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Associations between relevant cardiovascular pharmacotherapies and incident heart failure in patients with atrial fibrillation: A cohort study in primary care

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Abstract

Objective—To study association between relevant cardiovascular pharmacotherapy and incident congestive heart failure (CHF) in patients with atrial fibrillation (AF) treated in primary health care.

Methods—Study population included all adults (n=7,975) aged 45 years and older diagnosed with AF at 75 primary care centers in Sweden between 2001–2007. Outcome was defined as a first diagnosis of CHF post AF diagnosis. Association between CHF and treatment with relevant cardiovascular pharmacotherapies (beta-blockers, calcium blockers, digitalis, diuretics, RAS-blockers and statins) was explored using Cox regression analysis with hazard ratios (HRs) and 95% CIs. Adjustments were made for age, sociodemographic variables and co-morbid conditions (with or without cardiovascular disorders).

Results—During a mean of 5.7 years (SD 2.3) of follow-up, totally 1,552 patients (19.5%; 803 women and 749 men) had a recorded CHF-diagnosis. Thiazides (HR 0.74, 95% CI 0.65–0.84), vessel active calcium channel blockers (HR 0.76, 95% CI 0.67–0.86), and non-selective beta-blockers (HR 0.84, 95% CI 0.72–0.98), with specifically sotalol representing 80% of non-selective beta-blockers (HR 0.81, 95% CI 0.69–0.97), were associated with lower CHF risk in fully adjusted

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models. Loop diuretics (HR 1.41, 95% CI 1.25–1.57) were associated with a higher risk. Findings for thiazides and vessel active channel blockers were consistent in the tested subgroups.

Conclusions—In this clinical setting, we found that thiazides, vessel active calcium channel blockers and non-selective beta-blockers (specifically sotalol) were associated with a lower risk of incident CHF among patients with AF. The findings of the present study need to be confirmed in other settings.

Condensed abstract

We studied the risk of incident heart failure among patients with atrial fibrillation in primary health care in association with different classes of anti-hypertensive drugs. Our main findings were that thiazides, vessel active calcium channel blockers and non-selective beta-blockers (specifically sotalol) were associated with a lower risk of incident congestive heart failure among patients with atrial fibrillation. RAS-blockers were associated with neither increased nor decreased risk of congestive heart failure.

Keywords

Atrial fibrillation; congestive heart failure; gender; drug treatment

1. Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia in the global population. In Sweden, the prevalence of a registered diagnosis of AF has been estimated at 2% [1] and to be almost 3% in individuals aged above 20 years [1,2].

Congestive heart failure (CHF) and AF are interrelated conditions [3,4]; CHF is three times more common among patients with AF than in patients without AF [5]. Among the elderly population, CHF is the most common cardiovascular (CVD) condition [6] and, according to a recent American study, incident CHF in patients with AF has not declined over time [7]. Furthermore, CHF is associated with increased mortality in patients with AF [5], on a par with stroke [8]. We have also found hypertension to be associated with a lower risk of incident CHF among AF patients [9], which is why it is of great interest to study the effect of different classes of antihypertensive drugs on CHF development in patients with AF.

The most effective drugs associated with preventing incident CHF among patients with hypertension are, according to a systematic review, diuretic drugs. Thiazides are the most frequently used diuretic drugs, followed by angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) [10]. However, less is known about the preventive effect of these drugs on incident CHF in patients with AF. We have found in a previous study that prescribed thiazides, calcium channel blockers and statins were associated with a lower mortality rate among patients with AF [11], and that patients with AF and concomitant heart failure have a lower mortality rate when prescribed calcium channel blockers and statins [12].

AF is more common among men [1], and men develop AF, on average, five years earlier than women [13]. By contrast, women with AF have been shown to have a higher risk of stroke and of mortality than men with AF [14].

We hypothesized that there may be differences in the associated risk of incident CHF in those treated with different cardiovascular drugs in patients with AF. Accordingly, the aim was to study relevant cardiovascular pharmacotherapies and the associated risk of incident CHF in patients with AF. We also aimed to explore potential differences among men and women as well as in those over and under 75 years of age.

