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RESEARCH ARTICLE

Characterizing atrial fibrillation in patients with and without heart failure across the ejection fraction spectrum: Incidence, prevalence, and treatment strategies

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Aims Heart failure (HF) and atrial fibrillation (AF) often coexist. We explored AF incidence, prevalence, and treatment strategies in patients with versus without HF across the ejection fraction (EF) spectrum.

Methods and results We analysed patients with HF from the Swedish HF Registry (1 December 2005–31 December 2021), matched 1:1 by sex, age, and county of residence to patients without HF from Statistics Sweden. Two study cohorts were derived (i) to assess AF prevalence and treatments, and (ii) to evaluate AF incidence and related predictors. Overall, 195 106 patients were considered, 50% of them with HF (of whom 54% with HF with reduced [HFrEF], 23% mildly reduced [HFmrEF], and 23% with preserved EF [HFpEF]). From 2006 to 2021, AF prevalence increased in both patients with (57% to 58%) and without HF (8% to 11%). HF patients, particularly if with HFrEF, were more likely receiving AF treatments than those without HF. Over time, antiarrhythmic use decreased, while rate control drugs and oral anticoagulant use, and AF-related procedures increased, regardless of HF and EF. During a median follow-up of 3.7 years, in 86 210 patients without AF, incident AF risk was two-fold higher in HF versus non-HF (hazard ratio [HR] 2.76, 95% confidence interval [CI] 2.45–3.12), highest in HFpEF (HR 3.12, 95% CI 2.65–3.67) versus HFrEF (HR 2.68, 95% CI 2.34–3.06) and HFmrEF (HR 2.53, 95% CI 2.17–2.94).

Conclusions Atrial fibrillation prevalence, anticoagulant use, and AF-related procedures increased over time regardless of HF, with HF patients more likely receiving AF treatments. In HF, despite higher AF prevalence and incidence in HFpEF, AF treatment use remained modest, calling for further implementation.

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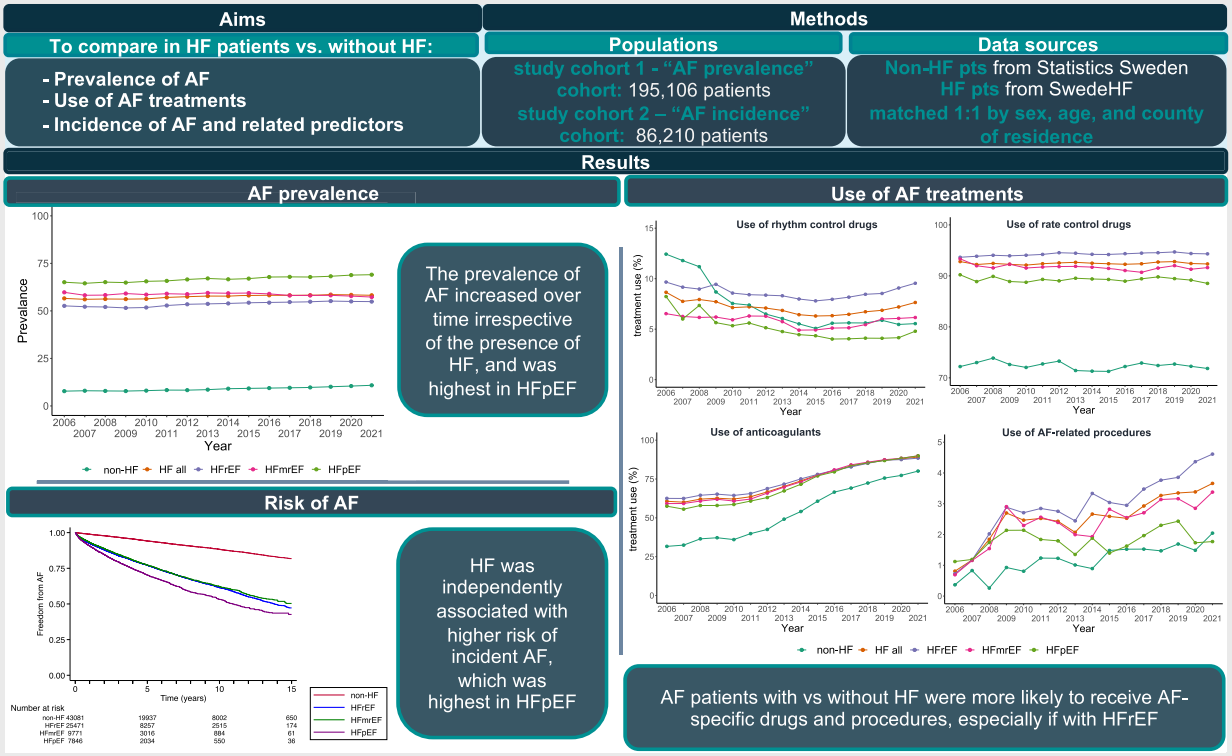
Graphical Abstract



Atrial fibrillation (AF) in patients with versus without heart failure (HF) across the ejection fraction spectrum. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SwedeHF, Swedish Heart Failure Registry.

Keywords Atrial fibrillation • Heart failure • Antiarrhythmics • Registry • SwedeHF

Introduction

Despite heart failure (HF) and atrial fibrillation (AF) having reached epidemic sizes over the last years and frequently coexisting, the understanding of their shared epidemiology and interaction, involving structural remodelling, neurohormonal activation, inflammation and haemodynamic changes, remains poor.[1]

The estimated prevalence of AF in patients with HF has been shown to vary depending on the study setting and AF definition, and is generally reported to be higher in HF with preserved (HFpEF) and mildly reduced (HFmrEF) ejection fraction (EF), ranging 32%–65% and 29–60%, respectively, as compared with HF with reduced EF (HFrEF) where it is shown ranging 27–53%.[1–3] Estimates on the incidence of AF in HF are even more imprecise, with studies inconsistently suggesting a higher risk of new onset of AF in either HFpEF or HFrEF, or no difference in risk across the EF subtypes[1,4] These data highlight that we are still far from a clear understanding of the epidemiology of the interaction between AF and HF.

Comorbidity burden often challenges the achievement of optimal medical treatment for several conditions including HF, due to perceived or actual intolerability and contraindications, and suboptimal patients' adherence.[5] Although currently available evidence indicates that the presence of AF might affect the likelihood of receiving guideline-directed medicine for HF,[6] there is limited understanding of whether the management of AF differs in patients with versus without HF, and in HF with different EF phenotypes.[2] AF treatment approaches likely vary within HF due to differences in available evidence, comorbidity prevalence, and underlying pathophysiological mechanisms across the EF spectrum. However, data are limited on these regards.[2]

Therefore, in the current analysis of a large nationwide real-world population, we aimed to compare in patients with versus without HF across the EF spectrum (i) prevalence of AF, (ii) implementation of AF treatment including electrophysiological strategies, and (iii) incidence of AF and related independent predictors in those without AF.

Methods

The study population consisted of the HF population from the Swedish Heart Failure Registry (SwedeHF) matched 1:1 by sex, year of birth and, for individuals <90 years old, county of residence with a non-HF cohort chosen by Statistics Sweden, drawn at random from the Swedish population.

Data sources

The study population was retrieved from SwedeHF and linked to the National Patient Register, the Cause of Death Register, the Swedish Prescribed Drug Register, and Statistics Sweden. A complete description of these data sources is available in online supplementary *Methods* and *Table S1*.

Derivation of the study cohorts

The full selection process of the study population is reported in online supplementary *Figure S1*. Two study cohorts were derived: study cohort 1 where we assessed prevalence of AF and AF treatment patterns over time; and study cohort 2 where we assessed incidence and predictors of new-onset AF.

