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Original article

The association between relevant co-morbidities and prevalent as well as incident heart failure in patients with atrial fibrillation

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ABSTRACT

Background: Congestive heart failure (CHF) is a serious complication in patients with atrial fibrillation (AF).
Objective: To study associations between relevant co-morbidities and CHF in patients with AF.
Methods: Study population included all adults (n = 12,283) ≥45 years diagnosed with AF at 75 primary care centers in Sweden 2001–2007. Logistic regression was used to calculate odds ratios with 95% confidence intervals (CIs) for the associations between co-morbidities, and prevalent CHF. In a subsample (n = 9424), (excluding patients with earlier CHF), Cox regression was used to estimate hazard ratios with 95% CIs for the association between co-morbidities, and a first hospital diagnosis of CHF, after adjustment for age and socio-economic factors.
Results: During 5.4 years' follow-up (standard deviation 2.5), 2259 patients (24.0%; 1135 men, 21.8%, and 1124 women, 26.7%) were diagnosed with CHF. Patients with hypertension were less likely to have CHF, while a diagnosis of coronary heart disease, valvular heart disease, diabetes, or chronic obstructive pulmonary disease (COPD), was consistently associated with CHF among men and women. CHF was more common among women with depression. The relative fully adjusted risk of incident CHF was increased for the following diseases in men with AF: valvular heart disease, cardiomyopathy, and diabetes; and for the following diseases in women: valvular heart disease, diabetes, obesity, and COPD. The corresponding risk was decreased among women for hypertension.
Conclusions: In this clinical setting we found hypertension to be associated with a decreased risk of CHF among women; valvular heart disease and diabetes to be associated with an increased risk of CHF in both sexes; and cardiomyopathy to be associated with an increased risk of CHF among men.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the population, with a prevalence of 2% in Sweden, defined as a recorded diagnoses in the nationwide patient register [1]. Even if ischemic stroke is the most important complication among patients with AF [2], i.e. with a five times higher risk compared to individuals without AF [3], there are also other risks with AF. Congestive heart failure (CHF) and AF are interrelated [4,5], with CHF being three times more common among AF patients compared to non-AF individuals [6]. Among elderly, CHF is the most common cardiovascular disease (CVD) [7], and, according to a recent study in the USA, the development of CHF after a diagnosis of AF has not declined over time [8]. Furthermore, CHF in AF patients is also associated with an increased mortality [6], with one study finding

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a doubled mortality compared to AF patients without CHF [8]. CHF is also the most common cause of death among AF patients, corresponding to 30% of deaths [9].

AF is also associated with other CVDs. Coronary heart disease (CHD) is a common comorbidity in AF [10], as well as an important risk factor for both CHF [11], and mortality [12] among AF patients. In a Japanese study, the existence of structural heart disease, i.e. myocardial infarction, valvular heart disease, and cardiomyopathy, was found to be the only predictive factor for development of CHF among AF patients [13]. In a study of women with AF in the USA, modifiable risk factors such as obesity, hypertension, smoking, and diabetes accounted for the majority of the female population's risk of incident CHF [14]. In addition, hypertension is common in AF and also regarded as a risk factor for future CHF [15]. Additionally, some respiratory diseases are associated with AF, i.e. chronic obstructive pulmonary disease (COPD) [16,17], and obstructive sleep apnea [18], and with CHF [19,20]. Furthermore, the rate of CHF among AF patients varies in different countries, and other than clinical factors seems to be of importance for the development of CHF [9].

Thus, it is important to study risk factors for the development of CHF in patients with AF. Actually, one study in the USA found a 2-fold higher rate of CHF than those of stroke or transient ischemic attack (TIA) [8], suggesting why it is possible that prevention of CHF needs to be prioritized in AF treatment as much as the prevention of ischemic stroke.

There are also gender differences as regards to AF, with AF being more common among men [1], and being diagnosed on average five years earlier among men than among women [21]. On the other hand, women with AF exhibit both a higher risk of stroke as well as of mortality than men with AF [22]. Thus, it is important to analyze men and women separately.

CHF could be prevented in AF, provided that the relevant risk factors are known, and under the hypothesis that cardiovascular co-morbidities and sociodemographic factors are important for the development of CHF. The aims herein were therefore to study the association between relevant co-morbidities and CHF among men and women with AF in Swedish primary care, and to study factors associated with a first hospital diagnosis of CHF among patients with AF who still had not developed CHF. We hypothesized that both co-morbid CVD conditions, such as hypertension, CHD, valvular heart disease, cardiomyopathy, and cerebrovascular diseases, as well as other important diseases, including diabetes, depression and anxiety, and socio-demographic factors, could affect the risk of incident CHF in AF patients.