2. Methods

2.1 Design

This study used individual-level patient data from 75 primary health care centers (PHCCs), 48 of which were located in Stockholm County. Individuals that attended any of the participating PHCCs between 2001 and 2007 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 database constructed using the Total Population Register, the Inpatient Register and the Swedish Cause of Death Register, which contains individual-level data on age, sex, education and hospital admissions for all residents registered in Sweden. Thus, a new research database 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 was used for the follow-up.

Ethical approvals were obtained from regional boards at Karolinska Institutet and the University of Lund.

2.2 Study population

The study included patients that had been diagnosed with AF as identified by the presence of the ICD-10 code (10th version of the WHO's International Classification of Diseases) for atrial fibrillation (I48) in patients' medical records. Patients with a first diagnosis of CHF during the period were identified, and patients with a first hospital episode of CHF before, or in the same year, as the first AF diagnosis were excluded (n=2,859), as well as patients with a first CHF after AF diagnosis but before 2006 (n=552), or deceased before 2006 (a further 211 patients excluded). In addition, as we also included patients with a new CHF diagnosis in primary care, a total of 124 patients were excluded with an AF diagnosis the same year or after CHF diagnosis, and 562 with a primary care diagnosis of CHF before 2006. In total, 4,308 patients were excluded from the analyses. Included in the study were the following: 7,975 individuals (4,510 men and 3,465 women), 1,552 (803 men and 749 women) with and 6,423 without a recorded episode of CHF, 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, and with data on neighborhood socioeconomic status.

2.3 Pharmacotherapies

Data on dispensed prescriptions of drugs, classified according to the Anatomic Therapeutic Chemical (ATC) Classification, were collected from the Swedish Prescribed Drug Register (National Board of Health and Welfare) from 1 July 2005, i.e. when the register became operational, and until 31 December 2010 [15,16]. Substances were recorded, meaning that medical drugs could be single-substance drugs, or combined medical drugs with the substances recorded separately, e.g. a RAS-blocking agent combined with a thiazide, which would thus be recorded into two separate groups. Digitalis agents (C01AA) were recorded. Diuretic drugs (C03) were recorded as thiazides or related agents, also registered when in combination with other drugs (C03A, C03B, C03E, C09B and C09DA), loop diuretics (C03C) or aldosterone antagonists (C03DA). Furthermore, the following cardiovascular agents were recorded: beta blockers with beta-1-selective agents (C07AB and C07FB) and non-selective agents (C07AA and C07AG), calcium channel blockers with heart-active agents (C08DA) and vessel-active agents (C08CA and C08DB), and RAS-blocking agents with ACE inhibitors (C09AA and C09BA) and angiotensin receptor blocking (ARB) agents (C09CA, C09DA and C09DB). In addition, sotalol was recorded separately (C07AA07). Statins (C10AA) were also recorded.

2.4 Outcome variable

Time to first CHF episode during the study period (from registration of first AF diagnosis during 2001–2007; until end of follow-up, December 31, 2010), was defined as having a hospital or primary care diagnosis of CHF ICD-10 code (I50 or I110).

2.5 Demographic and socioeconomic variables

Sex: 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 as they rarely develop AF and CHF.

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). Information on education was missing for 409 subjects.

Marital status was classified as married, unmarried, divorced or widowed. Information on marital status was missing for 14 subjects.

The neighborhood socioeconomic status (SES) areas were categorized into three groups according to the neighborhood index: 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 (middle SES or deprivation level).

2.7 Co-morbidities

We identified the following cardiovascular co-morbidities from the EPRs among individuals in the study population: hypertension (I10–15), coronary heart disease (CHD; I20–25), non-rheumatic valvular diseases (I34–38), cardiomyopathy (I42) and cerebrovascular diseases

(CVDs; I60–69). No diagnosis of rheumatic valvular diseases (I05–08) was recorded. In addition, we also included obesity (E65-E68), diabetes mellitus (E10–14), COPD (J40-J47), obstructive sleep apnea syndrome (G47), depression (F32–F34, F38–F39) and anxiety disorders (F40–41). We also had access to diagnoses from hospital records and the Cause of Death Register for data regarding myocardial infarction (I21), ischemic stroke (I63) and hemorrhagic stroke (I60–62). Thus, diagnoses of CHD and CVDs included data from primary care and from hospital records.