In both cohorts, patients registered between 1 December 2005 (availability of data on pharmacological treatments from the Swedish Prescribed Drug Register) and 31 December 2021 were analysed. Patients with missing data for EF (whether with HF), education, family type and income were excluded. In the HF population, if there was more than one registration for the same patient, only the first was considered.

For deriving study cohort 1, the entire SwedeHF population was selected based on the criteria mentioned above. To derive study cohort 2, patients with AF at the index date or with a history of AF were first excluded, including both HF and non-HF patients.

If either an HF or non-HF patient was removed from study cohort 1 or 2, the corresponding matched patient was also removed. Additionally, unmatched patients (HF without a non-HF, or non-HF without HF) were excluded from both cohorts.

Definitions

Atrial fibrillation was defined using International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, Tenth Revision (ICD-10) codes for 'atrial fibrillation and flutter', 'paroxysmal atrial fibrillation', 'persistent atrial fibrillation' and 'permanent atrial fibrillation' obtained from the National Patient Register. HF was identified using ICD-9 and ICD-10 codes in the National Patient Register or SwedeHF registration, with HF subtypes categorized by EF.[7,8] AF-specific drugs included rhythm and rate control medications and anticoagulants. AF-related procedures were defined as electrical cardioversion, ablations, left atrial appendage closure, maze surgery, and His-bundle ablation. Detailed definitions are provided in online supplementary *Methods* and *Tables S1* and *S2*.

Statistical analysis

The annual prevalence of AF, use of AF drugs and AF-related procedures were separately assessed in patients with AF, with and without HF, also according to EF, and were calculated as reported in online supplementary *Methods*. Patient characteristics were reported as absolute frequencies (%) for categorical variables and compared across groups by chi-square test. The median (Q1–Q3) was reported for continuous variables, and differences across groups were assessed by the Kruskal–Wallis test. In the cohort of patients without a history of AF (defined as above), the risk of new-onset AF was assessed by the Kaplan–Meier method and compared in HFpEF, HFmrEF, and HFrEF versus no HF by univariable and multivariable Cox regression models stratified for matched pairs, adjusting for variables listed in *Table 2*. The same models were used to identify other patient characteristics independently associated with the risk of AF onset. Censoring was performed at 15 years, death, emigration from Sweden, and, for the HF-free controls, HF diagnosis. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Missing data in the SwedeHF population are listed in *Tables 1* and *2*, while there were no missing data for the non-HF-matched population. No variable including missing values was included in multivariable models.

A p-value of <0.05 (two-sided) was considered statistically significant for all analyses. Data management and statistical analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA) and R v.4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The establishment of the HF registry, the linkage across registries and the current analysis were approved by the Swedish Ethical Review Authority and conform with the Helsinki Declaration.

Results

Baseline characteristics of study cohort 1 and analysis of atrial fibrillation prevalence

The study cohort consisted of 195 106 patients (97 553 with and 97 553 without HF), of which 63% were men, and the median age was 75 years (Q1–Q3: 66–82). Patients with versus without HF had higher comorbidity burden and use of medications. HF versus non-HF patients were more likely living alone, having lower levels of education and with lower disposable income (*Table 1*).

Among patients with HF, 54% had HFrEF, 23% HFmrEF, and 23% HFpEF. Patients with HFpEF were more likely female (53%) and significantly older compared with HFmrEF and HFrEF. The burden of comorbidities was higher in patients with HFpEF versus HFmrEF and HFrEF, except for ischaemic heart disease which was more prevalent in patients with HFmrEF (54%) and HFrEF (53%) than in those with HFpEF (45%). Loop diuretics were more frequently used in HFpEF, whereas beta-blockers, sodium–glucose cotransporter 2 inhibitors (SGLT2i), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors (ARNi) and mineralocorticoid receptor antagonist (MRA) were more frequently used in HFrEF than HFmrEF and HFpEF. Across the EF spectrum, patients with HFpEF were more likely living alone, having lower levels of education and with less disposable income (*Table 1*).

Prevalence of AF was overall 56% in HF patients, and more specifically 66% in HFpEF, 58% in HFmrEF and 52% in HFrEF, versus 8.5% in those without HF (*Table 1*).

Table 1 Baseline characteristics of study cohort 1 (prevalence of atrial fibrillation and use of treatment strategies)

