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ORIGINAL ARTICLE

Newly diagnosed atrial fibrillation and hospital utilization in heart failure: a nationwide cohort study

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Abstract

Aims Atrial fibrillation (AF) constitutes a major burden to health services, but the importance of incident AF in patients with heart failure (HF) is unclear. We examined the associations between incident AF and hospital utilization in patients with HF.
Methods and results In a nationwide matched-cohort study of HF patients, we identified patients diagnosed with incident AF between 2008 and 2018 in the Danish Heart Failure Registry (*N* = 4463), and we compared them to matched referents without AF (*N* = 17 802). Incident AF was associated with a multivariable-adjusted 4.8-fold increase (95% CI 4.1–5.6) and 4.3-fold increase (95% CI 3.9–4.8) in the cumulative incidence of inpatient and outpatient contacts within 30 days, respectively. At 1 year, the cumulative incidence ratios were 1.8 (95% CI 1.7–1.9) and 1.4 (95% CI 1.4–1.5). Incident AF was also associated with increases in the total numbers of inpatient and outpatient hospital contacts within 30 days (multivariable-adjusted rate ratio 1.4, 95% CI 1.4–1.5, and 1.6, 95% CI 1.6–1.7, respectively). At 1 year, the ratios were 2.2 (95% CI 2.1–2.3) and 2.0 (95% CI 1.9–2.1). The multivariable-adjusted proportion of bed-day use among HF patients with incident AF was 10.9-fold (95% CI 9.3–12.9) higher at 30 days and 5.3-fold (95% CI 4.3–6.4) higher at 1 year compared with AF-free referents.
Conclusions Incident AF in HF is associated with earlier hospital contact, more hospital contacts, and more hospital bed-days. More evidence on interventions that may prevent the risk and subsequent burden of AF in HF is urgently needed.

Keywords Atrial fibrillation; Heart failure; Hospitalizations; Healthcare

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Introduction

Heart failure (HF) is a growing worldwide epidemic with a global prevalence of 64 million cases in 2017,[1] and projection studies suggest that the prevalence will increase in the future.[2,3] Among Europeans, the lifetime risk of HF is 28% in women and 33% in men at the age of 55 years,[4] and among Americans 20% and 21%, respectively, at the age of 40 years.[5] HF is associated with considerable morbidity and high mortality,[6] is a leading cause of hospitalizations and outpatient visits,[7] and is associated with substantial healthcare expenditures that will likely rise.[2] Therefore, HF constitutes a major burden to public health and health services.

Patients with incident HF have a two-fold increased risk of incident atrial fibrillation (AF),[8] and ~10% of patients with HF developed AF after ~2.5 years of follow-up according to UK primary care data.[9] Incident AF in HF patients is considered an adverse prognostic indicator of HF, with an approximately two-fold increased rate of death compared with HF patients without AF.[8,10] AF constitutes a major burden to health services, including hospitalizations and health expenditures,[11,12] but the consequence of incident AF on hospital utilization in the HF setting is unclear.

Therefore, the objective of the present study was to quantify hospital utilization associated with incident AF among patients with HF.

Methods

Setting and data sources

The Danish Heart Failure Registry (DHFR) is a nationwide clinical quality database established in 2003 that comprises inpatients and outpatients with incident HF.[13] The objectives of the DHFR are to monitor and improve the quality of care for Danish patients with HF. HF has to be diagnosed or validated by a cardiologist, and reporting of HF patients from all Danish hospitals is mandatory.[13] The source population for our investigation included patients diagnosed with incident HF from 2008 to 2018. The inclusion criteria of the registry include a first-time diagnosis of HF and diagnostic criteria from the National Society for Cardiology and European Society of Cardiology: HF symptoms and objective signs of HF, and/or a possible clinical improvement on HF treatment. Exclusion criteria include HF caused by uncorrectable structural heart disease, HF caused by valvular heart disease, HF caused by rapid heart rhythm (including AF), isolated right-sided HF, HF diagnosed concurrently with a primary diagnosis of acute myocardial infarction, or HF patients diagnosed and treated by a private practitioner of cardiology. The cardiologist identified the conditions in the patient's medical records.

We linked data of the DHFR to data from three national registries. The Danish National Patient Registry was established in 1977 and contains prospectively registered information on all inpatients and after 1995 also all outpatients.[14] Data included individual-level information on dates of admission and discharge, surgical procedures performed, and one primary diagnosis and one or more secondary diagnoses per discharge. The coding of diagnoses followed the Danish version of the International Classification of Diseases Eighth Revision (ICD-8) before 1994 and the 10th Revision (ICD-10) from 1994 and onwards. The physician who discharged a patient coded all diagnoses for that patient.

The Danish National Prescription Registry contains individual-level data on all dispensed prescriptions since 1994 and was used to retrieve information on pharmacological treatments.[15] The coding of medications follows the Anatomical Therapeutic Chemical Classification System.

Statistics Denmark provided information on family income and highest completed education.

The Danish Civil Registration System contains daily updated individual-level information on sex, date of birth, vital statistics, and migration. All Danish citizens are assigned a unique 10-digit civil registration number that enables unambiguous linkages of data between registries.

Supporting Information, *Table S1* presents the definition of variables and data sources.

Design and study population

We designed a nationwide registry-based matched-cohort study. From the DHFR population, we first excluded patients with any diagnosis of AF (including AF and atrial flutter, and referred to as AF hereafter) identified in the Danish National Patient Registry prior to or on the same day as the diagnosis of HF to ensure that only individuals at risk of incident AF were included in the study population (Supporting Information, *Table S2*). Furthermore, to ensure sufficient time for the registry-based identification of history of diseases, we excluded HF patients who lived in Denmark for <5 years. We identified all HF patients with newly diagnosed AF. We matched each HF patient with newly diagnosed AF to HF referents without AF and followed all patients for hospital contacts, admissions, and bed-day use.