Methods

Design

The study used individual-level patient data from 75 primary health care centers (PHCCs), 48 of which were located in Stockholm County. Individuals attending any of the participating PHCCs between 2001 and 2008 were included in the study. We used *Extractor* software (http://www.slso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx; accessed September 19, 2010) to extract individual electronic patient records (EPRs). National identification numbers were replaced with new unique serial numbers to ensure anonymity. The files were linked to a dataset including data from the Total Population Register, the National Patient Register (NPR), and the Swedish Cause of Death Register, which contains individual-level data on age, sex, education, cause of death, and hospital diagnosis for all residents registered in Sweden. Thus, a new research dataset containing clinical data and information on socioeconomic status on the individuals (n = 1,098,420) registered at the 75 PHCCs was created. Data from the Cause of Death Register were used for the follow-up.

The investigation conforms with the principles outlined in the Declaration of Helsinki. Ethical approvals were obtained from regional boards at Karolinska Institutet and the University of Lund.

Study population

The study included all patients with diagnosed AF, identified by the presence of the ICD-10 code (10th version of the World Health Organization's International Classification of Diseases) for atrial fibrillation (I48) in patients' medical records at the PHCCs. The following cardiovascular-related disorders were used as covariates: hypertension, CHD, cerebrovascular diseases (CVD), and diabetes mellitus (for specific codes, see below). Patients with CHF during the study period were identified in two ways, either through a diagnosis in the EPR in the PHCC or through a hospital diagnosis. In total, 12,283 individuals (6646 men and 5637 women), aged 45 years or older at the time of AF diagnosis and who visited any of the 75 participating PHCCs from January 1, 2001, until December 31, 2007, with data on neighborhood socioeconomic status available, were included in the study. In the subset studying first hospital CHF diagnosis, patients with an earlier CHF were excluded (n = 2859), yielding 9424 patients (5211 men and 4213 women) in the analysis.

Outcome variable

For logistic regression: prevalent CHF. For Cox and Laplace regression: time from first AF diagnosis to first hospital diagnosis of CHF (until December 31, 2010).

Demographic and socio-economic variables

Sex was stratified into men and women.

Individuals were divided into the following *age groups* 45–54, 55–64, 65–74, 75–84, and ≥85 years. Individuals younger than 45 years were excluded.

Educational level was categorized as ≤9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling), and >12 years (college and/or university studies).

Marital status was classified as married, unmarried, divorced, or widowed.

Neighborhood socioeconomic status (SES) was categorized into three groups according to the neighborhood index: more than one standard deviation (SD) below the mean (high SES or low deprivation), more than one SD above the mean (low SES or high deprivation), and within one SD of the mean (middle SES or deprivation). The neighborhood index was based derived from the following four variables: low educational status (<10 years of formal education), low income (<50% of the median individual income from all sources), unemployment, and receipt of social welfare. The neighborhood deprivation index was categorized into three groups: more than one standard deviation (SD) below the mean (high SES or low deprivation level), more than one SD above the mean (low SES or high deprivation level), and within one SD of the mean (moderate SES or moderate deprivation level).

Co-morbidities

We identified the following cardiovascular co-morbidities from the EPRs among the individuals in the study population: hypertension (I10–15); CHD (I20–25), also including registered hospitalizations for myocardial infarction from the NPR; CHF (I50 or I110), also including hospitalizations for CHF from the NPR; non-rheumatic valvular diseases (I34–38); cardiomyopathy (I42); CVD (I60-69), also including registered hospitalizations for

ischemic or hemorrhagic stroke from the NPR; diabetes mellitus (E10–14); obesity (E65–E68); COPD (J40–J47); obstructive sleep apnea syndrome (G47); depression (F32–F34, F38–F39); and anxiety disorders (F40–41). No diagnosis of rheumatic valvular diseases (I05–08) was recorded.

Results were also estimated by CHA_2DS_2-VASc scores, however after omitting the CHF item, with scores between 0 and 7 for men, and 1 and 8 for women.

Statistical analyses

Analyses were performed stratified by sex. Differences in means and distributions between individuals with or without CHF were compared by Student's *t*-test, chi-square analysis, and Fisher's exact test. Age-adjustment for co-morbidity was performed by logistic regression, and for marital status and socio-economic factors by ANCOVA.

For individuals with prevalent CHF, i.e. earlier or newly diagnosed, multivariate logistic regression was performed to study the associations with background factors (n = 11,659, with data missing on marital status in 51 and educational level in 1042 individuals). A significant interaction was found regarding marital status and sex.