2.7 Statistical analyses

We used Student's t-test to study differences in age between subjects, with or without incident CHF diagnosis during follow-up, and chi-square test was used to study differences in age distribution. Differences in distributions of sociodemographic data, comorbidity and prescribed drugs were otherwise performed by using age-adjusted logistic regression or analysis of co-variance (ANCOVA).

Cox regression with hazard ratios (HRs) and 95% confidence interval (95% CI), using time to first diagnosis of CHF as the outcome was used. The following were studied in the analyses: Digitalis, thiazides, loop diuretics, aldosterone antagonists, beta blockers, calcium channel blockers, RAS-blocking agents, and statins, with subdivision for beta blockers into beta-1-selective or unselective, calcium channel blockers into heart or vessel active, and RAS blockers into ACE inhibitors and ARB. In the full model, we adjusted for sex, age, socioeconomic factors, co-morbidities and drug classes. The regression models were also tested for possible interactions between (with confirmed interactions between age and marital status, and age and neighborhood status).

We also stratified Cox regression into subgroups, i.e. men and women, subjects aged <75 and ≥75 years of age, and with or without concomitant cardiovascular diseases, i.e. CHD, valvular heart disease, cardiomyopathy and cerebrovascular diseases. We used 75 years as the cut-off for age as this is the cut-off for high age in CHA_2DS_2-VASc.

Furthermore, owing to the results for the non-selective beta-blocking agents we decided to perform a separate analysis for sotalol, and also an analysis of RAS-blockers and thiazides in combination or not.

A *p*-value for two-sided tests of <0.01 was considered statistically significant 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 Cox regression. All analyses were performed in STATA 15.1.

3. Results

Table 1 shows the characteristics of the study population of 7,975 individuals (4,510 men and 3,465 women), with 1,552 (19.5%) having a recorded episode of CHF (out of which 1,416 were recorded from electronic hospital records). A total of 1,710 patients (21.4%) died during follow-up; 925 men (20.5%), and 785 women (22.7%). Characteristics divided by sex are shown in Supplementary Table 1. Overall, men were significantly younger and had a

higher educational level than women, while significantly more women were widowed than men. Hypertension was more common among women, and cardiomyopathy was more common among men. The mean follow-up time was 5.70 years (standard deviation (SD) 2.34 years), and HRs were calculated based on 45,465 person-years at risk; 26,044 among men and 19,421 among women.

Table 2 shows rates of dispensed pharmacological drugs in subjects with or without incident CHF diagnosis during follow-up, with age-adjusted p-values shown, and p-values <0.01 regarded as significant. Regarding differences by sex, men with new CHF comprised more digitalis and loop-diuretic prescriptions, and less thiazides, beta-1-selective beta blockers and vessel selective calcium receptor blockers; women with a new CHF diagnosis comprised more digitalis, loop-diuretics prescriptions, and aldosterone antagonists dispenses, and less thiazides, vessel selective calcium receptor blockers and statins (Supplementary Table 2).

Cox regression models are shown in Table 3 for all subjects with incident CHF as outcome, also characterized into subgroups, i.e. for men and women, low or high age (<75 years and ≥75 years), and with or without cardiovascular co-morbidities (CHD, valvular heart disease, cardiomyopathy and cerebrovascular diseases). Differences by groups were tested by interactions, finding significant differences by low or high age-group for loop diuretics, and for beta-1-selective beta blockers, and by inclusion of cardiovascular co-morbidity or not for loop diuretics and vessel active calcium channel blockers. Dispensing of thiazides and vessel active calcium blockers were associated with a lower risk of incident CHF in general as well as in all studied subgroups, and loop diuretics were associated with a higher risk in general and in all subgroups. Non-selective beta blockers were associated with a lower risk in general, and in patients without cardiovascular co-morbidities, and aldosterone antagonists with a higher risk in general, among women and among patients aged ≥ 75 years. Beta-1-selective beta blockers were associated with a lower risk only among patients aged < 75 years, heart active calcium channel blockers with a lower risk in patients with cardiovascular co-morbidities, and statins with a lower risk in women, patients aged < 75 years, and in patients with cardio-vascular comorbidities.

