IN HFpEF VERSUS HFmrEF VERSUS HFrEF. Risk factors for and consequences of AF have been well studied in general, but their independent roles in according to EF have not been compared (3-10,12-14,26,27).

Despite well-characterized differences in HFpEF versus HFrEF, in this extensively adjusted analysis, the independent associations with AF were remarkably similar, both in kind and in magnitude, in all 3 EF groups. This suggests that AF is similarly and intimately tied to the HF syndrome and not an independent age- and comorbidity-related bystander. Associations included higher age and greater duration of HF, as expected. Alcohol dependency is rarely available in clinical studies but here was quite common and strongly associated with AF. We tend to associate AF with female sex, particularly in HFpEF (9), but after adjustment, female sex was strongly associated with a lower risk of AF, suggesting that our clinical observations may be a biased reflection of the higher age among women with HF-driving AF. Paradoxically, prior myocardial infarction was associated with lower prevalence of AF. Although speculative, perhaps in the presence of a high-risk etiology, HF develops regardless of AF, whereas in the absence of a distinct etiology AF may contribute to the development (and symptoms and signs) of HF.

Two exceptions were the association between NT-proBNP and AF and the inverse association between diabetes and AF, which were observed in HFpEF but not in HFmrEF or HFrEF. This may reflect a greater relative contribution of AF to filling pressures and, by extension, signs and symptoms in HFpEF, and supports the practice in contemporary HFpEF or HFmrEF trials of requiring greater NT-proBNP levels for eligibility in AF and stratifying by AF to ensure a proper case mix, as well as minimizing the role of confounding due to signs, symptoms, and outcomes being caused by AF rather than

TABLE 3 Event Rates for Clinical Outcomes in SR and AF According to EF: HFpEF, HFmrEF, and HFrEF

	n	Events/PY	Incidence Rate/1,000 PY (95% CI)	1-Yr Freedom From Outcome (95% CI) (%)
All-cause mortality				
HFpEF				
SR	3,345	1,287/8,986	143 (136–151)	83 (82–84)
AF	6,250	2,882/14,859	194 (187–201)	78 (77–79)
HFmrEF				
SR	3,585	1,094/10,693	102 (96.4–109)	88 (87–89)
AF	5,312	2,273/13,612	167 (160–174)	81 (79–82)
HFrEF				
SR	10,767	3,571/31,722	112 (109–116)	86 (85–86)
AF	12,187	5,355/30,966	173 (168–178)	80 (79–80)
HF or death				
HFpEF				
SR	3,345	1,653/7,561	219 (208–229)	72 (70–73)
AF	6,250	3,722/11,534	323 (313–333)	63 (62–64)
HFmrEF				
SR	3,585	1,513/9,162	165 (157–174)	78 (76–79)
AF	5,312	3,038/10,720	283 (274–294)	66 (64–67)
HFrEF				
SR	10,767	5,629/23,682	238 (232–244)	67 (66–68)
AF	12,187	7,377/22,207	332 (323–340)	60 (59–61)
Stroke/TIA or death				
HFpEF				
SR	3,345	1,378/8,657	159 (151–168)	81 (80–83)
AF	6,250	3,093/14,187	218 (211–226)	76 (75–77)
HFmrEF				
SR	3,585	1,213/10,320	118 (111–124)	86 (85–87)
AF	5,312	2,448/12,978	189 (181–196)	78 (77–79)
HFrEF				
SR	10,767	3,866/30,708	126 (122–130)	84 (83–85)
AF	12,187	5,723/29,713	193 (188–198)	77 (77–78)

AF = atrial fibrillation; PY = person-years; SR = sinus rhythm; other abbreviations as in Tables 1 and 2.

HF. The paradoxical negative association between diabetes and AF could potentially be explained by its role in driving HFpEF (regardless of rhythm) (29), whereas in the absence of diabetes other risk factors for HF would be more prominent, such as AF.

AIM 3. INDEPENDENT ASSOCIATION BETWEEN AF AND OUTCOMES IN HFpEF AND HFrEF. Patients with HFpEF versus HFmrEF and HFrEF had slightly higher risk of death, the composite of death or HF hospitalization, and the composite of death or stroke or TIA, which is consistent with an unselective cohort (30), but not trial settings where prognosis is much better in HFpEF than HFrEF (31).