Heart failure patients with newly diagnosed atrial fibrillation

We identified all HF patients with a new primary or secondary hospital diagnosis of AF (or atrial flutter) from the National Patient Registry after their HF diagnosis (Supporting Information, *Table S2*). Both inpatient and outpatient diagnoses were included. The index date was the date of newly diagnosed AF, which we defined as the discharge day for inpatients and the first date of the diagnosis for outpatients.

Matched referents

We matched each AF case with up to four HF patients without AF (Supporting Information, *Figure S1*). Matching variables included age at HF diagnosis, sex, and age at index date. Including both age at HF and age at AF index date prevented selective survival bias due to the impossibility of selecting HF patients with high short-term mortality as referents. The index date for each matched referent was the case index date, that is, the date of newly diagnosed AF. Sampling of referents was with replacement, so a referent may have been sampled more than once. A referent that became an AF case at an older age led to censoring at the time of AF diagnosis.

Hospital utilization

We examined three measures of hospital-related activity, each stratified into inpatient and outpatient care. A hospital contact was any inpatient or outpatient hospital contact with a registered primary diagnosis. We did not include emergency room contacts because the diagnostic validity in the

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setting is low for many diagnoses.[16] First, we examined the risk of having at least one hospital contact within 30 days and 1 year, respectively, after the index date. Second, we counted the number of hospital contacts within 30 days and 1 year after the index date, respectively. Third, we examined the number of bed-days, which included any hospitalization with at least one overnight stay.

Covariates

Covariates included sex, age, lifestyle factors, clinical data, co-morbidities, and socio-economic factors (Supporting Information, *Tables S1* and *S3*).

Lifestyle factors included weekly alcohol consumption and smoking. We applied the definitions of elevated alcohol consumption pertained to the DHFR. The definition was more than 14 drinks per week for women and 21 drinks per week for men until 1 July 2015. After that date, the registry applied a lower threshold of elevated drinking, namely, more than 7 drinks per week for women and 14 drinks per week for men. Smoking status was classified as current smoker, former smoker, or never smoker. Information on alcohol consumption and smoking status was reported at the diagnosis of HF.

Clinical data included left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) Classification. Categorization of LVEF followed the universal LVEF classification groups,[17] but to account for the patients with very low LVEF, we added a category $<$25% ($\geq$50%, $>$40–49%, 25–40%, or $<$25%). The patients underwent echocardiography between 7 days after the diagnosis of HF and up to 6 months before the diagnosis of HF if the cardiologist considered the examination relevant. NYHA classification was categorized as I, II, or III/IV and reported at the diagnosis of HF or up to 12 weeks after the diagnosis.

Co-morbidities included history of myocardial infarction, ischaemic stroke, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, and overweight/obesity. Furthermore, we calculated a modified Charlson Comorbidity Index that did not include AIDS because of a very low prevalence. History of co-morbidities was ascertained up to and including the day before the index date.

Socio-economic factors comprised family income and highest completed education. Family income was the yearly disposable equivalent income, which is a comparable measure between families that accounts for the number of family members that live together and their ages. Statistics Denmark generated the measure for a family by adding the income of all the family members and dividing by a weighted average number of people in the family. We categorized level of education into the following International Standard Classification of Education (ISCED) groups. Group 1 included early childhood, primary education, and lower secondary educations (ISCED 0–2). Group 2 included general upper secondary education and vocational upper secondary education (ISCED 3). Group 3 included short-cycle tertiary, medium-length tertiary, bachelor's level educations or equivalent, second cycle, master's level or equivalent, and PhD level (ISCED 5–8). ISCED 4 does not exist in Denmark.

Medications included angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) (Supporting Information, *Table S3*). The definition of use was at least one redeemed prescription within the last 6 months before the index date. Furthermore, we examined use of oral anticoagulants within 3 months after AF and the use of loop diuretics 3 months prior to index date.

Statistical methods

We used time-to-event analyses to examine time to the first hospital contact. Time at risk began on the first day after the index date and ended on the earliest of date of death, last follow-up, heart transplantation, at 30 days or 1 year, whichever came first. We used the Aalen–Johansen estimator, which accounted for the competing risk of death, to estimate the cumulative incidence of first hospital contact with 95% confidence interval (95% CI). We used the pseudo-value approach to estimate multivariable-adjusted cumulative incidence ratios between HF patients with and without AF.[18]

We used negative binomial regression to estimate the number of hospital contacts per 1000 risk-days and the percentage of risk-days spent in hospital bed, respectively. Time at risk began on the first day after the index date and ended on date of death, date of end of follow-up, heart transplantation, or date of emigration, at 30 days or 1 year, whichever came first. To account for different lengths of risk periods, days at risk was logarithmized and included in the models to provide a rate per risk-day. We estimated the ratio between AF cases and referents at 30 days and 1 year.

We performed five pre-specified subgroup analyses. First, we stratified by sex. Second, we stratified by age group $\geq$75 vs. $<$75 years at index date. Third, we stratified by LVEF level categorized into $\leq$40%, $>$40–49%, and $\geq$50%. Fourth, we stratified by time with HF $\leq$ 1 vs. $>$1 year. Fifth, we stratified by educational level. We tested for interactions by adding interaction terms to the multivariable models.

We used Stata statistical software (StataCorp. 2019: Release 16.1, College Station, TX: StataCorp LLC) for all data management and statistical analyses.

Missing data

Variables with missing values included LVEF, NYHA class, alcohol use, and smoking status. We used multiple imputa-

tion to account for missing values in all analyses except the analyses of LVEF groups and level of education in which we excluded patients with missing LVEF and educational level, respectively. The imputation model included case/referent status, age at HF, sex, age at matching, time since diagnosis of HF, highest level of education, family income, history of acute myocardial infarction, stroke, diabetes, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, overweight/obesity, use of ACE inhibitor/ARB treatment, beta-blocker, MRA, the Charlson Comorbidity Index, and an outcome indicator. We created 10 imputed datasets and combined the estimates with Rubin's rules. We used the mi command in Stata to perform multiple imputation.