In a separate analysis, we also performed analyses for sotalol, i.e. the mostly used of the non-selective beta-blockers (1,140 out of 1,407, i.e. 81.0% out of all non-selective beta-blockers; 675 among men and 465 among women). In the full model using Cox regression the HR was 0.81 (95% CI 0.69–0.97); in men 0.81 (95% CI 0.64–1.02), and women 0.80 (95% CI 0.62–1.04); in patients aged <75 years HR 0.81 (95% CI 0.63–1.03), and aged ≥75 years 0.78 (95% CI 0.61–1.00, p=0.048); and finally in patients with cardiovascular diseases 0.72 (95% CI 0.55–0.94), and in patients without cardiovascular diseases 0.88 (95% CI 0.70–1.11). No significant interactions when testing for sub-groups were found.

We also tested the combination of thiazides and RAS-blockers, with the following HRs (with 95% CI) vs use of neither thiazides nor RAS-blockers (n=3,242; 40.7%): RAS-blockers (n=2,279; 28.6%) 1.13 (0.99–1.29), thiazides (n=611; 7.7%) 0.72 (0.58–0.90), and RAS blockers and thiazides combined (n=1,843; 23.1%) 0.77 (0.65–0.90).

4. Discussion

The main finding of this study was that thiazides and vessel selective calcium receptor blockers were associated with a lower risk of incident CHF, among both men and women, as well as among younger and elderly individuals. Non-selective beta blockers, more specifically sotalol, were associated with a lower risk of incident CHF risk among patients under 75 years of age. On the other hand, loop-diuretics were associated with a higher risk of incident CHF among men and women.

One might have expected a lower CHF associated with some of the other pharmacotherapies, especially RAS-blockers [10]. However, the results in this observational study could be influenced by different factors, and competing risk factors could contribute to CHF especially among elderly individuals, and also confounding by indication [17]. Furthermore, differences may exist between patients with and without AF and the risk of CHF, which may explain why our results differ from other studies concerning the risk of CHF associated with cardiovascular drugs [10]. In addition, it is possible that certain drugs were prescribed due to concomitant diseases before the CHF occurred.

The effect of thiazides on incident CHF concurs with earlier findings [10]. However, in the review by Sciarretta, the effect was seen in all diuretics when used as antihypertensive therapy [10], while we saw different results depending on the kind of diuretic used; with an excess risk found for the use of loop diuretics.

The negative effect associated with the use of loop diuretics is in line with an earlier reported finding with an associated increase in mortality among AF patients younger than 80 years of age who were using loop diuretics [11]. As these drugs are often prescribed to patients with CHF, the most likely explanation is that these patients did have prior symptoms associated with CHF, e.g. leg edema, before they were diagnosed with CHF. Thus, our finding of an increased risk of CHF in patients who were using loop diuretics was likely confounded by indication, or reversed causation.

The associations between vessel selective calcium channel blockers and a reduced risk of incident CHF are also of interest. Previous studies have shown conflicting results regarding calcium channel blockers in relation to heart failure; one review reported a reduced rate of CHF in individuals prescribed antihypertensive agents [18], and another a positive effect by calcium channel blockers, although with a less positive effect than thiazides and RAS-agents [10]. In contrast, another review reported an increased risk of incident CHF [19]. Calcium channel blockers may, however, be beneficial in patients with CHF with preserved ejection fraction (HFpEF) [20]. This type of CHF is regarded to be more common among elderly individuals, especially women, and also to be more common in primary care. The rate of dispensed calcium channel blockers was considerably lower than that of RAS-blockers and of beta blockers.

Regarding beta blockers, non-selective beta blockers, especially sotalol, were associated with a lower CHF risk, which was seen among patients younger than 75 years of age. We found no statistically significant effect of beta-1-selective beta blockers, although point estimates indicated a lower risk. Beta-1-selective agents were dominant among beta-blockers

in our study, which is in contrast to the situation during the late 1990s [21] when sotalol was prescribed to 25% of AF patients in primary care, and sotalol accounted for 78% of prescribed non-selective beta-blockers in the present AF cohort [22], and 80% of the dispensed prescriptions in this specific study. Sotalol has a more specific anti-arrhythmic profile in maintaining sinus rhythm in contrast to the beta-1-selective agents and other beta-blockers [22], and this could possibly explain the positive effect we found. However, owing to adverse events, the use of sotalol for AF patients in primary care decreased during the early years of the 21st century [22]. Beta blockers have also been shown to be effective in preventing CHF in patients with hypertension [23]. However, it has been questioned if beta-blockers are effective in patients with concomitant AF and CHF, and the effect on mortality has been neutral, in comparison with CHF patients with sinus rhythm where beta-blockers are associated with reduced mortality [24].