Characteristics	Non-HF (*n* = 97 553)	HF (*n* = 97 553)	*p*-value	HFrEF (*n* = 52 309)	HFmrEF (*n* = 22 716)	HFpEF (*n* = 22 528)	*p*-value within EF	Missing data (%)[a]
Index year, *n* (%)								
2005–2010	30 312 (31)	30 312 (31)	1.00	16 970 (32)	6516 (29)	6826 (30)	<0.001	
2011–2015	26 889 (28)	26 889 (28)		14 383 (27)	6069 (27)	6437 (29)		
2016–2021	40 352 (41)	40 352 (41)		20 956 (40)	10 131 (45)	9265 (41)		
Demographics								
Male sex, *n* (%)	61 737 (63)	61 737 (63)	1.00	37 099 (71)	14 105 (62)	10 533 (47)	<0.001	
Age, years, median [IQR]	75 [66–82]	75.0 [66–82]	1.00	73.0 [64–80]	76.0 [67–82]	79.0 [72–85]	<0.001	
Clinical parameters								
Location, inpatient, *n* (%)		40 746 (42)		20 820 (40)	8365 (37)	11 561 (51)	<0.001	
Follow-up referral, *n* (%)								
Primary care/other		57 295 (62)		34 236 (69)	13 280 (62)	9779 (47)	<0.001	5.7
Hospital		64 335 (69)		39 510 (78)	14 183 (65)	10 642 (50)	<0.001	4.3
LVEF, *n* (%)								
HFrEF		52 309 (54)						
HFmrEF		22 716 (23)						
HFpEF		22 528 (23)						
Duration of HF >6 months, *n* (%)		44 621 (47)		22 251 (43)	10 689 (48)	11 681 (54)	<0.001	2.6
NYHA class, *n* (%)								
I		8290 (12)		3795 (10)	2559 (16)	1936 (14)	<0.001	29
II		34 230 (49)		19 101 (48)	8751 (54)	6378 (47)		
III		25 101 (36)		15 515 (39)	4657 (29)	4929 (36)		
IV		1870 (2.7)		1214 (3.1)	268 (1.7)	388 (2.8)		
BMI ≥30 kg/m^2, *n* (%)		18 045 (27)		8924 (24)	4408 (29)	4713 (32)	<0.001	32
Systolic blood pressure, mmHg, median [IQR]		125.0 [112–140]		120 [110–139]	130 [116–140]	130 [120–145]	<0.001	2.0
Diastolic blood pressure, mmHg, median [IQR]		73 [65–80]		72 [65–80]	75 [66–80]	72 [65–80]	<0.001	1.9
Mean arterial pressure >90 mmHg, *n* (%)		48 664 (51)		24 248 (47)	12 183 (55)	12 233 (56)	<0.001	1.9
Heart rate >70 bpm, *n* (%)		48 731 (52)		27 012 (54)	10 693 (49)	11 026 (52)	<0.001	4.6
eGFR (ml/min/1.73 m^2), *n* (%)								
<15		843 (0.9)		428 (0.8)	207 (0.9)	208 (0.9)		
15–30		4676 (4.9)		2251 (4.4)	1000 (4.5)	1425 (6.5)		
30–60		31 717 (33)		15 792 (31)	7223 (32)	8702 (40)		
≥60		58 730 (61)		33 177 (64)	13 887 (62)	11 666 (53)		
Potassium (mmol/L), *n* (%)[b]								
Normakalaemia		72 860 (93)		39 117 (93)	17 391 (93)	16 352 (91)	<0.001	20
Hypokalaemia		3363 (4.3)		1524 (3.6)	780 (4.2)	1059 (5.9)		
Hyperkalaemia		2220 (2.8)		1277 (3.0)	473 (2.5)	470 (2.6)		
Haemoglobin, g/L, median [IQR]		133 [120–145]		136 [123–147]	133 [120–144]	128 [116–140]	<0.001	4.8
NT-proBNP (pg/ml), above median within EF, *n* (%)		27 692 (50)		14 699 (50)	6496 (50)	6497 (50)	1.00	43
Medications and devices, *n* (%)								
ACEi/ARB/ARNi	28 020 (30)	82 029 (88)	<0.001	46 083 (93)	19 207 (88)	16 739 (77)	<0.001	4.7
MRA	4414 (4.7)	37 906 (41)	<0.001	22 454 (45)	7246 (33)	8206 (38)	<0.001	4.7
Digoxin	955 (1.0)	13 804 (15)	<0.001	7419 (15)	2908 (13)	3477 (16)	<0.001	4.7
Loop diuretic	6655 (7.2)	65 952 (71)	<0.001	35 625 (72)	13 713 (63)	16 614 (77)	<0.001	4.7
Nitrate	4280 (4.6)	25 452 (27)	<0.001	13 836 (28)	6263 (29)	5353 (25)	<0.001	4.7
Platelet inhibitor	22 590 (24)	43 187 (46)	<0.001	24 338 (49)	10 292 (47)	8557 (39)	<0.001	4.7
Oral anticoagulant	2688 (2.9)	16 950 (18)	<0.001	8569 (17)	4141 (19)	4240 (19)	<0.001	4.7
Statin	22 748 (24)	47 855 (51)	<0.001	26 241 (53)	11 707 (54)	9907 (46)	<0.001	4.7
Beta-blocker	23 433 (25)	82 576 (89)	<0.001	45 533 (92)	19 089 (88)	17 954 (83)	<0.001	4.7
ICD	30 (0.0)	4129 (4.2)	<0.001	3309 (6.3)	553 (2.4)	267 (1.2)	<0.001	
CRT	35 (0)	6283 (6.2)	<0.001	5071 (10)	839 (3.7)	373 (1.0)	<0.001	
SGLT2i	379 (0.4)	2016 (2.2)	<0.001	1415 (2.9)	371 (1.7)	230 (1.1)	<0.001	4.7
History and comorbidities, *n* (%)								
Smoking	850 (0.9)	4403 (4.5)	<0.001	2760 (5.3)	970 (4.3)	673 (3.0)	<0.001	
Alcohol	1425 (1.5)	3164 (3.2)	<0.001	1943 (3.7)	622 (2.7)	599 (2.7)	<0.001	
Diabetes	8097 (8.3)	25 110 (26)	<0.001	13 234 (25)	5611 (25)	6265 (28)	<0.001	
Hypertension	20 576 (21)	63 471 (65)	<0.001	30 830 (59)	15 384 (68)	17 257 (77)	<0.001	
Ischaemic heart disease	12 923 (13)	50 363 (52)	<0.001	27 826 (53)	12 345 (54)	10 192 (45)	<0.001	
Peripheral artery disease	2524 (2.6)	8453 (8.7)	<0.001	4365 (8.3)	1988 (8.8)	2100 (9.3)	<0.001	
Stroke	8554 (8.8)	13 438 (14)	<0.001	6787 (13)	3116 (14)	3535 (16)	<0.001	
Atrial fibrillation	8295 (8.5)	55 032 (56)	<0.001	27 082 (52)	13 087 (58)	14 863 (66)	<0.001	

Table 1 (Continued)

Characteristics	Non-HF (*n* = 97 553)	HF (*n* = 97 553)	*p*-value	HFrEF (*n* = 52 309)	HFmrEF (*n* = 22 716)	HFpEF (*n* = 22 528)	*p*-value within EF	Missing data (%)[a]
Atrial fibrillation type			<0.001				<0.001	
Paroxysmal	1210 (14)	6041 (11)		2822 (10)	1479 (11)	1740 (12)		
Persistent	250 (3.0)	2592 (4.7)		1383 (5.1)	636 (4.9)	573 (3.9)		
Permanent	677 (8.2)	8752 (16)		3592 (13)	2309 (18)	2851 (19)		
Unknown/unclassified	6158 (74)	37 647 (68)		19 285 (71)	8663 (66)	9699 (65)		
Anemia	3521 (3.6)	12 389 (13)	<0.001	5454 (10)	2966 (13)	3969 (18)	<0.001	
Obesity	719 (0.7)	5380 (5.5)	<0.001	2465 (4.7)	1279 (5.6)	1636 (7.3)	<0.001	
Valvular disease	1921 (2.0)	19 391 (20)	<0.001	8565 (16)	4716 (21)	6110 (27)	<0.001	
Liver disease, *n* (%)	667 (0.7)	2033 (2.1)	<0.001	1109 (2.1)	409 (1.8)	515 (2.3)	0.001	
Malignant cancer within 3 years	10 801 (11)	12 076 (12)	<0.001	5930 (11)	2956 (13)	3190 (14)	<0.001	
Renal failure	1740 (1.8)	11 975 (12)	<0.001	6006 (11)	2676 (12)	3293 (15)	<0.001	
Obstructive sleep apnoea	1326 (1.4)	3933 (4.0)	<0.001	1860 (3.6)	965 (4.2)	1108 (4.9)	<0.001	
Depression	2270 (2.3)	3529 (3.6)	<0.001	1869 (3.6)	770 (3.4)	890 (4.0)	0.004	
Charlson comorbidity index								
0–1	69 295 (71)	29 204 (30)	<0.001	16 162 (31)	6777 (30)	6265 (28)	<0.001	
2–3	20 371 (21)	37 401 (38)		20 427 (39)	8691 (38)	8283 (37)		
4–7	6506 (6.7)	25 340 (26)		13 058 (25)	5885 (26)	6397 (28)		
≥8	1381 (1.4)	5608 (5.7)		2662 (5.1)	1363 (6.0)	1583 (7.0)		
Socio-economic characteristics, *n* (%)								
Family type, living alone	42 016 (43)	46 323 (47)	<0.001	23 850 (46)	10 391 (46)	12 082 (54)	<0.001	
Children	83 333 (85)	82 177 (84)	<0.001	43 356 (83)	19 422 (85)	19 399 (86)	<0.001	
Education								
Compulsory school	37 817 (39)	41 849 (43)	<0.001	21 700 (41)	9477 (42)	10 672 (47)	<0.001	
Secondary school	37 442 (38)	38 794 (40)		21 509 (41)	9062 (40)	8223 (36)		
University	22 294 (23)	16 910 (17)		9100 (17)	4177 (18)	3633 (16)		
Disposable income (100 SEK), above median within year	51 915 (53)	45 718 (47)	<0.001	26 144 (50)	10 851 (48)	8723 (39)	<0.001	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SEK, Swedish krona; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SwedeHF Swedish Heart Failure Registry.

[a]Missing (%) is for SwedeHF only. There is no missing for HF-free matched controls.

[b]Hypokalaemia, normokalaemia, and hyperkalaemia were defined as serum potassium levels of <3.5, 3.5–5.0, and ≥5.0 mEq/L, respectively.