Ethics

The Danish Health Data Authority, Statistics Denmark, and the Danish Data Protection Agency approved this study. Registry-based studies do not require approval from an ethics committee according to Danish law.

Results

Characteristics of patients

We identified 27 947 patients diagnosed with incident HF from 2008 through 2018 with no history of AF. Among all HF patients, 4471 patients were diagnosed with incident AF during follow-up. At 10 years after the diagnosis of HF, the cumulative incidence of AF was 23.5% when accounting for the competing risk of death. The incidence rate of AF was 45.4 per 1000 person-years. We excluded eight of the 4471 AF cases (mean age at HF diagnosis 96.1 years; mean age at AF diagnosis 98.6 years) because no AF-free referents could be matched. The study population consisted of 4463 AF cases and 17 802 AF-free matched referents (balance of covariates presented in Supporting Information, *Table S4*). Of the 17 802 matched referents, 4327 patients were selected as referents more than once and 1455 referents later became AF cases. At the diagnosis of AF, the mean age was 74 years, the proportion of female patients was 29%, and the median time with HF was 1.2 years (*Table 1*). Among AF cases, 47% had a history of hypertension, 32% had a history of acute myocardial infarction, and 21% had a history of diabetes. The median Charlson Comorbidity Index was 3 (inter-quartile range 2–5) among AF cases and 2 (inter-quartile range 1–4) among referents (Supporting Information, *Table S5*). The respective use of ACE inhibitors/ARBs, beta-blockers, and MRA (classified at the time of incident AF diagnosis) was higher among AF cases at the index day (*Table 1*). Within 3 months after the diagnosis of AF, 44.2% of patients diagnosed between 2008 up to and including 2013 redeemed at least one prescription of an oral anticoagulant, while 53.8% of patients diagnosed from 2014 up to and including 2018 redeemed at least one prescription. The mortality rate was 177.1 per 1000 person-years among AF cases and 88.7 per 1000 person-years among matched referents. In a multivariable-adjusted Cox model, the hazard ratio for death between AF cases and matched referents was 1.91 (95% CI 1.81–2.02).

Time to first hospital contact

Half of the AF cases had encountered at least one inpatient contact 7.8 months after AF, while half of the referents encountered at least one contact 4.5 years after index date. The cumulative incidences of first inpatient contact were 25.3% among AF cases and 5.2% among referents at 30 days (*Figure 1* and *Table 2*). At 1 year, the cumulative incidences were 56.3% and 23.5%, respectively. The multivariable-adjusted cumulative incidence ratio associated with incident AF was 4.8 (95% CI 4.1–5.6) at 30 days and 1.8 (95% CI 1.7–1.9) at 1 year. When examining outpatient contacts, half of the AF cases had encountered at least one contact 2.3 months after AF, while half of the referents encountered at least one contact 1.5 years after index date. At 30 days, the cumulative incidence of first outpatient contact was 38.3% among AF cases and 10.6% among referents. At 1 year, the cumulative incidences were 69.8% and 43.1%, respectively. The multivariable-adjusted cumulative incidence ratio associated with incident AF was 4.3 (95% CI 3.9–4.8) at 30 days and 1.4 (95% CI 1.4–1.5) at 1 year.

Number of inpatient and outpatient contacts

During the initial 30 days, AF cases had 28.1 inpatient contacts per 1000 risk-days, while the matched AF-free referents had 19.9 inpatient contacts (*Table 3*). The multivariable-adjusted rate ratio associated with incident AF was 1.4 (95% CI 1.4–1.5). At 1 year after incident AF, the number of inpatient contacts per 1000 risk-days was 8.8, while the matched referents had 3.7 contacts. The multivariable-adjusted rate ratio was 2.2 (95% CI 2.1–2.3). Counting outpatient contacts, AF cases had 30.3 per 1000 risk-days compared with 18.7 among referents. The multivariable-adjusted rate ratio was 1.6 (95% CI 1.6–1.7). At 1 year, the number of outpatient contacts per 1000 risk-days was 10.6 among AF cases and 3.9 among referents, which corresponded to a multivariable-adjusted rate ratio of 2.0 (95% CI 1.9–2.1).

Table 1 Characteristics of HF patients with incident AF and matched referents at index date

	AF cases *N* = 4463	Referents *N* = 17 802
Socio-demographics		
Age (years), mean (SD)	73.7 (11.4)	73.6 (11.3)
Female sex, *N* (%)	1295 (29.0)	5153 (29.0)
Family income[a] (€), median (Q1–Q3)	23 097 (19 283–31 120)	23 439 (19 434–31 453)
Highest completed education, *N* (%)		
Group 1	2199 (51.5)	8947 (52.4)
Group 2	1544 (36.2)	6170 (36.1)
Group 3	528 (12.4)	1964 (11.5)
Lifestyle factors, *N* (%)		
Elevated alcohol consumption	362 (9.5)	1237 (8.1)
Smoking status		
Never	1065 (26.7)	4101 (25.2)
Former	1857 (46.6)	7532 (46.3)
Current	1064 (26.7)	4636 (28.5)
Clinical data, *N* (%)		
LVEF		
<25%	1076 (24.7)	3628 (20.8)
25–40%	2671 (61.4)	11 161 (64.1)
>40–49%	296 (6.8)	1314 (7.6)
≥50%	311 (7.1)	1302 (7.5)
NYHA class		
I	499 (12.7)	2729 (16.7)
II	2361 (59.9)	9989 (61.2)
III/IV	1082 (27.5)	3593 (22.0)
Time since HF (years), median (Q1-Q3)	1.2 (0.2–3.5)	1.2 (0.4–3.4)
Age at HF, mean (SD)	71.5 (11.4)	71.4 (11.4)
History of co-morbidity, *N* (%)		
Myocardial infarction	1404 (31.5)	5946 (33.4)
Any stroke/TIA	697 (15.6)	1950 (11.0)
Diabetes mellitus	956 (21.4)	3149 (17.7)
COPD	696 (15.6)	2029 (11.4)
Hypertension	2100 (47.1)	7562 (42.5)
Chronic kidney disease	460 (10.3)	1228 (6.9)
Overweight/obesity[a]	394 (8.8)	954 (5.4)
Modified CCI, *N* (%)		
0	0	0
1–2	2070 (46.4)	10 430 (58.6)
3–4	1185 (26.6)	4292 (24.1)
5–6	655 (14.7)	1979 (10.1)
7–8	316 (7.1)	732 (4.1)
≥9	237 (5.3)	551 (3.1)
Current HF medication[b], *N* (%)		
ACE inhibitors/ARBs	2806 (62.9)	9475 (53.2)
Beta-blockers	2669 (56.8)	8888 (49.9)
MRAs	1036 (23.2)	3269 (18.4)
Loop diuretics	1925 (43.1)	4707 (26.4)