On the other hand, the lack of effect of RAS-blockers, both ACE inhibitors and ARBs, is surprising, and we do not have a sufficient explanation for this unexpected finding. RAS-blockers seem to prevent incident AF [25], and are effective in preventing CHF in patients with hypertension [23]. In a previous study in patients with AF on the association between prescribed drugs and mortality, RAS-blockers did neither increase nor decrease the mortality risk [11]. This finding could be an effect of confounding by indication, e.g. patients with a higher cardiovascular risk, such as the presence of CHD as in the present study, or perhaps with signs of CHF without a definite diagnosis, might be prescribed RAS-blockers more often than those without such signs.

There are several limitations of this study, which must be kept in mind when interpreting the results. As this is an observational study, the findings may have been subject to confounding by indication [17]. To account for this effect, we also analyzed data with concomitant cardiovascular diseases excluded. We used data from registers and electronic patient records. One question raised by the findings, especially on the results from loop diuretics, is that when a CHF diagnosis is set it seems to be at a late rather than at an early stage. The study sample is a selected group, i.e. patients with a diagnosis of AF 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]. However, we do not know the validity of registered diagnoses in primary health care (accounting for 9% of the total events of incident CHF), and there might be both over- and under-estimation of diagnoses, in particular with CHF. For CHF diagnoses registered in hospital records, good validity has been shown [26], and in a meta-analysis the sensitivity of a CHF diagnosis from registers was found to be around 75% [27]. Clinical data were also highly complete [28]. We did not have access to doses of the retrieved drugs, which is especially of importance for diuretic drugs. Severity of CHF and CHD were not available to us from the patient records, even if it is probable that these patients from primary care had less severe CHF than patients from hospital care. Besides, patients in primary care probably more often have a CHF with preserved ejection fraction. As severity of CHF is an important factor for mortality, this is also a major limitation of the study. Besides, 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. In addition, we did not have access to renal function data. All these mentioned factors could have affected the results, and yielded discrepant findings.

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. We used the Swedish Prescribed Drug Register [15,16], in which dispensed prescriptions of drugs are registered, and thus showed a higher probability of being used compared to only prescription data. Besides, 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 society. Most patients with hypertension and diabetes are actually cared for in primary care in Sweden [29]. However, access to diagnoses of CHD and CVDs from hospital records is important, as these diagnoses are not always identified in primary care in Stockholm County, Sweden [30]. Moreover, randomized controlled trials often exclude individuals with co-morbidities, such as patients with AF 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, our findings suggest that the risk of developing CHF may be reduced in AF patients in primary care by use of thiazides, and vessel active calcium channel blockers in general and consistently in all studied subgroups. The use of these drugs in patients with AF is also supported by previous studies where they have been shown to be associated with a lower risk of mortality, also in patients with AF and concomitant CHF. Other drugs showed an effect in some specific subgroups, such as non-selective beta blockers, specifically sotalol, beta-1-selective beta blockers, heart active calcium channel blockers and statins. However, we believe that the present observational study needs to be interpreted with caution, as confounding by indication may explain some of our results. More studies focusing on patients with AF treated in a primary care setting with data on severity of CHF, ejection fraction and kidney function are needed to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

ACE	Angiotensin converting enzyme
AF	Atrial fibrillation

ANCOVA	Analysis of co-variance
ARB	Angiotensin receptor blockers
ATC	Anatomic Therapeutic Chemical
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cerebro-vascular disease
EPR	Electronic patient record
HR	Hazard ratio
ICD	International Classification of Diseases
PHCC	Primary health care centre
RAS	Renal angiotension system
SD	Standard deviation
SES	Socio-economic status
WHO	World Health Organisation

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Table 1

Data for patients aged ≥45 years with diagnoses of AF and with or without newly diagnosed chronic heart failure (*n*=7,975) in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007 (patients with first CHF diagnosis recorded earlier than first AF diagnosis, and earlier than 2006 are excluded)