The annual prevalence of AF slightly increased over time in both patients with (from 57% in 2006 to 58% in 2021) and without HF (from 7.8% in 2006 to 11% in 2021); in patients with HF, a slight increase was observed in HFrEF (from 53% in 2006 to 55% in 2021) and in HFpEF (from 65% in 2006 to 69% in 2021) but not in HFmrEF where it slightly decreased (from 60% in 2006 to 57% in 2021) (*Figure 1*).

Treatment of atrial fibrillation

Over time, patients with AF and HF were more likely prescribed with AF-specific drugs as compared with those with AF but without HF; among HF patients, use was lower with increasing EF. The use of rhythm control drugs decreased over time (in non-HF from 12% in 2006 to 5.5% in 2021, in HF from 8.7% to 7.6%, in HFrEF from 9.7% to 9.5%, in HFmrEF from 6.5% to 6.2%, in HFpEF 8.2% to 4.8%) (*Figure 2*). Patients with persistent AF were more likely treated with rhythm control drugs than those with paroxysmal or permanent AF (online supplementary *Table S3*). Dronedarone (2.9%) and flecainide (1.3%) were the most frequently used rhythm control drugs in patients without HF, while amiodarone (6.3%) and dronedarone (1%) were the most used in those with HF (online supplementary *Figure S2*). The trend in use of rate control drugs remained stable (in non-HF patients from 72% in 2006 to 72% in 2021, in HF from 93% to 92%, in HFrEF from 94% to 94%, in HFmrEF from 93% to 92%, in HFpEF 90% to 88%) (*Figure 2*); beta-blockers were the drug of choice, non-dihydropyridine calcium channel blockers (NDCC) were the least likely used, and digoxin use most markedly declined in HF and non-HF patients over time (online supplementary *Figure S3*). Anticoagulant use increased overall (in non-HF patients from 32% in 2006 to 80% in 2021, in those with HF from 61% to 89%, in HFrEF from 62% to 88%, in HFmrEF from 59% to 90%, in HFpEF 57% to 90%) (*Figure 2*), with decreasing use of vitamin K antagonists and a shift towards use of direct oral anticoagulants (DOACs) since 2018, becoming the drug of choice regardless of HF status and EF (online supplementary *Figure S4*).

Patients with versus without HF were more likely undergoing AF-related procedures regardless of EF. Procedures use was limited but increased over time (in non-HF patients from 0.4% in 2006 to 2% in 2021, in those with HF from 0.8% to 3.7%, in HFrEF from 0.7% to 4.6%, in HFmrEF from 0.7% to 3.4%, in HFpEF 1.1% to 1.8%) (*Figure 2*), but the overall increase was smaller in HFpEF.[7,8] The most common procedures included electrical cardioversion (in non-HF patients from 0.4% in 2006 to 1.9% in 2021, in those with HF from 0.4% to 3.5%, in HFrEF from 0.5% to 4.4%, in HFmrEF from 0.3% to 3.2%, in HFpEF from 0.4% to 1.7%) and pulmonary vein isolation ablation (in non-HF patients from 0% in 2006 to

Table 2 Baseline characteristics of study cohort 2 (incidence of atrial fibrillation)

Characteristics	Non-HF (*n* = 43 105)	HF (*n* = 43 105)	*p*-value	HFrEF (*n* = 25 478)	HFmrEF (*n* = 9779)	HFpEF (*n* = 7848)	*p*-value within EF	Missing data (%)[a]
Index year, *n* (%)								
2005–2010	12 580 (29)	12 580 (29)	1.00	7648 (30)	2556 (26)	2376 (30)	<0.001	
2011–2015	12 108 (28)	12 108 (28)		7197 (28)	2614 (27)	2297 (29)		
2016–2021	18 417 (43)	18 417 (43)		10 633 (42)	4609 (47)	3175 (40)		
Demographics								
Male sex, *n* (%)	26 875 (62)	26 875 (62)	1.00	17 311 (68)	5976 (61)	3588 (46)	<0.001	
Age, years, median [IQR]	72 [62–80]	72 [62–80]	1.00	70 [61–78]	72 [62–80]	76 [67–83]	<0.001	
Clinical parameters								
Location, inpatient, *n* (%)		10 439 (24)		6510 (26)	1608 (16)	2321 (30)	<0.001	
Follow-up referral, *n* (%)								
Primary care/other		10 974 (26)		4534 (18)	2857 (30)	3583 (48)	<0.001	3.9
Hospital		30 438 (74)		20 069 (82)	6542 (70)	3827 (52)		
LVEF, *n* (%)								
HFrEF		25 478 (59)						
HFmrEF		9779 (23)						
HFpEF		7848 (18)						
Duration of HF >6 months, *n* (%)		16 894 (40)		9302 (37)	3998 (42)	3594 (48)	<0.001	2.4
NYHA class, *n* (%)								
I		4665 (15)		2219 (11)	1551 (22)	895 (19)	<0.001	27
II		16 060 (51)		9840 (51)	3965 (55)	2255 (48)		
III		9837 (31)		6866 (35)	1577 (22)	1394 (30)		
IV		726 (2)		528 (2.7)	82 (1.1)	116 (2.5)		
BMI ≥30 kg/m^2, *n* (%)		8033 (27)		4475 (25)	1918 (29)	1640 (34)	<0.001	31
Systolic blood pressure, mmHg, median [IQR]		127 [112–140]		122 [110–140]	130 [118–144]	135 [120–150]	<0.001	2.1
Diastolic blood pressure, mmHg, median [IQR]		71 [65–80]		71 [65–80]	74 [65–80]	70 [65–80]	<0.001	2.0
Mean arterial pressure >90 mmHg, *n* (%)		21 452 (51)		11 833 (47)	5250 (55)	4369 (57)	<0.001	2.0
Heart rate >70 bpm, *n* (%)		19 144 (46)		11 974 (48)	3836 (41)	3334 (44)	<0.001	3.0
eGFR (ml/min/1.73 m^2), *n* (%)								
<15		461 (1.1)		235 (0.9)	111 (1.2)	115 (1.5)	<0.001	1.7
15–30		1772 (4.2)		917 (3.6)	366 (3.8)	489 (6.4)		
30–60		11 479 (27)		6454 (26)	2418 (25)	2607 (34)		
≥60		28 622 (68)		17 549 (70)	6680 (70)	4393 (58)		
Potassium (mmol/L), *n* (%)[b]								
Normakalaemia		33 953 (93)		20 162 (93)	7934 (94)	5857 (92)	<0.001	16
Hypokalaemia		1343 (3.7)		742 (3.4)	264 (3.1)	337 (5.3)		
Hyperkalaemia		1054 (2.9)		665 (3.1)	206 (2.5)	183 (2.9)		
Haemoglobin, g/L, median [IQR]		134 [121–145]		135 [123–147]	133 [121–145]	128 [116–140)	<0.001	5.2
NT-proBNP (pg/ml), above median within EF, *n* (%)		12 594 (50)		8751 (58)	2102 (37)	1741 (39)	<0.001	41
Medications and devices, *n* (%)								
ACEi/ARB/ARNi[c]	11 544 (27)	38 831 (90)	<0.001	23 914 (94)	8823 (90)	6094 (78)	<0.001	
MRA[c]	1754 (4.1)	16 400 (38)	<0.001	11 266 (44)	2696 (28)	2438 (31)	<0.001	
Digoxin[c]	88 (0.2)	960 (2.2)	<0.001	719 (2.8)	115 (1.2)	126 (1.6)	<0.001	
Diuretic[c]	2306 (5.3)	27 597 (64)	<0.001	17 302 (68)	4952 (51)	5343 (68)	<0.001	
Nitrate[c]	1555 (3.6)	13 780 (32)	<0.001	8156 (32)	3463 (35)	2161 (28)	<0.001	
Platelet inhibitor[c]	9133 (21)	27 535 (64)	<0.001	16 377 (64)	6589 (67)	4569 (58)	<0.001	
Oral anticoagulant[c]	376 (0.9)	1579 (3.7)	<0.001	942 (3.7)	343 (3.5)	294 (3.7)	0.63	
Statin[c]	9330 (22)	24 708 (57)	<0.001	14 674 (58)	6062 (62)	3972 (51)	<0.001	
Beta-blocker[c]	8542 (20)	37 431 (87)	<0.001	23 186 (91)	8309 (85)	5936 (76)	<0.001	
ICD[d]	12 (<1)	2062 (4.8)	<0.001	1679 (6.6)	250 (2.6)	133 (1.7)	<0.001	
CRT[d]	0 (0)	899 (2.1)	<0.001	753 (3.0)	110 (1.1)	36 (0.5)	<0.001	
SGLT2i[c]	155 (0.4)	1090 (2.5)	<0.001	804 (3.2)	200 (2.0)	86 (1.1)	<0.001	
History and comorbidities, *n* (%)								
Smoking	368 (0.9)	2621 (6.1)	<0.001	1726 (7)	556 (6)	339 (4)	<0.001	
Alcohol[c]	625 (1.4)	1505 (3.5)	<0.001	1006 (4)	264 (3)	235 (3)	<0.001	
Diabetes[c]	3056 (7.1)	11 268 (26)	<0.001	6541 (26)	2429 (25)	2298 (29)	<0.001	
Hypertension[c]	7445 (17)	26 627 (62)	<0.001	14 443 (57)	6258 (64)	5926 (76)	<0.001	
Ischemic heart disease[c]	4487 (10)	23 844 (55)	<0.001	14 172 (56)	5941 (61)	3731 (48)	<0.001	
Peripheral artery disease[c]	867 (2.0)	3578 (8.3)	<0.001	2021 (8)	797 (8)	760 (10)	<0.001	
Stroke[c]	2894 (6.7)	4615 (11)	<0.001	2583 (10)	1009 (10)	1023 (13)	<0.001	
Anemia[c]	1236 (2.9)	4818 (11)	<0.001	2443 (10)	1081 (11)	1294 (16)	<0.001	