For patients with incident CHF, excluding those with a CHF diagnosis before the first registered AF diagnosis (n = 2859), follow-up analyses were performed, firstly by using Cox regression estimating hazard ratios (HRs) with 95% confidence intervals (CIs), using time to the first hospital diagnosis of CHF as the outcome (n = 9424). Secondly, Laplace regression was used to calculate the difference in years until the first 25% had had a first hospital diagnosis of CHF [23]. As a consequence of this approach, different distributions and calculations were used to obtain estimates from both Cox and Laplace regression. Thus, we considered the results to be more robust when findings were statistically significant with both methods. The regression models were also tested for possible interactions, and a significant interaction was found between sex and hypertension. All models were presented stratified by sex. The Cox and Laplace regression models were adjusted for the following variables in separate models: age, socio-demographic factors (educational level, marital status, and neighborhood socio-economic status), co-morbidities (hypertension, CHD, valvular heart disease, cardiomyopathy, diabetes, obesity, COPD, obstructive sleep apnea syndrome, depression, and anxiety). In the fully adjusted models, only those co-morbidities that were significantly associated with the outcome for either men or women (in models adjusted for age and socio-demographic factors) were included.

Results for newly diagnosed CHF were also calculated including CHA_2DS_2-VASc scores, with incidence rates per 100 patient-years, and trend analysis by Cuzick's non-parametric trend test, stratified by sex.

A p-value for two-sided tests of <0.01 was considered statistically significant in baseline comparisons due to the multiple comparisons between men and women. A two-sided p-value of <0.05 was considered statistically significant for variables in the logistic regression, Cox regression, and Laplace regression analyses. All analyses were performed in STATA 11.2 (StataCorp, College Station, TX, USA), with an amendment for Laplace regression provided by Professor Bottai [23].

Results

Characteristics of the entire study population consisting of patients with AF (n = 12,283), stratified by sex (6646 men and 5637 women), and into those with a diagnosis of CHF (yes/no) are shown in Table 1.

Odds from the multivariate logistic regression models of the association with prevalent CHF are shown in Table 2, stratified by sex, and also stratified by age group, i.e. 45–74 years and ≥75 years. Lower ORs were found for the highest educational level among both men and women, but when stratified by age only among men and women <75 years of age. A significant interaction was found regarding marital status and sex. CHF was more common among unmarried, divorced, or widowed men than in married men. However, CHF was not significantly more common in divorced men aged ≥75 years, and no significant differences were found among women with different marital status. CHF was more common among women living in low SES neighborhoods. CHF was significantly less common among men and women with hypertension in all analyses, including both age categories, i.e. 45–74 years and ≥75 years. CHF was consistently more common in those with valvular heart disease, CVD, and diabetes in both men and women and both in age-groups 45–74 years, and ≥75 years, while for cardiomyopathy this was not the case in the age category ≥75 years. CHF was also more common among women with obesity and sleep apnea disorder, but not significantly more common among women aged ≥75 years. COPD was consistently more common in both men and women with CHF.

In the analysis of incident CHF, i.e. a first hospital diagnosis of CHF, excluding patients with a recorded earlier CHF (n = 2859), the study sample consisted of 9424 individuals (5211 men and 4213 women). In total, 2259 patients (24.0%) were diagnosed with CHF during the follow-up of whom 1135 were men (21.8%) and 1124 were women (26.7%). The mean follow-up time until first hospital diagnosis of CHF in those without previous CHF was 5.4 years (standard deviation 2.5). Patients were followed for a total of 51,228 person-years: 28,974 person-years for men and 22,254 person-years for women.

The risks of a first hospital diagnosis for CHF are shown in Table 3. Time until the first 25% of patients were diagnosed with incident CHF are shown in Table 4. After adjustments for age, socio-demographic factors, and co-morbidities, an increased risk both for a first hospitalization and a shorter time until the first 25% had been diagnosed with CHF was found in men with valvular heart disease, cardiomyopathy, diabetes, COPD, or obstructive sleep apnea syndrome and, in women, with valvular heart disease, diabetes, or COPD. Among women with obesity, Cox regression showed a significantly increased risk for CHF albeit with no significant result when using Laplace regression. Among women with cardiomyopathy or obstructive sleep apnea syndrome a significantly shorter time until 25% had been diagnosed with CHF was found, albeit with a non-significant increased risk in Cox regression. Women with hypertension had a reduced risk of a hospital diagnosis for CHF and an increased time to a first hospital diagnosis for CHF.

Results were also estimated for a first hospital diagnosis of CHF by CHA_2DS_2-VASc score, showing a statistically significant trend for men and women (Table 5), and with incidence rates per 100 person-years of 3.92 (95% CI 3.70–4.15) for men, and 5.05 (95% CI 4.76–5.35) for women.

