ORIGINAL ARTICLE

Effects of prescribed antihypertensives and other cardiovascular drugs on mortality in patients with atrial fibrillation and hypertension: a cohort study from Sweden

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Although antihypertensive drugs are known to reduce mortality in individuals with hypertension, the effects of different cardiovascular pharmacotherapies on mortality among patients with hypertension and atrial fibrillation (AF) have been less thoroughly explored. To study mortality rates in men and women separately with hypertension and AF prescribed different cardiovascular pharmacotherapies. A cohort of men ($n=2809$) and women ($n=2793$) aged >45 years diagnosed with hypertension and AF were selected using patient records. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox regression, with all-cause mortality as the outcome. Analysis was performed on the whole population and after stratification by age and sex. Independent factors were prescribed pharmacotherapies. Adjustments were made for a propensity score comprising age, comorbidities, education and marital status. The higher the number of antihypertensive drugs prescribed, the lower the mortality rate (P -value for trend 0.005). Individuals prescribed 4–5 antihypertensive drugs had a lower risk of mortality than those prescribed 0–1 drugs (HR: 0.62; 95% CI: 0.45–0.86). The HRs for the following drug classes were: loop diuretics 1.39 (95% CI: 1.08–1.78), non-selective β -blockers 0.68 (95% CI: 0.53–0.88), angiotensin receptor blockers 0.75 (95% CI: 0.56–0.99) and statins 0.68 (95% CI: 0.53–0.88). AF patients with hypertension prescribed statins, non-selective β -blockers and angiotensin receptor blockers had low relative mortality risks, suggesting that these prescribed pharmacotherapies were beneficial. This needs to be further explored in other clinical settings.

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INTRODUCTION

Hypertension is treated with five main classes of antihypertensive pharmacotherapies that have been tested extensively in clinical trials: diuretics, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and calcium antagonists.¹ The most important aim of antihypertensive drug treatment is to reduce effectively vascular complications. Randomized controlled trials have previously shown that large reductions in the risk of macrovascular complications were achieved by large reductions in blood pressure and that treatment with any commonly used antihypertensive pharmacotherapy reduced the risk of major cardiovascular events.^{2–5} However, little is known about the effects of antihypertensive pharmacotherapies on mortality risk among patients with hypertension and concomitant atrial fibrillation (AF), as patients with comorbidities are often excluded from randomized trials.⁶

AF is the most common arrhythmia and its age- and sex-adjusted prevalence has been estimated at 1.4% in the Swedish population, with the prevalence of chronic AF being 1.0%,⁷ values consistent with those from studies from other countries (1–1.5% of the population).^{8,9} The lifetime risk of developing AF is, however, much higher, with AF estimated to affect about one-quarter of the population in Western countries.⁸ Hypertension is common among patients with AF. In a recent study, we showed that, in Sweden, 30% of men and 34% of women with AF attending primary health-care centers (PHCCs) were diagnosed with concomitant hypertension.¹⁰

As well as lowering blood pressure, antihypertensive pharmacotherapies exert additional effects on AF symptoms. First, selective- and non-selective β -blockers, which control the heart rhythm, are commonly prescribed to AF patients. Prescription of selective β -blockers has increased among patients with AF in primary care,

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whereas prescription of non-selective β -blockers, such as sotalol, has decreased.¹¹ Heart-active calcium antagonists are also of particular interest as they are prescribed to patients with AF to control the heart rate. Diuretics, which affect ion concentrations in the blood and consequently heart function, may be useful in treating arrhythmias such as AF. Apart from the five main classes of antihypertensive pharmacotherapies, potassium-saving diuretics (epplerone, spironolactone and amiloride)¹² are often prescribed to patients who are resistant to treatment with common antihypertensive drugs.¹³ Potassium-saving diuretics recapture potassium from urine and are recommended for use in patients with low potassium levels, such as patients on loop diuretics.

We hypothesize that prescription of antihypertensive drug classes may be associated with different all-cause mortality risks in patients with AF and concomitant hypertension. Moreover, there may be risk differences with regard to gender. Accordingly, the main aim of this study was to investigate the association between mortality risk and prescribed antihypertensives and other cardiovascular drugs in a cohort of 5602 hypertensive men and women with AF attending primary care centers in Sweden, with a mean follow-up time of 3.4 years. Age, cardiovascular comorbidities, education and marital status, which were established covariate factors that may influence mortality outcomes in men and women with AF and hypertension were accounted for.