Table 2 (Continued)

Characteristics	Non-HF (*n* = 43 105)	HF (*n* = 43 105)	*p*-value	HFrEF (*n* = 25 478)	HFmrEF (*n* = 9779)	HFpEF (*n* = 7848)	*p*-value within EF	Missing data (%)[a]
Obesity	319 (0.7)	2414 (5.6)	<0.001	1231 (5)	550 (6)	633 (8)	<0.001	
Valvular disease[c]	529 (1.2)	8895 (21)	<0.001	4743 (19)	1950 (20)	2202 (28)	<0.001	
Liver disease[c]	288 (0.7)	923 (2.1)	<0.001	549 (2)	169 (2)	205 (3)	<0.001	
Malignant cancer within 3 years[c]	4117 (10)	4849 (11)	<0.001	2637 (10)	1175 (12)	1037 (13)	<0.001	
Renal failure[c]	590 (1.4)	4560 (11)	<0.001	2477 (10)	960 (10)	1123 (14)	<0.001	
Obstructive sleep apnoea	564 (1.6)	1552 (3.6)	<0.001	802 (3.1)	364 (3.7)	386 (4.9)	<0.001	
Depression[c]	987 (2.3)	1797 (3.6)	<0.001	1038 (4.1)	386 (3.9)	373 (4.9)	0.014	
Charlson comorbidity index								
0–1	32 359 (75)	13 280 (31)	<0.001	8013 (31)	2951 (30)	2316 (30)	<0.001	
2–3	7752 (18)	16 862 (39)		10 228 (40)	3907 (40)	2727 (35)		
4–7	2465 (6)	10 652 (25)		6052 (24)	2354 (24)	2246 (29)		
≥8	529 (1.2)	2311 (5.4)		1185 (4.7)	567 (5.8)	559 (7.1)		
Socio-economic characteristics, *n* (%)								
Family type, living alone[c]	17 733 (41)	20 187 (47)	<0.001	11 716 (46)	4368 (45)	4103 (52)	<0.001	
Children	36 503 (85)	35 598 (83)	<0.001	20 731 (81)	8240 (84)	6627 (84)	<0.001	
Education[c]								
Compulsory school	15 226 (35)	17 545 (41)	<0.001	10 164 (40)	3786 (39)	3595 (46)	<0.001	
Secondary school	17 261 (40)	18 089 (42)		10 943 (43)	4179 (43)	2967 (38)		
University	10 618 (25)	7471 (17)		4371 (17)	1814 (19)	1286 (16)		
Disposable income (100 SEK), above median within year[c]	23 446 (54)	19 673 (46)	<0.001	11 994 (47)	4755 (49)	2924 (37)	<0.001	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SEK, Swedish krona; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SwedeHF Swedish Heart Failure Registry.

[a]Missing (%) is for SwedeHF only.

[b]Hypokalaemia, normokalaemia, and hyperkalaemia were defined as serum potassium levels of <3.5, 3.5–5.0, and ≥5.0 mEq/L, respectively.

[c]Variables included in the multivariable model.

[d]Variables excluded from the multivariable model for non-HF but included for HFrEF, HFmrEF, and HFpEF.

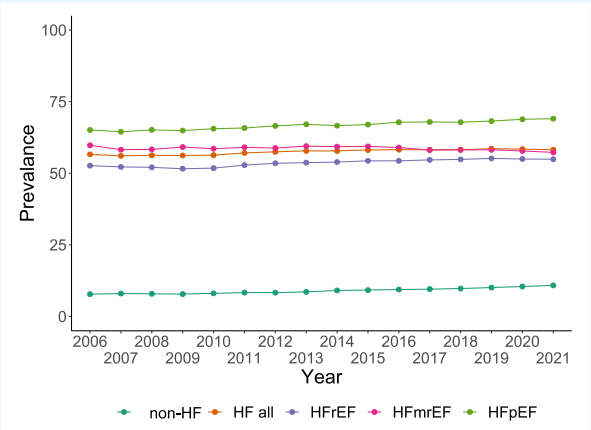


Figure 1 Prevalence of atrial fibrillation. The graph displays the annual prevalence of atrial fibrillation in patients with and without heart failure (HF), and across the ejection fraction spectrum. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

0.2% in 2021, in those with HF from 0.1% to 0.5%, in HFrEF from 0.1% to 0.7%, in HFmrEF from 0.1% to 0.5%, in HFpEF from 0.1% to 0.3%) (online supplementary *Figure S5*). Pulmonary vein isolation ablation was more likely with persistent versus paroxysmal and permanent AF (online supplementary *Table S3*). His-bundle ablation, maze surgery, and left atrial appendage closure were relatively rare (<0.1%, with an increase of ≤0.1% from 2006 to 2021), with stable utilization over time (online supplementary *Figure S5*).

Baseline characteristics of study cohort 2 and analysis of atrial fibrillation incidence and related predictors

The analysis focusing on incident AF included 86 210 patients without AF or history of AF at the index date (43 105 with HF and 43 105 controls), of whom 62% were men and median age was 72 years (Q1–Q3: 62–80). Among HF patients, 59% had HFrEF, 23% had HFmrEF and 18% had HFpEF. Differences in patient characteristics between AF patients with versus without HF and with HFpEF versus HFmrEF versus HFrEF were consistent with what observed for study cohort 1 (*Table 2*).