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SD, standard deviation; TIA, transient ischaemic attack.
We matched each HF patient with incident AF with up to four referents on age at diagnosis of HF, sex, and time since diagnosis of HF. Characteristics were collected at the time of AF diagnosis or corresponding age for referents, except alcohol use, smoking, LVEF, and NYHA, which were collected around the time of HF diagnosis. Missing, *N* (%): income 36 (0.2%); education: 913 (4.1); alcohol consumption: 3164 (14.2); smoking: 2010 (9.3); LVEF: 506 (2.3); and NYHA: 2012 (9.0).
[a]Defined by the International Classification of Diseases codes.
[b]Defined as fulfilling at least one prescription within 6 months prior to the index date, except loop diuretics for which the period was 3 months. Modified CCI did not include AIDS.

Total hospital bed-day use

During the initial 30 days after AF, AF cases spent 8.5% of risk-days as hospital inpatients, while the proportion was 0.9% for referents (*Table 4*). The multivariable-adjusted ratio of proportions was 10.9 (95% CI 9.3–12.9). At 1 year, the proportion of days was 5.8% among AF cases and 1.1% among referents. The multivariable-adjusted ratio of proportions was 5.3 (95% CI 4.3–6.4).

Subgroup and supplementary analyses

In the sex-specific analysis (Supporting Information, *Table S6*), we found evidence of a higher cumulative incidence

Figure 1 Cumulative incidence of first hospital contact after index date. The cumulative incidence accounted for the competing risk of death. AF, atrial fibrillation; HF, heart failure.