Discussion

The main finding of this study was the different risk factor patterns between men and women for incident CHF, defined as a first hospital diagnosis of CHF, with hypertension seeming to decrease the risk of CHF among women but not among men. In contrast, cardiomyopathy was associated with an increased risk of CHF in men but not in women (even if no significant interactions by gender were noted). Valvular heart disease, diabetes, and COPD were significantly associated with incident CHF in both men and women with AF. Obstructive sleep apnea syndrome was also

Table 1
Data for patients aged ≥45 years with diagnoses of atrial fibrillation ($N = 12,283$), and with or without congestive heart failure at baseline in primary care attending the 75 primary health care centers between January 1st 2001 and December 31st 2007.

	Men				Women			
	($N = 6646$)		Difference p-Values		($N = 5637$)		Difference p-values	
Number of patients	No CHF $n = 3790$ (57.0%)	CHF $n = 2856$ (43.0%)	Crude	Age-adjusted	No CHF $n = 2809$ (49.8%)	CHF $n = 2828$ (50.2%)	Crude	Age-adjusted
Number of deaths	687 (18.1%)	1296 (45.4)	<0.001	<0.001	600 (21.4)	1371 (48.5)	<0.001	<0.001
Age (years), mean (SD)	70.0 (10.1)	75.0 (9.5)	<0.001	-	74.6 (9.7)	79.6 (8.1)	<0.001	–
Age groups (years)			<0.001	-			<0.001	–
45–54	280 (7.4)	90 (3.2)			86 (3.1)	19 (0.7)		
55–64	885 (23.4)	337 (11.8)			386 (13.7)	135 (4.8)		
65–74	1259 (33.2)	783 (27.4)			791 (28.2)	475 (16.8)		
75–79	645 (17.0)	612 (21.4)			565 (20.1)	605 (21.4)		
80–84	481 (12.7)	602 (21.1)			551 (19.6)	813 (28.8)		
≥85	240 (6.3)	432 (15.1)			430 (15.3)	781 (27.6)		
Educational level			<0.001	<0.001			<0.001	<0.001
Compulsory schooling	1334 (36.4)	1152 (43.9)			1239 (47.6)	1360 (57.9)		
Secondary schooling	1400 (38.2)	967 (36.9)			915 (35.2)	713 (30.4)		
College and/or university studies	932 (25.4)	505 (19.3)			449 (17.3)	275 (11.7)		
Marital status			<0.001	<0.001			<0.001	<0.001
Married	2410 (63.8)	1540 (54.2)			987 (35.3)	676 (24.0)		
Unmarried	340 (9.0)	290 (10.2)			215 (7.7)	184 (6.5)		
Divorced	582 (15.4)	439 (15.5)			411 (14.7)	381 (13.5)		
Widowed	447 (11.8)	573 (20.2)			1184 (42.3)	1573 (55.9)		
Neighborhood SES			0.009	0.93			0.48	0.043
High	1575 (41.6)	1081 (37.9)			982 (35.0)	966 (34.2)		
Middle	1687 (44.5)	1343 (47.0)			1389 (49.5)	1388 (49.1)		
Low	528 (13.9)	432 (15.1)			438 (15.6)	474 (16.8)		
Diagnosis								
Hypertension	1650 (43.5)	1149 (40.2)	0.007	0.003	1488 (53.0)	1299 (45.9)	<0.001	<0.001
Coronary heart disease	690 (18.2)	1032 (36.1)	<0.001	<0.001	501 (17.8)	1011 (35.8)	<0.001	<0.001
Valvular heart disease	84 (2.2)	210 (7.4)	<0.001	<0.001	86 (3.1)	191 (6.8)	<0.001	<0.001
Cardiomyopathy	12 (0.3)	48 (1.7)	<0.001	<0.001	11 (0.4)	19 (0.7)	0.15	0.019
Cerebrovascular diseases	676 (17.8)	601 (21.0)	0.001	0.56	612 (21.8)	677 (23.9)	0.054	0.67
Diabetes mellitus	623 (16.4)	689 (24.1)	<0.001	<0.001	441 (15.7)	652 (23.1)	<0.001	<0.001
Obesity	201 (5.3)	151 (5.3)	0.98	<0.001	124 (4.4)	138 (4.9)	0.41	<0.001
COPD	287 (7.6)	423 (14.8)	<0.001	<0.001	267 (9.5)	439 (15.5)	<0.001	<0.001
Obstructive sleep apnea syndrome	35 (0.9)	29 (1.0)	0.70	0.16	8 (0.3)	18 (0.6)	0.051	0.010
Depression	230 (6.1)	182 (6.4)	0.61	0.56	287 (10.2)	340 (12.0)	0.031	0.010
Anxiety	100 (2.6)	83 (2.9)	0.51	0.57	151 (5.4)	162 (5.7)	0.56	0.42

Information on educational level and marital status is missing for some individuals.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; SD, standard deviation; SES, socioeconomic status.

significantly associated with incident CHF among men but not among women.