Incident AF occurred in 15% of the population (12 730 patients) over a median follow-up of 3.7 years (Q1–Q3: 3.70–3.76), with an overall incident rate of 31/1000 patient-years. More specifically, 23% of HF (22% of HFrEF, 21% of HFmrEF and 25% of HFpEF) and 7% of non-HF patients developed AF, with incidence rates of 55/1000 patient-years in HF (53 in HFrEF, 52 in HFmrEF, 71 in HFpEF) versus 12/1000 patient-years in non-HF. The incidence rates for AF were: 82/1000 patient-years for HF (80 for HFrEF,

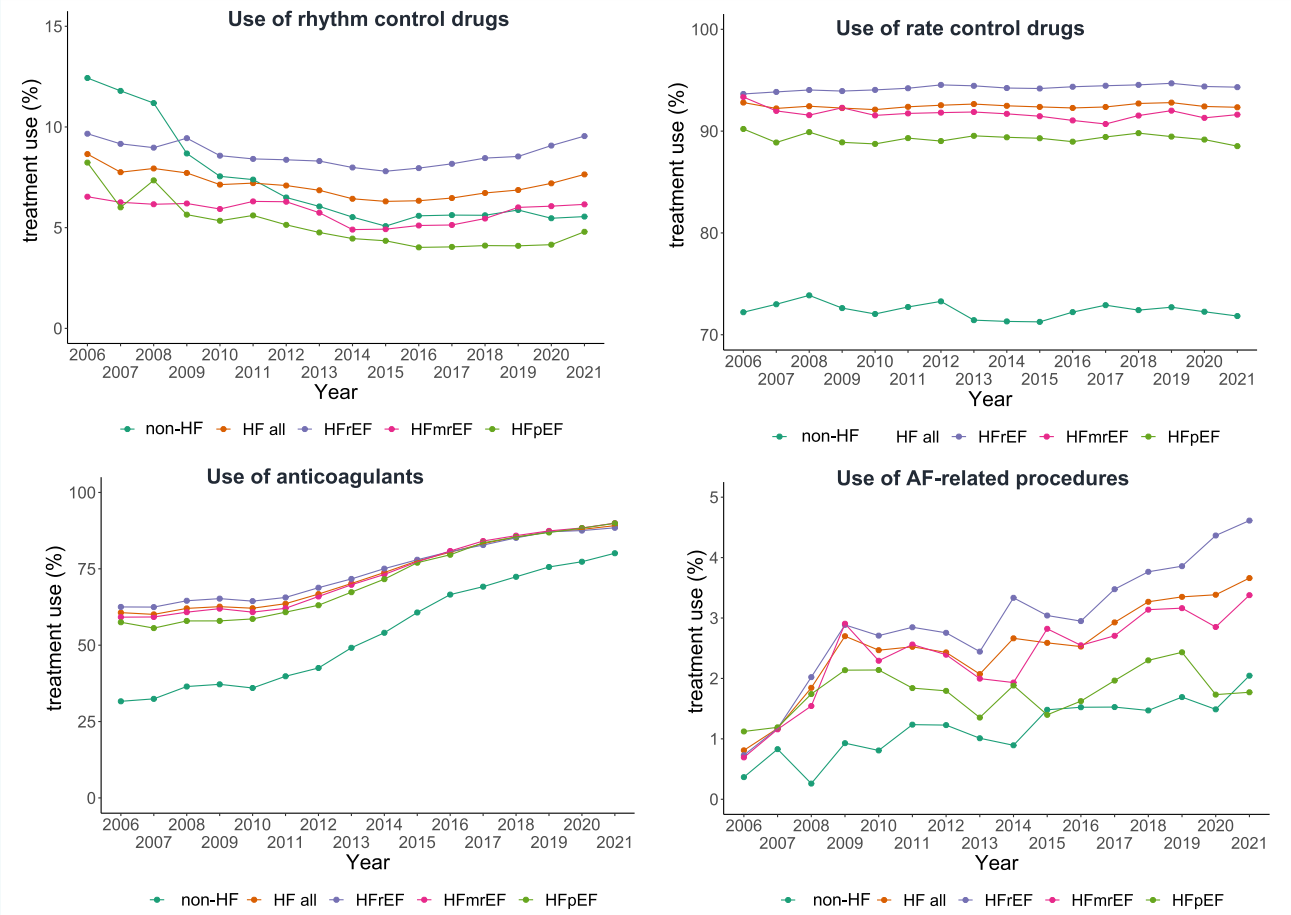


Figure 2 Use of atrial fibrillation (AF) treatments. The graph depicts the use of AF treatments in patients with and without heart failure (HF), and across the ejection fraction spectrum. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

72 for HFmrEF, and 101 for HFpEF) and 11 for non-HF at 1 year, 59/1000 patient-years for HF (56 for HFrEF, 55 for HFmrEF, and 76 for HFpEF) and 12 for non-HF at 5 years, and 56 per 1000 patient-years for HF (53 for HFrEF, 52 for HFmrEF, and 72 for HFpEF) and 12 for non-HF at 10 years. The crude risk of incident AF was four-fold higher in HF versus non-HF (HR 4.52, 95% CI 4.33–4.72), and higher in HFpEF (HR 5.55, 95% CI 5.24–5.87) versus HFrEF (HR 4.23, 95% CI 4.05–4.43) and HFmrEF (HR 4.08, 95% CI 3.85–4.31) (*Figure 3*). After adjustments, the risk of incident AF was two-fold higher in patients with versus without HF (adjusted HR 2.76 95% CI 2.45–3.12), and higher in HFpEF (adjusted HR 3.12, 95% CI 2.65–3.67) versus HFrEF (adjusted HR 2.68, 95% CI 2.34–3.06) and HFmrEF (adjusted HR 2.53, 95% CI 2.17–2.94).

Patient characteristics independently associated with higher risk of incident AF included use of renin–angiotensin–aldosterone system inhibitors (RAASi) and ARNi, beta-blockers, implantable cardioverter-defibrillator (ICD) and pacemaker, oral anticoagulants, digoxin, loop diuretic, no use of statins and cardiac resynchronization therapy (CRT). As regards comorbidities, history of valvular disease, hypertension, peripheral artery disease, renal failure and anemia were associated with higher risk (*Figure 4*).

Few differences in patient characteristics associated with incident AF were observed across the EF spectrum as compared with the overall analysis. In HFrEF, no use of SGLT2i use was identified as independently associated with incident AF. History of malignant cancer in the previous 3 years, alcohol consumption and depression predicted AF in non-HF; ischeamic heart disease, stroke and depression in HFrEF; history of malignant cancer in the previous 3 years and no depression in HFpEF. Low educational level and income independently predicted AF onset in non-HF and HFrEF, while income alone predicted AF onset in HFmrEF (online supplementary *Figure S6*).