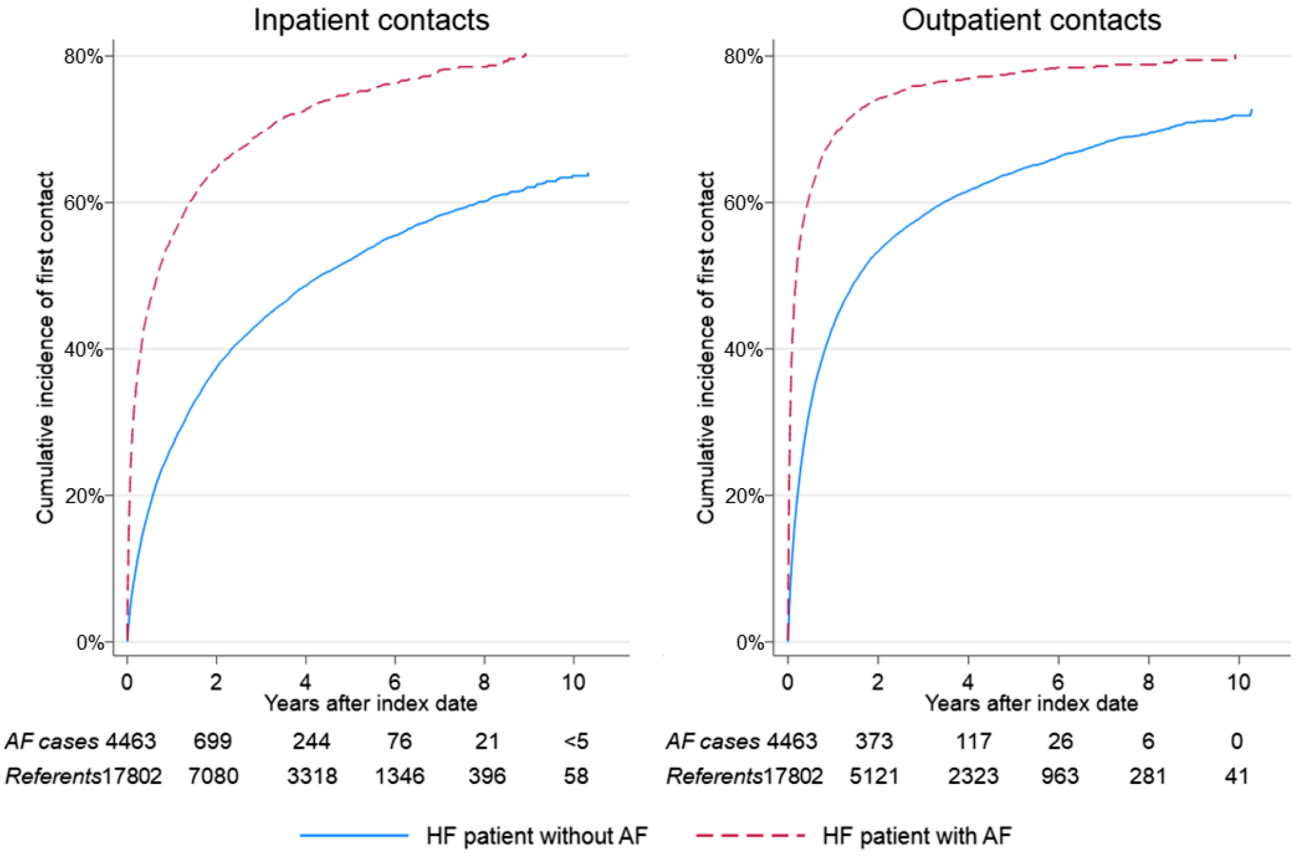

Table 2 Incident AF and time to first hospital contact

	Inpatient contact			Outpatient contact		
	Cumulative incidence, % (95% CI)	Cumulative incidence ratio		Cumulative incidence, % (95% CI)	Cumulative incidence ratio	
		Model 1	Model 2		Model 1	Model 2
30 days after index date						
AF cases	25.3 (24.0–26.7)	5.36 (4.71–6.11)	4.76 (4.07–5.58)	38.3 (36.8–39.7)	4.73 (4.31–5.18)	4.33 (3.91–4.81)
Referents	5.2 (4.9–5.5)	1.00 (ref)	1.00 (ref)	10.6 (10.1–11.0)	1.00 (ref)	1.00 (ref)
1 year after index date						
AF cases	56.3 (54.8–57.9)	2.03 (1.95–2.11)	1.78 (1.71–1.85)	69.8 (69.4–69.8)	1.58 (1.54–1.62)	1.43 (1.39–1.47)
Referents	23.5 (25.8–27.1)	1.00 (ref)	1.00 (ref)	43.1 (42.4–43.9)	1.00 (ref)	1.00 (ref)

AF, atrial fibrillation; CI, confidence interval.
Model 1: adjusted for age at heart failure, time with heart failure, and sex. Model 2: adjusted as Model 1 + family income, educational level, alcohol use, smoking status, left ventricular ejection fraction, New York Heart Association class, history of myocardial infarction, history of stroke, history of diabetes, history of chronic obstructive pulmonary disease, history of hypertension, history of chronic kidney disease, history of obesity, Charlson Comorbidity Index, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, use of beta-blockers, and use of mineralocorticoid receptor antagonists.

ratio of first hospital contact for outpatients among men vs. women at 1 year (1.5, 95% CI 1.4–1.5 vs. 1.3, 95% CI 1.3–1.4, $P < 0.001$, Supporting Information, *Table S7*). Statistical evidence supported a higher rate ratio of number of inpatient contacts among women at 30 days (1.5, 95% CI 1.4–1.6 vs. 1.4, 95% CI 1.3–1.4, $P < 0.01$) and 1 year (2.4, 95% CI 2.2–2.7 vs. 2.1, 95% CI 1.9–2.2, $P = 0.002$) but not when considering outpatients care (Supporting Information, *Table S8*). There was no substantial difference between men and women in the proportion of days in hospital bed (Supporting Information, *Table S9*).

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Table 3 Incident AF and number of hospital contacts

	Inpatient contacts			Outpatient contacts		
	Number of contacts per 1000 risk-days (95% CI)	Rate ratio (95% CI)		Number of contacts per 1000 risk-days (95% CI)	Rate ratio (95% CI)	
		Model 1	Model 2		Model 1	Model 2
30 days after index date						
AF cases	28.1 (27.1–29.1)	1.42 (1.36–1.47)	1.41 (1.36–1.47)	30.3 (29.4–31.3)	1.62 (1.57–1.68)	1.63 (1.57–1.68)
Referents	19.9 (19.6–20.2)	1.00 (ref)	1.00 (ref)	18.7 (18.5–19.0)	1.00 (ref)	1.00 (ref)
1 year after index date						
AF cases	8.8 (8.4–9.3)	2.39 (2.28–2.51)	2.16 (2.06–2.27)	10.6 (10.2–11.0)	2.13 (2.05–2.22)	1.97 (1.89–2.05)
Referents	3.7 (3.6–3.8)	1.00 (ref)	1.00 (ref)	4.9 (4.9–5.0)	1.00 (ref)	1.00 (ref)

AF, atrial fibrillation; CI, confidence interval.
Model 1: adjusted for age at heart failure, time with heart failure, and sex. Model 2: adjusted as Model 1 + family income, educational level, alcohol use, smoking status, left ventricular ejection fraction, New York Heart Association class, history of myocardial infarction, history of stroke, history of diabetes, history of chronic obstructive pulmonary disease, history of hypertension, history of chronic kidney disease, history of obesity, Charlson Comorbidity Index, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, use of beta-blockers, and use of mineralocorticoid receptor antagonists. Outpatient contacts within 30 days: one patient with four referents was excluded because of an unlikely high number of hospital contacts within 30 days.

Table 4 Incident AF and proportion of days spent in hospital bed

	Proportion of days spent in a hospital bed, % (95% CI)	Ratio of proportions (95% CI)	
		Model 1	Model 2
30 days after index date			
AF cases	8.5 (7.5–9.5)	10.36 (8.81–12.18)	10.94 (9.25–12.94)
Referents	0.9 (0.8–1.0)	1.00 (ref)	1.00 (ref)
1 year after index date			
AF cases	5.7 (4.8–7.0)	5.65 (4.55–7.01)	5.26 (4.32–6.40)
Referents	1.1 (1.0–1.2)	1.00 (ref)	1.00 (ref)

AF, atrial fibrillation; CI, confidence interval.
Model 1: adjusted for age at heart failure, time with heart failure, and sex. Model 2: adjusted as Model 1 + family income, educational level, alcohol use, smoking status, left ventricular ejection fraction, New York Heart Association class, history of myocardial infarction, history of stroke, history of diabetes, history of chronic obstructive pulmonary disease, history of hypertension, history of chronic kidney disease, history of obesity, Charlson Comorbidity Index, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, use of beta-blockers, and use of mineralocorticoid receptor antagonists.

In the age-stratified analysis (sample characteristics, Supporting Information, *Table S10*), we found statistical evidence of a higher cumulative incidence ratio of first hospital contact among the younger age group at 1 year for both inpatients (1.9, 95% CI 1.8–2.1 vs. 1.6, 95% CI 1.5–1.7, $P < 0.001$) and outpatients (1.5, 95% CI 1.4–1.5 vs. 1.4, 95% CI 1.3–1.4, $P = 0.02$), and we noted no substantial differences at 30 days (Supporting Information, *Table S11*). We found statistical evidence of a higher rate ratio of number of inpatient contacts at 30 days (1.5, 95% CI 1.5–1.6 vs. 1.3, 95% CI 1.2–1.4, $P < 0.001$) and 1 year (2.3, 95% CI 2.2–2.5 vs. 2.0, 95% CI 1.9–2.2, $P = 0.03$) among patients aged 75 or older, but not for outpatient contacts (Supporting Information, *Table S12*). There were no substantial differences in the analysis of days in hospital bed (Supporting Information, *Table S13*).