When examining associations between all patients with a prevalent diagnosis of CHF and background factors, a significant interaction was found regarding marital status and sex. Being unmarried, divorced or widowed were significantly more common in men with both AF and CHF, but non-significant in women. Among the co-morbidities, hypertension was less common in those with both AF and CHF and in both men and women. As expected, CHD, valvular heart disease, cardiomyopathy (in those under 75 years), diabetes, and COPD were more common in patients with both AF and CHF compared with patients with AF but without CHF.

As regards to incident CHF, hypertension was associated with a reduced CHF risk and a longer time until first CHF diagnosis among women but not among men. Female sex has been associated with CHF with preserved ejection fraction in AF, and an effective antihypertensive treatment could be one possible explanation to the seemingly "protective" effect of hypertension toward CHF development among women. This could be supported by findings in an earlier study where treatment with non-selective beta-blockers and angiotensin receptor blockers were associated with a reduced mortality [24]. Interestingly, left ventricular hypertrophy, often associated with hypertension, has not found to be an independent risk factor for CHF among AF patients [13]. Valvular heart disease among men and women, and cardiomyopathy among men, were associated with incident CHF in accordance with an earlier study [13]. Cardiomyopathy was not associated with incident CHF among women, which could be due to few cases and low statistical power. Diabetes was associated with incident CHF among both men and women, and is a known risk factor for both AF and CHF, including CHF in AF [8]. We found no significant effect from an earlier myocardial infarction; in contrast to the study by Fukuda et al., myocardial infarction was one of the included signs of structural heart disease of significance for incident CHF [13].

Some discrepancies between the Cox and Laplace regression models were found among women, i.e. regarding cardiomyopathy, obesity, and obstructive sleep apnea syndrome. However, as these diagnoses were seldom present, especially among women, results should be interpreted with caution.

We also found CHA_2DS_2-VASc to be related to incident CHF. CHA_2DS_2-VASc, which is intended to estimate the risk of ischemic stroke in AF patients, seems to be useful to estimate the risk of CHF as well. This represents a novel and potentially important finding that needs to be further explored.

There are several limitations of this study. The study sample is a subgroup of the AF population, i.e. patients with concomitant diagnoses of AF and CHF registered in primary health care. In another study it was found that 36% of all registered AF patients in Stockholm County were not registered with a diagnosis in primary health care [1]. Results cannot be generalized to all AF or CHF

Table 2
Multivariate logistic regression for the association between congestive heart failure and socio-economic factors and co-morbidity for patients aged ≥45 years with diagnoses of atrial fibrillation (n = 11,659) in primary care attending the 75 primary health care centers between January 1st 2001 and December 31st 2007.