Discussion

The key findings of this registry-based comparative assessment of the epidemiology and treatment strategies for AF in patients with versus without HF were (i) the prevalence of AF increased over time irrespective of the presence of HF; (ii) HF versus non-HF patients were more likely to receive AF-specific drugs and procedures, especially in HFrEF versus HFmrEF and HFpEF;

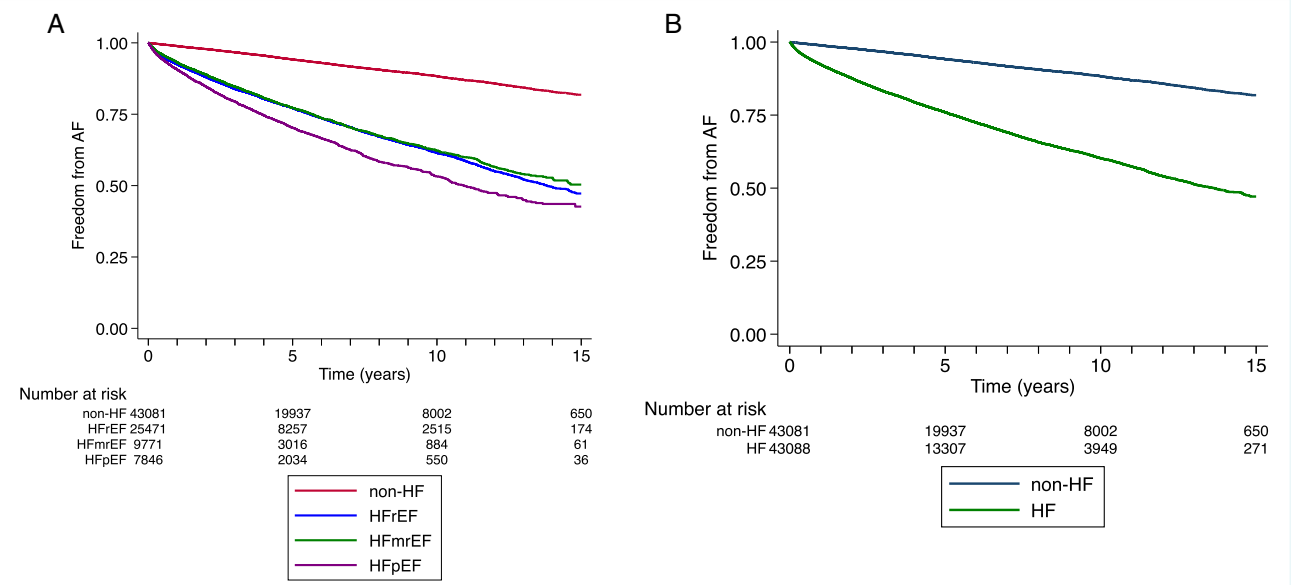


Figure 3 Incidence of atrial fibrillation (AF). The graph displays the Kaplan–Meier curve for AF onset across all population subgroups (*A*) and in patients with versus without heart failure (HF) (*B*). HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection.

(iii) there was no consistent rise in the use of specific AF-related drugs and procedures despite temporal increase in AF prevalence; (iv) HF was independently associated with higher risk of incident AF, which was higher with HFpEF as compared with HFrEF and HFmrEF; (v) established risk factors from previous population studies were overall confirmed as independent predictors of AF onset, with potential protective effects of SGLT2i in HFrEF[9–11] (*Graphical Abstract*).

Prevalence of atrial fibrillation

Recent epidemiological studies suggest that AF prevalence has been increasing by 33% during the last 20 years in the worldwide population, likely attributable to the aging population, improved survival to other cardiovascular diseases, better diagnostics, and increased awareness and therefore earlier and more likely identification of AF.[12,13] Approximately 9 million people in Europe have AF (a prevalence of 2–3%), expected to further increase up to 17.9 million by 2060.[13] Therefore, the increasing AF prevalence over time documented in our analysis is consistent with previous data.

We observed that the prevalence of AF in HF was 58%, with a consistent increase over time. This rise is likely attributable also to the close connection between the two conditions, stemming from intrinsic pathophysiological mechanisms, the burden of shared comorbidities, and the aging population.[13] Our results on AF prevalence across the EF spectrum are challenging to compare with previous studies as it ranged from 27% (European Society of Cardiology [ESC] HF Long-Term Registry) to 53% (SwedeHF) in HFrEF, from 29% (ESC HF Long-Term Registry) to 60% (SwedeHF) in HFmrEF, and from 32% (Framingham Heart Study) to 65% (SwedeHF) in HFpEF.[1–3] A potential explanation for this heterogeneity in prevalence estimates across studies may lie in the differences in study design, population characteristics and AF definition, beyond potential geographical variations. However, the highest prevalence estimates are derived from SwedeHF, which might be linked with the availability of more recent data as compared with previous studies, reflecting prolonged longevity, increased multimorbidity and surveillance in the general population, the inclusion of both inpatients and outpatients, and the use of multiple data sources. In the present study, AF prevalence was higher in HFpEF than HFmrEF and HFrEF, and two-thirds of patients with HFpEF had AF. This is consistent with the current paradigm linking HFpEF with inflammation, arterial hypertension, renal insufficiency, obesity and multimorbidity burden, as well as with the more likely diagnosis of HFpEF in patients with AF given the overlapping symptoms, signs and alterations in diagnostics and biomarkers.[7,14]

Use of atrial fibrillation treatments and procedures

There is limited real-world evidence on AF treatment use in patients with and without HF. Our analysis showed lower use of rhythm control, especially catheter ablation, compared with the EORP-AF registry.[15] This may reflect the challenges in identifying the population that benefits most from rhythm control versus rate control, since no randomized controlled trials (RCTs) have conclusively favoured one strategy over the other in terms of reducing all-cause mortality and systemic embolism risk.[16] The recent EAST-AFNET 4 supported early rhythm control, with either pharmacological therapy or ablation, in recently diagnosed AF patients stressing the importance of intervention rather than accepting AF in HF as based on previous studies.[16,17] As regards catheter ablation, the underutilization might reflect conflicting trial results and