	Men and women (n=7,975)		
Number of patients (%)	**No CHF *N=6,423***	**CHF during follow-up *N=1,552* (19.5%)**	**Age-adjusted Difference**
Number of deaths (%)	1111 (17.3)	599 (38.6)	
Age (years), mean (SD)	71.7 (10.1)	77.1 (8.5)	<0.001
Age groups (years),			<0.001
45–54	364 (5.7)	20 (1.3)	
55–64	1,261 (19.6)	128 (8.3)	
65–74	2,031 (31.6)	360 (23.2)	
75–79	1,171 (18.2)	357 (23.0)	
80–84	991 (15.4)	404 (26.0)	
≥85	605 (9.4)	283 (18.2)	
Educational level			<0.001
Compulsory schooling	2,498 (40.7)	715 (50.3)	
Secondary schooling	2,279 (37.1)	475 (33.4)	
College and/or university studies	1,366 (22.2)	233 (16.4)	
Marital status			0.003
Married	3,338 (52.1)	648 (41.8)	
Unmarried	545 (8.5)	132 (8.5)	
Divorced	971 (15.2)	217 (14.0)	
Widowed	1,555 (24.3)	555 (35.8)	
Neighborhood SES			0.54
High	2,504 (39.0)	539 (34.7)	
Middle	2,989 (46.5)	763 (49.2)	
Low	930 (14.5)	250 (16.1)	
Diagnosis			
Hypertension	3,080 (48.0)	785 (50.6)	0.73
CHD	1,156 (18.0)	502 (32.4)	<0.001

	Men and women (n=7,975)		
Number of patients (%)	**No CHF *N*=6,423**	**CHF during follow-up *N*=1,552 (19.5%)**	**Age-adjusted Difference**
Valvular heart disease	167 (2.6)	78 (5.0)	<0.001
Cardiomyopathy	23 (0.4)	10 (0.6)	0.020
CVDs	1,224 (19.1)	369 (23.8)	0.14
Obesity	321 (5.0)	79 (5.1)	<0.001
Diabetes	1,021 (15.9)	348 (22.4)	<0.001
COPD	536 (8.4)	204 (13.1)	<0.001
Obstructive sleep apnea syndrome	42 (0.7)	16 (1.0)	0.006
Depression	505 (7.9)	145 (9.3)	0.072
Anxiety	247 (3.9)	74 (4.8)	0.22

Information on educational level and (n=409) marital status (n=14) is missing for some individuals.

Table 2

Dispensed medication data for patients aged ≥45 years with diagnoses of AF and chronic heart failure (*n*=7,975) in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007

	Men and women (n=7,975)		
	No CHF *N=6,423*	**CHF during follow-up *N=1,552* (19.5%)**	**Difference Age-adjusted**
Digitalis (C01A)	1,800 (28.0)	581 (37.4)	<0.001
Any diuretic treatment (C03)	3,758 (58.5)	1,098 (70.8)	<0.001
Thiazides (C03A, C03B, C03E, C09B C09DA)	2,067 (32.2)	387 (24.9)	<0.001
Loop diuretics (C03C)	2,358 (36.7)	867 (55.9)	<0.001
Aldosterone antagonists (C03DA)	522 (8.1)	193 (12.4)	<0.001
All beta blockers (C07)	5,028 (78.3)	1,083 (69.8)	<0.001
Beta1-selective agents (C07AB, C07F)	4.582 (71.3)	962 (62.0)	<0.001
Non-selective beta blockers (C07AA)	1,199 (18.7)	208 (13.4)	0.038
Calcium channel blockers (C08)	2,362 (36.8)	459 (29.6)	<0.001
Heart active (C08D)	380 (5.9)	78 (5.0)	0.61
Vessel selective (C08C, C09DB)	2,061 (32.1)	393 (25.3)	<0.001
RAS-blocking agents (C09)	3,101 (51.7)	800 (51.6)	0.10
ACE inhibitors (C09A, C09B)	2,366 (36.8)	558 (36.0)	0.55
ARB (C09C, C09D)	1,617 (25.2)	349 (22.5)	0.40
Statins (C10AA)	2,443 (38.0)	440 (28.4)	<0.001

Table 3

Cox regression models for patients (*n*=7,557) aged 45–104 years with AF and newly diagnosed congestive heart failure attending the 75 PHCCs between July 1st 2005 and December 31st 2007; also stratified by sex, age-group and with or without cardiovascular co-morbidities, respectively.