When stratifying by LVEF group (Supporting Information, *Table S14*), we noted no substantial differences in cumulative incidence ratios of first contact across the groups, but the statistical precision was low (Supporting Information, *Table S15*). We found no substantial difference in number of hospital contacts at 30 days or 1 year (Supporting Information, *Table S16*) nor in the analyses of bed-day use (Supporting Information, *Table S17*). In a supplemental analysis, we noted no substantial differences between patients with LVEF $\leq$ 40% and patients with LVEF <25% (Supporting Information, *Tables S18–S20*).

In the analysis of time to first contact stratified by time with HF (Supporting Information, *Table S21*), we found statistical evidence of a higher cumulative incidence ratio at 30 days among patients with HF > 1 year for both inpatient (3.5, 95% CI 2.7–4.5 vs. 8.2, 95% CI 6.3–10.9, $P < 0.001$) and outpatient care (3.3, 95% CI 2.9–3.9 vs. 6.1, 95% CI 5.1–7.2, $P < 0.001$, Supporting Information, *Table S22*). Furthermore, the cumulative incidence ratio at 1 year was also higher for patients with HF > 1 year and inpatient care (1.6, 95% CI 1.5–1.7 vs. 2.0, 95% CI 1.9–2.1, $P < 0.001$). In the analysis of number of contacts, we found evidence of a higher rate ratio at 30 days among patients with

HF $\leq$ 1 year for inpatient (1.5, 95% CI 1.4–1.6 vs. 1.4, 95% CI 1.3–1.4, P = 0.03) and outpatient care (1.7, 95% CI 1.6–1.8 vs. 1.5, 95% CI 1.5–1.6, $P < 0.001$, Supporting Information, *Table S23*). At 1 year, the rate ratio was higher among patients with HF $\leq$ 1 year for inpatient care (1.9, 95% CI 1.8–2.1 vs. 2.0, 95% CI 1.9–1.2, P = 0.002). There was evidence of a higher ratio of proportions of bed-days for patients with HF $>$ 1 year at 30 days (7.8, 95% CI 6.5–9.2 vs. 16.2, 95% CI 12.2–21.4, $P < 0.001$) and 1 year (3.5, 95% CI 3.1–4.1 vs. 7.5, 95% CI 5.3–10.5, $P < 0.001$, Supporting Information, *Table S24*).

In the analysis stratified by highest educational level (Supporting Information, *Table S25*), we noted no substantial differences across the groups (Supporting Information, *Table S26*). In the analysis of number of hospital contacts, we noted a lower rate ratio among patients with the highest level of education at 30 days for inpatient care (Group 1: 1.5, 95% CI 1.4–1.6 vs. Group 2: 1.4, 95% CI 1.3–1.5 vs. Group 3: 1.3, 95% CI 1.2–1.4, Supporting Information, *Table S27*). At 30 days, the proportion of days spent in hospital bed was higher among patients in Group 3 (Group 1: 9.9, 95% CI 8.1–12.1 vs. Group 2: 11.2, 95% CI 8.8–14.3 vs. Group 3: 23.0, 95% CI 15.3–37.7), but the statistical precision was low (Supporting Information, *Table S28*).

In an analysis stratified by inpatient/outpatient registration of AF, the results showed that patients diagnosed with AF in inpatient settings had shorter time to first hospital contact, had more hospital contacts, and spent more time in hospital bed (Supporting Information, *Tables S29–S34*).

We performed an additional analysis, in which we examined HF-related contacts, defined as all ICD-10 I50 contacts. We noted that incident AF was associated with increased rate of HF-related hospital contact, larger number of HF-related hospital contacts, and increased proportion of HF-related days spent in hospital bed (Supporting Information, *Tables S35–S37*).

Discussion

In this nationwide study of patients with incident HF, we found that incident AF was associated with considerable increases in hospital utilization, particularly within the initial 30 days after the diagnosis. After 30 days of follow-up, incident AF was associated with an almost 5-fold increased risk of at least one inpatient contact, an ~4-fold increased risk of at least one outpatient contact, a 41% increase in number of inpatient contacts, a 63% increase in number of outpatient contacts, and an ~11-fold increase in hospital bed-day use. At 1 year, incident AF was associated with an ~4-fold increased risk of at least one inpatient contact, a 43% increased risk of at least one outpatient contact, an ~2-fold increase in respective numbers of inpatient and outpatient contacts, and >5-fold increase in bed-day use. In our subgroup analyses, we found statistical evidence of higher risk of first outpatient contact among men at 1 year, higher risk of first hospital contact among the younger patients at 1 year, and a higher number of inpatient contacts among women and patients aged 75 years or older at both 30 days and 1 year. Additionally, patients with HF for more than 1 year had higher risk of first hospital contact and higher utilization of bed-days, but the number of hospital contacts was higher for patients with HF for up to 1 year. We noted no differences of clinical significance by baseline LVEF and educational level. Our analysis of oral anticoagulant use showed that only about half of the patients redeemed a prescription of oral anticoagulant within 3 months after AF, but the proportion increased by almost 10 percentage points in the study period.