Number of patients	Men			Women		
	All N = 6273 OR (95% CI)	<75 years N = 3578 OR (95% CI)	≥75 years N = 2695 OR (95% CI)	All N = 4936 OR (95% CI)	<75 years N = 1842 OR (95% CI)	≥75 years N = 3094 OR (95% CI)
Age, years	**1.05 (1.05–1.06)**	**1.04 (1.03–1.06)**	**1.06 (1.04–1.09)**	**1.07 (1.06–1.08)**	**1.06 (1.04–1.08)**	**1.05 (1.03–1.07)**
Educational level						
Compulsory schooling	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Secondary schooling	0.95 (0.84–1.08)	0.85 (0.72–1.01)	1.04 (0.86–1.25)	**0.86 (0.75–0.98)**	0.82 (0.65–1.04)	0.88 (0.74–1.04)
College and/or university studies	**0.84 (0.72–0.97)**	**0.76 (0.62–0.93)**	0.93 (0.74–1.16)	**0.80 (0.66–0.97)**	**0.71 (0.52–0.97)**	0.89 (0.69–1.14)
Marital status						
Married	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unmarried	**1.87 (1.55–2.27)**	**1.92 (1.52–2.42)**	**1.75 (1.24–2.47)**	1.26 (0.98–1.63)	1.44 (0.98–2.12)	1.10 (0.78–1.54)
Divorced	**1.38 (1.18–1.60)**	**1.49 (1.24–1.81)**	1.17 (0.90–1.53)	1.15 (0.95–1.40)	1.25 (0.94–1.67)	1.04 (0.80–1.36)
Widowed	**1.36 (1.16–1.60)**	**1.61 (1.20–2.17)**	**1.24 (1.02–1.51)**	1.13 (0.97–1.31)	1.22 (0.93–1.59)	1.05 (0.87–1.26)
Neighborhood SES						
High	0.93 (0.82–1.05)	0.91 (0.76–1.09)	0.96 (0.79–1.15)	1.11 (0.96–1.28)	1.07 (0.83–1.38)	1.14 (0.96–1.36)
Middle	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Low	1.07 (0.89–1.29)	1.19 (0.93–1.52)	0.94 (0.71–1.24)	**1.25 (1.02–1.52)**	1.19 (0.86–1.66)	1.25 (0.98–1.59)
Diagnosis						
Hypertension	**0.80 (0.71–0.89)**	**0.80 (0.69–0.94)**	**0.80 (0.68–0.94)**	**0.66 (0.59–0.75)**	**0.63 (0.50–0.78)**	**0.68 (0.58–0.79)**
Coronary heart disease	**2.11 (1.86–2.38)**	**2.16 (1.81–2.58)**	**2.04 (1.72–2.43)**	**2.25 (1.96–2.59)**	**2.23 (1.72–2.88)**	**2.25 (1.90–2.66)**
Valvular heart disease	**3.47 (2.62–4.59)**	**3.70 (2.49–5.49)**	**3.30 (2.22–4.89)**	**2.37 (1.77–3.17)**	**2.94 (1.81–4.76)**	**2.07 (1.44–2.98)**
Cardiomyopathy	**9.43 (4.81–18.47)**	**9.69 (4.79–19.58)**	5.47 (0.64–45.47)	2.24 (0.99–5.07)	**3.36 (1.09–10.28)**	1.28 (0.38–4.23)
Cerebrovascular diseases	1.09 (0.95–1.25)	**1.23 (1.00–1.51)**	0.96 (0.80–1.16)	1.11 (0.96–1.28)	1.29 (0.97–1.70)	1.06 (0.89–1.25)
Diabetes mellitus	**1.63 (1.42–1.86)**	**1.73 (1.45–2.08)**	**1.50 (1.21–1.85)**	**1.68 (1.44–1.96)**	**2.01 (1.55–2.60)**	**1.53 (1.26–1.86)**
Obesity	1.27 (0.99–1.62)	1.26 (0.96–1.66)	1.20 (0.68–2.13)	**1.79 (1.34–2.38)**	**1.87 (1.31–2.68)**	1.53 (0.95–2.47)
COPD	**1.86 (1.56–2.21)**	**1.57 (1.23–2.01)**	**2.25 (1.75–2.90)**	**1.83 (1.52–2.20)**	**2.13 (1.58–2.86)**	**1.63 (1.29–2.06)**
Obstructive sleep apnea syndrome	1.32 (0.77–2.28)	1.24 (0.68–2.28)	1.68 (0.46–6.16)	**2.86 (1.13–7.23)**	**3.93 (1.13–13.74)**	2.09 (0.53–8.19)
Depression	1.00 (0.80–1.25)	0.86 (0.63–1.19)	1.14 (0.82–1.59)	1.20 (0.98–1.45)	1.19 (0.85–1.66)	1.20 (0.94–1.53)
Anxiety	0.97 (0.69–1.36)	0.87 (0.54–1.41)	1.03 (0.63–1.68)	1.06 (0.81–1.39)	1.31 (0.84–2.05)	0.94 (0.68–1.31)

Information on educational level and marital status is missing for some individuals.
COPD, chronic obstructive pulmonary disease; SES, socioeconomic status.
Bold values are statistically significant.

patients or to patients in other settings. The findings may have been subject to confounding by indication and to survival bias [25]. All these mentioned factors could have affected the results, and yielded discrepant findings. Severity of CHF and CHD were not classified in the patient records, even if it is likely that patients from primary care had less severe CHF than patients from hospital care, and probably more often CHF with relative well-preserved ejection fraction. Patients could, however, not be classified regarding ejection fraction, where CHF with reduced ejection fraction in AF patients is associated with a higher mortality [26]. Additionally, we could not classify whether the patients had left ventricular hypertrophy or not. Furthermore, we did not have access to some other risk factors for CHF, i.e. metabolic factors such as insulin resistance or the metabolic syndrome. Moreover, a diagnosis of obesity is rarely registered in the electronic patient records, and an obesity diagnosis probably reflects a more severe

Table 3
Cox regression models (with hazard ratios and 95% confidence interval) for incident hospital diagnosis of CHF among patients aged ≥45 years with diagnoses of atrial fibrillation (n = 9424) in primary care attending the 75 primary health care centers between January 1st 2001 and December 31st 2007; patients with a known hospital episode of CHF excluded.