	All	Men	Women	Interaction	Patients aged <75 years	Patients aged ≥75 years	Interaction	Patients without cardiovascular comorbidities	Patients with cardiovascular comorbidities	Interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)	HR (95% CI)	p-value
	***n*=7,557**	***n*=4,510**	***n*=3,465**		**n=4,107**	**n=3,450**		***n*=4,638**	***n*=2,919**	
Digitalis	1.03 (0.92–1.15)	0.98 (0.84–1.15)	1.03 (0.88–1.21)	ns	0.96 (0.79–1.17)	1.01 (0.88–1.16)	ns	0.94 (0.79–1.11)	1.03 (0.89–1.21)	ns
Thiazides	**0.74 (0.65–0.84)**	**0.72 (0.60–0.87)**	**0.67 (0.55–0.81)**	ns	**0.72 (0.57–0.91)**	**0.70 (0.59–0.82)**	ns	**0.73 (0.60–0.89)**	**0.69 (0.58–0.83)**	ns
Loop diuretics	**1.41 (1.25–1.57)**	**1.41 (1.20–1.65)**	**1.21 (1.03–1.43)**	ns	**1.74 (1.42–2.12)**	**1.17 (1.01–1.34)**	**0.003**	**1.46 (1.23–1.73)**	**1.19 (1.02–1.39)**	**0.045**
Aldosterone antagonists	**1.22 (1.04–1.44)**	1.06 (0.81–1.38)	**1.25 (1.00–1.55)**	ns	0.90 (0.66–1.21)	**1.34 (1.10–1.64)**	ns	1.13 (0.88–1.46)	1.25 (1.00–1.55)	ns
Beta-1-selective blockers	0.96 (0.86–1.08)	0.89 (0.77–1.04)	0.99 (0.83–1.18)	ns	**0.75 (0.62–0.92)**	1.04 (0.90–1.19)	**0.024**	1.02 (0.86–1.21)	0.86 (0.74–1.01)	ns
Non-selective beta blockers	**0.84 (0.72–0.98)**	0.87 (0.70–1.07)	0.81 (0.64–1.01)	ns	0.80 (0.63–1.01)	0.86 (0.69–1.05)	ns	**0.76 (0.60–0.96)**	0.91 (0.74–1.12)	ns
Heart active calcium channel blockers	0.81 (0.64–1.03)	0.72 (0.51–1.02)	0.85 (0.61–1.18)	ns	0.74 (0.50–1.10)	0.83 (0.62–1.12)	ns	0.96 (0.69–1.34)	**0.66 (0.47–0.93)**	ns
Vessel active calcium channel blockers	**0.76 (0.67–0.86)**	**0.72 (0.60–0.87)**	**0.69 (0.57–0.83)**	ns	**0.69 (0.55–0.86)**	**0.72 (0.61–0.85)**	ns	**0.59 (0.48–0.73)**	**0.80 (0.68–0.95)**	**0.031**
ACE inhibitors	1.06 (0.95–1.19)	1.03 (0.88–1.21)	0.94 (0.79–1.12)	ns	1.00 (0.82–1.21)	0.98 (0.85–1.13)	ns	0.96 (0.81–1.14)	0.99 (0.84–1.15)	ns
ARB	1.10 (0.97–1.26)	1.06 (0.88–1.28)	1.05 (0.86–1.27)	ns	0.94 (0.75–1.17)	1.10 (0.93–1.30)	ns	1.15 (0.95–1.41)	0.97 (0.81–1.17)	ns
Statins	0.91 (0.80–1.03)	0.86 (0.73–1.02)	**0.82 (0.67–0.99)**	ns	**0.80 (0.66–0.97)**	0.86 (0.73–1.01)	ns	0.97 (0.79–1.18)	**0.68 (0.58–0.80)**	ns

Models are adjusted for sex, age, socio-demographic status (educational level, marital status and neighborhood SES), drug treatment and co-morbidity (myocardial infarction, valvular heart disease, cardiomyopathy, cerebrovascular diseases, hypertension, obesity, diabetes, COPD, obstructive sleep apnea syndrome depression and anxiety); however, in patients with

Interaction terms are included (age and marital status, and age and neighborhood SES)

HRs and 95% CIs are shown. Statistically significant HRs are highlighted in bold