A diagnosis of incident AF in HF is likely a risk marker that represents several interrelated clinical and non-clinical aspects rather than being a strong causal factor for hospital needs *per se*. First, incident AF may represent progression of HF disease associated with clinical and haemodynamic deterioration, such as pulmonary congestion and/or hypotension, and AF may be diagnosed before or after acute decompensation. Second, HF and AF share several risk factors, such as hypertension, obesity, and ischaemic heart disease, and incident AF may mark the intensity and/or the duration of exposure. Third, frailty and prevalent AF commonly coexist,[19–21] and incident AF may be a manifestation of decreased physiological reserve or a consequence of frailty-related diagnostic evaluation. Frailty in AF is associated with high mortality[19,22]; however, no study has to our knowledge examined the association between frailty and hospital utilization in AF. Fourth, HF patients often suffer from multimorbidity, which may lead to frequent hospital contact and earlier detection of undiagnosed AF.

Data on hospital utilization associated with incident AF in HF are sparse. Results from the Beta-blocker Evaluation of Survival Trial have shown that incident AF was associated an ~2-fold increase in all-cause hospitalizations measured as days per patient.[23] However, hospitalization days did not account for the risk time pertained to each patient, and the analysis was not based on real-world data. Analyses of the HF Long-Term Registry of European Society of Cardiology showed that prevalent AF was associated with HF hospitalizations with the following hazard ratios by LVEF: 1.04 (95% CI 0.89–1.21) if LVEF $<$ 40%, 1.43 (95% CI 1.09–1.88) if LVEF 40–49%, and 1.49 (95% CI 1.20–1.85) if LVEF $\geq$ 50%.[24] However, information on AF was limited to a prevalent disease, and it is likely that such patients represent a preselected survivor group. Moreover, information of HF hospitalizations was only available for 84% of the study participants. Finally, the definition of HF hospitalization only included the first event during follow-up and did not reflect the total burden.

Analyses based on data from the PARADIGM-HF study reported that incident AF in HF was associated with a hazard

ratio of 2.11 (95% CI 1.58–2.81) for HF hospitalization.[25] Based on data from the CHARM trial, incident AF was associated HF hospitalization both among patients with preserved ejection fraction (LVEF $>$ 40%) and patients with low ejection fraction (LVEF $<$ 40).[26] A study based on data from the COMET trial has reported an association between baseline AF and the composite of hospitalizations and death.[27] However, the analyses from PARADIGM-HF and CHARM did not include other reasons for hospitalizations, such as AF-related contacts. None of the studies included separate data on outpatient contacts. Furthermore, the analyses only included first HF hospitalization.

Our results demonstrated important time-related insights into the clinical course. Strength of the association between incident AF and the risk of having at least one contact attenuated from 30 days to 1 year. Furthermore, the association with days spent in hospital bed declined substantially at 1 year of follow-up. However, the respective number of inpatient and outpatient contacts increased from 30 days to 1 year. Our data suggest that most incident AF patients rapidly needed hospital contact that often requires admission for several days, and the number of contacts was higher after 30 days up to 1 year but with fewer bed-days. The distinction between inpatient and outpatient care is important because the location of care represents the severity of disease, as the prognosis associated with inpatients with HF is poor,[28] and the economic costs are higher for inpatient care among HF patients worldwide.[29] We observed a higher risk of at least one inpatient contact at 1 year and a higher number of outpatient contacts at 30 days.

Our study demonstrates that incident AF constitutes a substantial disease burden among patients with HF from a short-term and long-term perspective. The high proportion of patients that develops AF after HF place demands on health service resources. The high numbers of excess hospital contacts and days spent in hospital bed are central to inform policy decisions and planning of strategies to improve care pathways and expectedly reduce strain on healthcare. National spending data from the USA in 2016 have shown that the healthcare spending of HF was $51.2bn for inpatient care and $6.9bn for outpatient care, whereas the spending of AF and atrial flutter was $29.8bn for inpatient care and $29.4bn for outpatient care.[30] However, the economic burden of incident AF in HF is yet unclarified and still needs examination to complement decisions.

Our results also underline the importance of identifying targets for preventive efforts of AF in HF. AF and HF have complex interrelations, with both conditions sharing risk factors and adverse prognosis, and both conditions predisposing to each other. We have recently reported analysing observational data that HF patients that received guideline-based care of high quality have lower risk of incident AF.[31] As recently underscored in a National Heart, Lung, and Blood Institute research statement, there is an imperative to investigate strategies for diagnosing and preventing AF in individuals with HF.[32] For instance, after a diagnosis of HF, there is uncertainty regarding the most appropriate strategies to screen for AF, and it is unclear whether early detection of asymptomatic AF will prevent hospitalizations and complications and reduce mortality rate. Further, the evidence base to prevent AF, particularly in individuals with HF with preserved LVEF, is lacking. The excess hospital utilization in HF patients with new-onset AF provides further motivation to pursue randomized controlled trials of standard and novel treatments to prevent AF in patients with HF in the setting of reduced and preserved LVEF. Incident AF in HF may also suggest the need to optimize and/or intensify medical treatment for HF. In a recent scientific statement on HF patients with reduced LVEF and AF, the American Heart Association underscores that the treatment strategy should include maximally tolerated guideline-directed HF therapy and lifestyle and aggressive risk factor management, in addition to therapy targeted for AF.[33]

Limitations

When excluding patients with history of AF at the diagnosis of HF, we missed patients with AF whose diagnosis was not recorded in the registries. The time of the development of AF may be wrong, as we only have information on the time of the diagnosis, a point in time that could mark symptom worsening or onset of another morbidity. Furthermore, we were unable to classify the type of AF. Information on clinical characteristics including LVEF was ascertained at the diagnosis of HF and may have changed over years.

As we analysed observational, non-randomized, data; we cannot prove causal relations. Even though we included and adjusted for several important covariates, we cannot rule out residual confounding. For instance, we were unable to adjust for body mass index, severity of concomitant disease, systolic blood pressure, natriuretic peptides, and measures of renal function.

Lastly, generalizability may be limited by the rather restrictive inclusion and exclusion criteria of the DHFR and the fact that the population consisted mainly of European ancestry. The prevalence of HF with preserved LVEF was lower in our study than reported in most population- or community-based studies. For example, the Framingham Heart Study has demonstrated a higher burden of prevalent AF among HF patients with preserved LVEF and that may account for the lower proportion of patients with preserved LVEF.[8] Furthermore, different care practices and organizations between countries may influence whether patients are referred to inpatient or outpatient care. The low proportion of users of loop diuretics may reflect mild disease and thereby reduce the generalizability of our findings.