	Men			Women		
	Age-adjusted	Adjusted for age and socio-demography	Fully adjusted	Age-adjusted	Adjusted for age and socio-demography	Fully adjusted
Diagnosis						
Hypertension	1.11 (0.99–1.25)	1.12 (0.99–1.26)	1.08 (0.95–1.22)	**0.87 (0.77–0.98)**	**0.87 (0.76–0.98)**	**0.83 (0.73–0.95)**
Myocardial infarction	1.12 (0.91–1.37)	1.13 (0.91–1.39)	–	1.05 (0.84–1.31)	1.07 (0.84–1.37)	–
Valvular heart disease	**2.20 (1.77–2.73)**	**2.10 (1.67–2.64)**	**2.12 (1.68–2.67)**	**1.70 (1.33–2.17)**	**1.66 (1.27–2.16)**	**1.64 (1.26–2.14)**
Cardiomyopathy	**4.04 (2.28–7.17)**	**4.12 (2.32–7.31)**	**4.25 (2.39–7.56)**	2.04 (0.97–4.30)	1.62 (0.67–3.90)	1.67 (0.69–4.04)
Cerebrovascular diseases	1.00	–	–	1.00	–	–
Diabetes mellitus	**1.53 (1.34–1.75)**	**1.52 (1.32–1.75)**	**1.47 (1.27–1.69)**	**1.40 (1.21–1.61)**	**1.39 (1.19–1.61)**	**1.39 (1.19–1.62)**
Obesity	**1.43 (1.09–1.88)**	**1.34 (1.01–1.77)**	1.15 (0.86–1.52)	**1.55 (1.17–2.04)**	**1.53 (1.14–2.04)**	**1.36 (1.01–1.83)**
COPD	**1.63 (1.37–1.92)**	**1.61 (1.36–1.92)**	**1.60 (1.35–1.90)**	**1.53 (1.30–1.81)**	**1.55 (1.30–1.85)**	**1.51 (1.26–1.80)**
Obstructive sleep apnea syndrome	**2.04 (1.20–3.47)**	**2.11 (1.24–3.58)**	**1.92 (1.13–3.29)**	**2.23 (1.06–4.70)**	2.20 (0.90–5.34)	2.15 (0.88–5.25)
Depression	1.02 (0.80–1.30)	1.01 (0.79–1.30)	–	1.06 (0.88–1.27)	1.11 (0.92–1.36)	–
Anxiety	1.16 (0.83–1.62)	1.11 (0.78–1.58)	–	1.14 (0.90–1.45)	1.23 (0.96–1.58)	–

Models are harmonized to include the same variables among men and women, otherwise are non-significant variables excluded. Fully adjusted includes adjustment for age, socio-demographic and all significant co-morbidity (hypertension, valvular heart disease, cardiomyopathy, diabetes, obesity, COPD, and obstructive sleep apnea syndrome) in models adjusted for age and socio-demographic factors (educational level, marital status, and neighborhood socio-economic status). (Model check did not reveal any significant interactions in full models.)
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.
Bold values are statistically significant.

Table 4
Laplace regression models (with years gained or lost until first 25% of incident diagnosis of CHF, and 95% confidence interval) among patients aged ≥45 years with diagnoses of atrial fibrillation (n = 9424) in primary care attending the 75 primary health care centers between January 1st 2001 and December 31st 2007; patients with a known hospital episode of congestive heart failure excluded.

	Men			Women		
	Age-adjusted	Adjusted for age and socio-demography	Fully adjusted	Age-adjusted	Adjusted for age and socio-demography	Fully adjusted
Diagnosis						
Hypertension	−0.24 (−0.59; 0.11)	**−0.47 (−0.92; −0.01)**	−0.30 (−0.74; 0.13)	**0.66 (0.03; 1.30)**	**0.78 (0.28; 1.28)**	**0.80 (0.26; 1.35)**
Myocardial infarction	−0.52 (−1.68; 0.64)	−0.55 (−1.27; 0.17)	–	0.00 (−1.24; 1.24)	−0.22 (−1.25; 0.80)	–
Valvular heart disease	**−2.00 (−2.54; −1.46)**	**−2.41 (−3.29; −1.52)**	**−2.45 (−3.52; −1.38)**	**−2.00 (−2.72; −1.28)**	**−2.06 (−2.78; −1.35)**	**−1.99 (−3.08; −0.91)**
Cardiomyopathy	**−5.43 (−8.19; −2.67)**	**−6.99 (−8.60; −5.38)**	**−5.78 (−7.15; −4.41)**	**−2.99 (−5.10; −0.88)**	−2.42 (−9.88; 5.03)	**−2.12 (−3.99; −0.26)**
Cerebrovascular diseases	0.00	–	–	0.00	–	–
Diabetes mellitus	**−1.34 (−2.15; −0.54)**	**−1.45 (−1.97; −0.94)**	**−1.47 (−2.05; −0.91)**	**−1.12 (−1.53; −0.71)**	**−1.13 (−1.73; −0.53)**	**−1.16 (−1.85; −0.46)**
Obesity	**−1.03 (−1.85; −0.21)**	−1.14 (−2.33; 0.05)	–	−1.24 (−3.10; 0.62)	−1.22 (−2.95; 0.51)	–
COPD	**−1.72 (−2.34; −1.11)**	**−1.66 (−2.47; −0.86)**	**−1.53 (−2.14; −0.91)**	**−1.93 (−2.55; −1.32)**	**−2.00 (−2.72; −1.28)**	**−1.76 (−2.45; −1.07)**
Obstructive sleep apnea syndrome	**−2.61 (−4.69; −0.53)**	**−3.13 (−4.79; −1.48)**	**−2.11 (−3.92; −0.31)**	**−1.99 (−3.03; −0.96)**	−1.46 (−3.49; 0.57)	**−2.68 (−4.78; −0.58)**
Depression	−0.14 (−0.76; 0.48)	−0.27 (−1.27; 0.73)	–	−0.20 (−0.87; 0.46)	−0.36 (−0.97; 0.26)	–
Anxiety	−0.64 (−2.13; 0.86)	−0.68 (−1.85; 0.48)	–	−0.63 (−1.87; 0.61)	−0.34 (−1.11; 0.43)	–