AF was associated with similarly increased risk of death in incident HFpEF and HFrEF in the Framingham Heart Study (13), whereas in the CHARM study, AF was associated with greater risk in HFpEF (14). However, whether AF is truly independently associated with worse outcomes remains controversial in HFrEF and has been poorly studied in HFpEF (9,15–21,32). We extend these findings in a large representative cohort and in HFmrEF and for additional types of outcomes. AF was distinctly and similarly associated with outcomes, with HRs narrowly ranging from 1.11 to 1.29 for the 3 predefined outcomes in the 3 EF groups. This differs from, for example, chronic kidney disease, which is common in HF regardless of EF, but a stronger risk marker in HFmrEF and HFrEF than in HFpEF (33). Although some patients with HFpEF and SR have a distinctly increased risk of stroke (34), the additional contribution of AF was similar in all EF groups. Furthermore, the risk of stroke was not increased by AF more than was the risk of death or HF hospitalization. This again suggests that HF regardless of EF might be similar with regard to interaction with AF and risk. We cannot determine whether AF was a risk marker or risk factor for outcomes. The high CHA_2DS_2VASc score and the suboptimal use of oral anticoagulation suggests that some mortality risk might have been AF as a risk factor for stroke (and, conversely, anticoagulation a risk factor for severe bleeding). However, AF was also associated with increased risk for HF hospitalization and may be both a marker of more severe neurohormonal activation and remodeling and a risk factor for HF progression and, as recently described, lack of response to beta-blocker therapy (35).

STUDY LIMITATIONS. In this population-wide registry study, the definition of AF was based on history or electrocardiogram, but not was adjudicated. We did not distinguish paroxysmal from permanent AF. We lacked information regarding class I and class III antiarrhythmic drug use. The inclusion criterion in SwedeHF registry was clinician-judged HF. Although this provides for pragmatic inclusion and generalizable findings, we cannot rule out inclusion of some patients with preserved EF that did not have HF, especially if AF might have been the driver of symptoms. This misclassification of exposure could explain the higher prevalence of AF in HFpEF. As in any study of clinical characteristics and outcomes (even from trial databases), we cannot establish causality between risk factors for and consequences of AF, but our adjustment for an extensive set of clinically relevant variables provides reassurance that the associations with AF are independent of most potential confounders.

CONCLUSIONS

AF was more common in HFpEF versus in HFmrEF versus in HFrEF, and much more common in all EF groups in this generalizable population-wide registry than in previous selective trial and cohort analyses.

The clinical associations with AF were similar regardless of EF. AF was similarly associated with increased risk of all cause death, HF hospitalization, and stroke or TIA regardless of EF. The public health burden of AF will increase further with an aging population and a greater proportion of patients with higher EF. Clinicians should be vigilant in detecting and treating AF in HF regardless of EF (2). Finally, these comprehensive data on AF in different EF groups may serve as reference material when considering HF and AF trial design and recruitment.

ACKNOWLEDGMENTS The authors thank local investigators contributing data to SwedeHF and staff at Uppsala Clinical Research Center for database management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: In HF, AF was more common and may be a stronger contributor to HF in HFpEF versus HFmrEF versus HFrEF. However, the associations between clinical characteristics and AF were similar regardless of EF, suggesting that drivers and consequences of AF may be similar regardless of EF.

COMPETENCY IN MEDICAL KNOWLEDGE 2: AF was much more common in HF, regardless of EF, in this generalizable population-wide registry than in previous selective trial and cohort analyses. AF was associated with not only increased risk of stroke, but also all-cause mortality and HF hospitalization, regardless of EF. Clinicians should be vigilant in detecting and treating AF in HF.

TRANSLATIONAL OUTLOOK: The role of AF as a cause versus as a consequence of HF, and how this may vary depending on EF and HF phenotype, requires further study.

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KEY WORDS atrial fibrillation, heart failure, phenotype, preserved ejection fraction, outcomes, registry

APPENDIX For a supplemental table, please see the online version of this paper.