Conclusions

This study underscores that incident AF in HF patients is associated with a high level of inpatient and outpatient hospital service utilization. Patients with incident AF have a shorter time to first hospital contact, more hospital contacts, and greater utilization of hospital bed-days. The high proportion of patients that develop AF after HF places demands on health service resources. Future studies need to address the screening and prevention of AF in HF and optimization of care pathways.

Conflict of interest

N.V., P.C., E.J.B., L.T., and S.P.J. declared no conflicts of interest. G.Y.H.L. is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. No fees are received personally. L.F. is an advisory board for Pfizer, BMS, and MSD.

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Supporting information

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

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References

1. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, Younis A, Dai H. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol* 2021. https://doi.org/10.1093/eurjpc/zwaa147
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG, American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**: 606–619.
3. Danielsen R, Thorgeirsson G, Einarsson H, Olafsson O, Aspelund T, Harris TB, Launer L, Gudnason V. Prevalence of heart failure in the elderly and future projections: the AGES-Reykjavik study. *Scand Cardiovasc J* 2017; **51**: 183–189.
4. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure: the Rotterdam Study. *Eur Heart J* 2004; **25**: 1614–1619.
5. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D, Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002; **106**: 3068–3072.
6. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, Grobbee DE. The prognosis of heart failure in the general population. The Rotterdam Study. *Eur Heart J* 2001; **22**: 1318–1327.
7. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner L, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation* 2020; **141**: e139–e596.
8. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016; **133**: 484–492.
9. Martín-Pérez M, Ruigómez A, Michel A, García Rodríguez LA. Incidence and risk factors for atrial fibrillation in patients with newly diagnosed heart failure. *J Cardiovasc Med (Hagerstown)* 2016; **17**: 608–615.
10. Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. *Circ Heart Fail* 2011; **4**: 740–746.
11. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011; **4**: 313–320.
12. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, Shah N, Chothani A, Savani GT, Mehta K, Parikh V, Rathod A, Badheka AO, Lafferty J, Kowalski M, Mehta JL, Mitrani RD, Viles-Gonzalez JF, Paydak H. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation* 2014; **129**: 2371–2379.
13. Schjodt I, Nakano A, Egstrup K, Cerqueira C. The Danish Heart Failure Registry. *Clin Epidemiol* 2016; **8**: 497–502.
14. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**: 30–33.
15. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**: 38–41.
16. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7**: 449–490.
17. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association. *Eur J Heart Fail* 2021; **23**: 352–380.
18. Parner ET, Andersen PK. Regression analysis of censored data using pseudo-observations. *Stata J* 2010; **10**: 408–422.
19. Wilkinson C, Clegg A, Todd O, Rockwood K, Yadegarfar ME, Gale CP, Hall M. Atrial fibrillation and oral anticoagulation in older people with frailty: a nationwide primary care electronic health records cohort study. *Age Ageing* 2020; **50**: 772–779.
20. Newman AB, Gottdiener JS, McBurnie MA, Hirsch CH, Kop WJ, Tracy R, Walston JD, Fried LP. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M158–M166.
21. Nadruz W Jr, Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, Griswold ME, Wagenknecht LE, Heiss G, Solomon SD, Skali H. Cardiovascular dysfunction and frailty among older adults in the community: the ARIC

study. *J Gerontol A Biol Sci Med Sci* 2017; **72**: 958–964.
22. Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. *Age Ageing* 2018; **48**: 196–203.
23. Aleong RG, Sauer WH, Davis G, Bristow MR. New-onset atrial fibrillation predicts heart failure progression. *Am J Med* 2014; **127**: 963–971.
24. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, de Mora Martin M, Polonski L, Silva-Cardoso J, Amir O, ESC-HFA HF Long-Term Registry Investigators. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018; **39**: 4277–4284.
25. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray J, PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2017; **70**: 2490–2500.
26. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA, CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006; **47**: 1997–2004.
27. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005; **26**: 1303–1308.
28. Ferreira JP, Metra M, Mordi I, Gregson J, Ter Maaten JM, Tromp J, Anker SD, Dickstein K, Hillege HL, Ng LL, van Veldhuisen DJ. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. *Eur J Heart Fail* 2019; **21**: 112–120.
29. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. *BMC Cardiovasc Disord* 2018; **18**: 74.
30. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, Bui AL, Campbell M, Duber HC, Dunn AC, Flaxman AD, Fitzmaurice C, Naghavi M, Sadat N, Shieh P, Squires E, Yeung K, Murray CJL. US health care spending by payer and health condition, 1996–2016. *JAMA* 2020; **323**: 863–884.
31. Vinter N, Cordsen P, Fenger-Grøn M, Lip GYH, Benjamin EJ, Frost L, Johnsen SP. Quality of care and risk of incident atrial fibrillation in patients with newly diagnosed heart failure: a nationwide cohort study. *Eur Heart J Qual Care Clin Outcomes* 2021. https://doi.org/10.1093/ehjqcco/qcab036
32. Al-Khatib SM, Benjamin EJ, Albert CM, Alonso A, Chauhan C, Chen PS, Curtis AB, Desvigne-Nickens P, Ho JE, Lam CS, Link MS. Advancing research on the complex interrelations between atrial fibrillation and heart failure: a report from a US National Heart, Lung, and Blood Institute virtual workshop. *Circulation* 2020; **141**: 1915–1926.
33. Gopinathannair R, Chen LY, Chung MK, Cornwell WK, Furie KL, Lakkireddy DR, Marrouche NF, Natale A, Olshansky B, Joglar JA. Managing atrial fibrillation in patients with heart failure and reduced ejection fraction: a scientific statement from the American Heart Association. *Circ Arrhythm Electrophysiol* 2021; **14**: e000078.