Models are harmonized to include the same variables among men and women, otherwise are non-significant variables excluded. Fully adjusted includes adjustment forage, socio-demographic and all significant co-morbidity (hypertension, valvular heart disease, cardiomyopathy, diabetes, COPD, and obstructive sleep apnea syndrome) in models adjusted for age and socio-demographic factors (educational level, marital status, and neighborhood socio-economic status). (Model check did not reveal any significant interactions in full models.)
COPD, chronic obstructive pulmonary disease.
Bold values are statistically significant.

Table 5
CHA_2DS_2-VASc scores and newly diagnosed CHF for patients with atrial fibrillation, stratified by sex.

CHA_2DS_2-VASc score	Men			Women		
	All	CHF events		All	CHF events	
	n	n (%)	Incidence rate	n	n (%)	Incidence rate
0	383	30 (7.8)	1.41 (0.99–2.03)	–	–	
1	755	89 (11.8)	2.03 (1.65–2.50)	131	19 (14.5)	2.60 (1.66–4.07)
2	1876	423 (22.6)	4.04 (3.67–4.44)	338	47 (13.9)	2.50 (1.88–3.33)
3	1379	356 (25.8)	4.66 (4.20–5.17)	1.427	385 (27.0)	5.13 (4.64–5.67)
4	586	165 (28.2)	5.16 (4.43–6.01)	1496	410 (27.4)	5.16 (4.68–5.68)
5	193	60 (31.1)	6.02 (4.67–7.75)	608	192 (31.6)	6.11 (5.30–7.04)
6	38	12 (31.6)	7.19 (4.93–12.50)	170	55 (32.4)	6.47 (4.96–8.43)
7	1	0 (0.0)	–	39	14 (35.9)	7.95 (7.71–13.43)
8	–	–	–	4	2 (50.0)	12.12 (3.03–48.46)
All	5211	1135 (21.8)	3.92 (3.70–4.15)	4213	1124 (26.7)	5.05 (4.76–5.35)

Incidence ratios for newly diagnosed CHF with 95% confidence intervals are shown per 100 patient-years at risk.
CHF, congestive heart failure.

condition. Similarly, a diagnosis of obstructive sleep apnea disorder was also relatively rare, which may be due to under-diagnosis. As severity of CHF is an important factor for mortality, the lack of access to data on severity of CHF is also a major limitation of the study. In addition, data on ejection fraction and criteria for diagnosis of CHF were not available. Moreover, AF could not be classified as paroxysmal, persistent, or permanent and heart rhythm could not be classified as sinus rhythm or fibrillation rhythm.

A major strength of this study was that we were able to link clinical data from individual EPRs to data from national demographic and socioeconomic registers with less than 1% of information missing. While many previous follow-up studies of AF have used hospital data, the current study used data from primary care, which may better reflect the risks associated with AF in less severe cases. Moreover, randomized controlled trials often exclude individuals with co-morbidities, such as AF patients with concomitant diabetes and CHF. In the current study, we had the possibility to include these patients in the analyses, which means that the findings are more representative of the variety of patients encountered in clinical practice today.

In conclusion, in this clinical setting with patients with AF treated in primary care, we found valvular heart disease, diabetes, and COPD to be consistently associated with increased risk of CHF in men and women, cardiomyopathy and obstructive sleep apnea syndrome with an increased risk of CHF among men, and hypertension with a decreased risk of CHF among women. Further studies in patients with AF from a primary care setting with data on severity of CHF, on ejection fraction, and of use of anti-hypertensive agents in relation to incident CHF are needed to further understand our findings. Based on the presence of relevant co-morbidities, preventive therapy could possibly be tailored to prevent the development of CHF in patients with AF.

Conflict of interest

Dr Holzmann received consultancy honoraria from Pfizer and Actelion. The other authors have no conflict of interest to disclose.

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