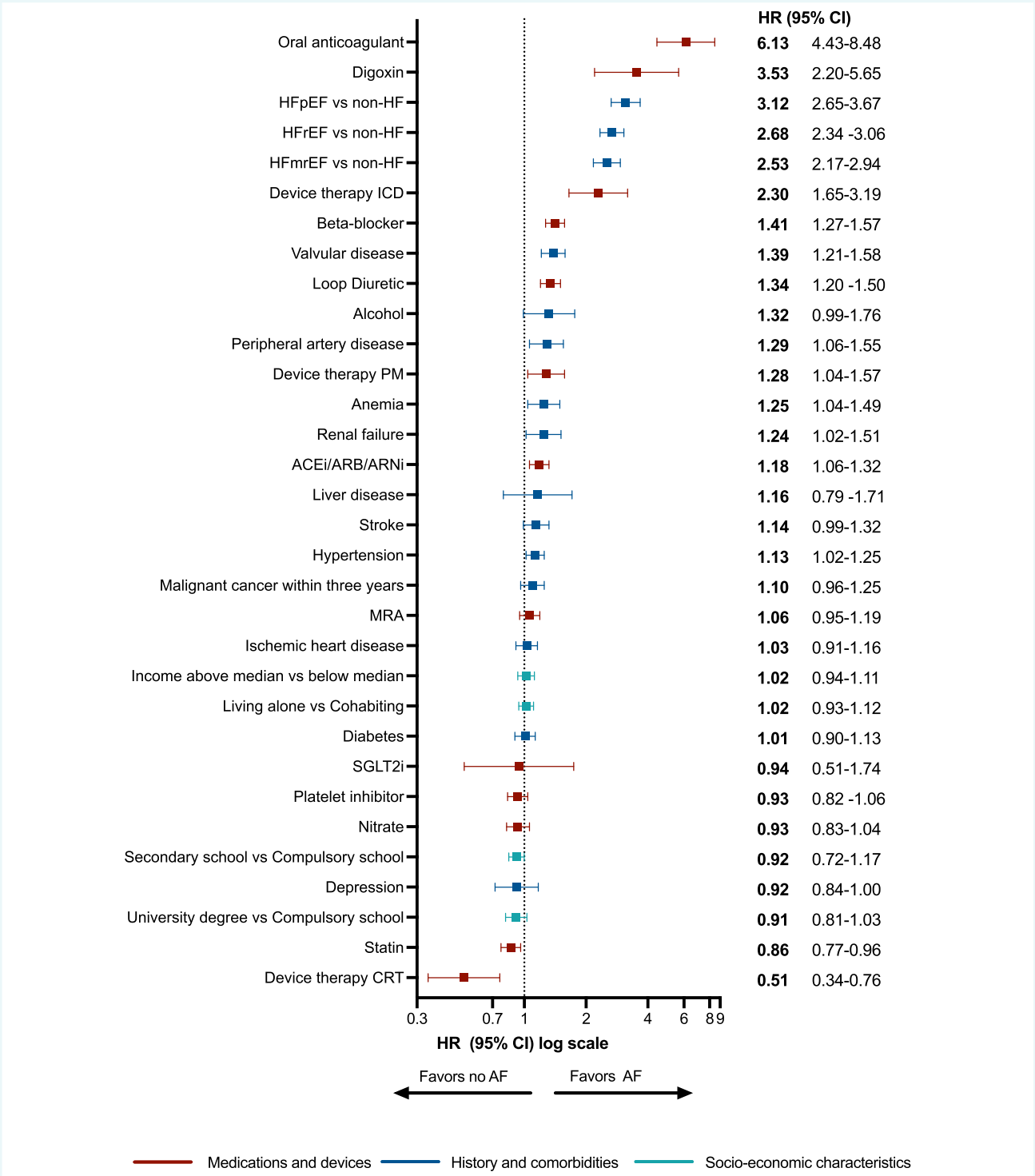


Figure 4 Independent predictors of incident atrial fibrillation (AF). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

the relatively small size of studies conducted in HF patients. The CASTLE-AF and CASTLE-HTx trials showed the superiority of catheter ablation compared with medical therapy in patients with HFrEF in preventing death or HF admissions.[18,19] In contrast, the RAFT-AF trial did not show a significant risk reduction in the primary endpoint of all-cause mortality and all HF events with catheter ablation versus rate control regardless of EF.[20] Consequently, while the latest AF and HF European guidelines suggest considering catheter ablation to reduce symptoms in selected AF patients with HF when antiarrhythmic drugs cannot be used (class IIa), the recent American AF guidelines provide a class I recommendation for improving symptoms and prognosis.[7,12,14,21] In our study, on the other hand, the use of pharmacological treatments for rate control remained stable over time, with beta-blockers steadily used as first-line therapy, whereas digoxin use decreased over time, possibly because of the results of several observational studies where it was linked with higher mortality.[22]

Anticoagulant use, particularly DOACs, increased over time in our analysis (from 80% to 89% in HF patients) indicating enhanced adherence to guideline-directed therapy, in accordance with the results from the GLORIA-AF registry where in Europe an early initiation of DOACs after newly diagnosed AF was more likely observed.[23]

The observed decrease in antiarrhythmic drug use, along with increased rate control medications and oral anticoagulant use, likely reflect evolving treatment paradigms related to safety concerns, limited long-term efficacy, evolving guidelines, and the rise of catheter ablation. However, our study may not fully capture recent trends toward earlier rhythm control, as shown in the EAST-AFNET 4 trial, potentially leading to implement rhythm control strategies.[17]

Furthermore, recent landmark trials, NOAH-AFNET 6 and ARTESIA have provided crucial insights into the management of device-detected, low-burden AF, potentially leading to more nuanced and personalized anticoagulation strategies.[24,25] While our study captures historical trends, these recent trial results may significantly influence future treatment patterns.

In our analysis, HFpEF patients received fewer AF treatments compared with HFrEF and HFrEF, with rhythm control drug use dropping from 8.2% to 4.8%, possibly because of the lack of dedicated randomized controlled trials guiding AF management in HFpEF. Pre-specified sub-analyses of CABANA and EAST-AFNET 4 support systematic rhythm control even in symptomatic patients with HFpEF, and suggest potential benefits in reducing cardiovascular outcomes with and an earlier consideration of catheter ablation in HFpEF patients with significant functional impairment.[26,27] Further insights will be offered by the ongoing CABA-HFPEF trial (NCT05508256), which is testing whether catheter ablation for AF can prevent adverse cardiovascular outcomes in patients with HFpEF or HFmrEF.

Risk and independent predictors of incident atrial fibrillation

We showed that the incidence of AF was higher in HF versus non-HF, and it was 1.2-fold higher in HFpEF compared with HFrEF. The higher incidence of AF in HFpEF patients likely reflects shared pathophysiological mechanisms, including left atrial remodelling, fibrosis, and neurohormonal activation, which contribute to the development and progression of both conditions, exacerbated by the presence of shared cardiovascular risk factors like hypertension, obesity, chronic kidney disease, diabetes and aging between AF and HF.[28] In our analysis, 25% of patients with HFpEF had an incident AF event over a median follow-up of 3.7 years, aligning with similar studies like the Olmsted County Community-Based Study, which reported a 32% incidence over a similar follow-up period.[29] Conversely, the CHARM-Preserved trial reported a lower AF incidence of 4.9% over 37.7 months, likely attributable to the inclusion of a lower-risk population (younger cohort with fewer comorbidities).[30]

In the overall cohort, patients using RAASi, ARNi, beta-blockers, ICD and pacemaker, oral anticoagulants, digoxin and loop diuretic, not on statins or CRT, and with history of valvular disease, hypertension, peripheral artery disease, renal failure and anemia were more likely to develop AF, aligning with established risk factors from previous studies.[9–11]

Anticoagulant use was associated with higher AF risk, suggesting previous AF episodes occurring outside hospital settings, potentially not recorded in the National Patient Register. Similarly, the independent association between diuretic use and incident AF in HF patients may reflect (i) HF severity and progression, predisposing to higher AF risk, and (ii) overlapping symptoms of HF and AF, indicating possible misdiagnosis.[7,14]

Our analysis found that anemia was independently associated with new-onset AF. Prior studies showed different results, with some suggesting a U-shaped relationship between haemoglobin levels and AF.[31] Potential explanations include decreased oxygen delivery causing myocardial changes or anaemia acting as a marker of overall comorbidity burden, consistent with findings from the ARIC study.[32]

RAASi showed inconsistent associations across the EF spectrum, with no protective effect against new-onset AF in HFrEF and HFpEF, and possible reduction in AF risk in HFmrEF. However, its protective role in preventing AF remains uncertain, with limited benefits in specific populations.[33] Notably, SGLT2i use was independently associated with a lower AF risk in HFrEF, as reported in a recent meta-analysis of randomized controlled trials.[34] However, our result should be interpreted with caution because of the low proportion of patients receiving SGLT2i.

Limitations

Despite matching and extensive adjustment, residual unmeasured confounding cannot be ruled out due to the observational nature of this study. Some AF cases might have been missed outside hospital settings. AF type was unavailable for all patients, leading to potential misclassification. Trends in AF may reflect changes in ICD and procedure code recording, not actual AF changes. Differences in diagnostic criteria, screening practices, or AF awareness over time may have affected detection rates and prevalence estimates. This study did not explore associations with other cardiovascular outcomes.

The generalizability of the described trends and treatment practices may be limited due to differences in healthcare systems, treatment practices, and population characteristics outside Sweden.

Conclusions

The prevalence of AF increased over time, as well as the use of anticoagulants and AF-related procedures. AF patients with versus without HF were more likely to receive AF-specific drugs and procedures. Despite the higher prevalence and incidence of AF in HFpEF versus HFrEF and HFmrEF, the use of AF drugs and procedures remained modest, highlighting the need to implement AF treatment in this HF subtype.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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