METHODS

Design

The study used individual-level patient data from 75 PHCCs, most of which are located in Stockholm County ($n=48$). 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/SLPOPPage1_10400.aspx; accessed 19 September 2010) to extract individual electronic patient records. National identification numbers were replaced with a new unique serial number to ensure anonymity.

The patient files were linked to data from the Total Population register, the In-patient Register and the Cause of Death Register,¹⁴ including individual-level data on age, gender, education and hospital admissions for all residents registered in Sweden. In this way, a new research database containing clinical and socioeconomic data on the 1 098 420 individuals registered at the 75 PHCCs was created.

Study population

All persons diagnosed with both hypertension and AF who attended the 75 PHCCs between 1 January 2001 and 31 December 2007 were included in this study. They were identified by the ICD-10 codes (10th version of the World Health Organization's International Classification of Diseases) for AF (I48) and hypertension (I10–I15) in the patients' medical records. In total, 2809 men and 2793 women ≥ 45 years of age at the time of their AF and hypertension diagnoses were identified and included.¹⁵

Comorbidities

The following cardiovascular disorders were used as covariates: coronary heart disease (I20–I25), congestive heart failure (CHF; I50 and I110) and cerebrovascular diseases (I60–I69), including intracranial bleeding (I60–I62) and peripheral embolism (I74). In addition, the presence of diabetes mellitus (E10–E14) was recorded.

Outcome variable

Time to death in the period between registration of the AF diagnosis and 31 December 2007.

Demographic, marital status and socioeconomic variables

Gender: 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. Age was also included in the analysis as a continuous variable (see Statistical analysis).

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).

Pharmacotherapies

Drugs prescribed in primary health care during the assessment period were recorded using the Anatomic Therapeutic Chemical Classification. Diuretic drugs (C03) were classified as thiazides, related agents, combined formulations with other drugs (C03A, C03B, C03E, C09B C09DA), loop diuretics (C03C) or potassium-saving diuretics (C03D), including aldosterone antagonists (C03DA). β -Blockers (C07) were divided into β_1 -selective and non-selective agents, that is, mostly sotalol (C07AA07).¹⁶ Calcium receptor-blocking agents (C08) were divided into vessel-selective (C08C, C09DB) and heart-selective agents (C08DB). Renin-angiotensin system (RAS) blockers were divided into ACE inhibitors (C09A) and ARBs (C09C). Lipid-lowering drugs (C10A), where statins (C10AA) dominated, were also included as a covariate.

In terms of prescription of antithrombotic drugs (B01A), patients were divided into three groups: no treatment, antiplatelet treatment (B01AC) and anticoagulant treatment (B01AA) (with or without antiplatelet treatment).

Statistical analysis

Differences in means and distributions between men and women were calculated using Student's *t*-test, χ^2 analysis and Fisher's exact test.

Follow-up analyses were performed using Cox regression (hazard ratios (HRs)), with time to death as the outcome. Analyses were performed separately for men and women, and for individuals aged < 80 and ≥ 80 years, to minimize the effects of interactions between age and sex. Eighty years has been commonly referred to as a cutoff age for stroke prophylaxis,¹⁷ as well as an age of increased prevalence and incidence of AF.¹⁸ Furthermore, the number of deceased women aged < 75 years was too low ($n=63$) to provide reliable results. Statistical power calculations for Cox regression with a dichotomous variable were performed with 80% power and an α -value of 0.05 to ensure sufficient detection of HRs in men and women.

A propensity score was estimated for each drug class separately.¹⁹ In Model A, the propensity scores included age group, cardiovascular comorbidity (diabetes, coronary heart disease, CHF and cerebrovascular diseases), educational level and marital status. In Model B, the propensity scores included all variables in Model A and all the antihypertensive drugs, antithrombotics and statins.

We also analyzed the association between the number of antihypertensive drugs prescribed and mortality in multivariable Cox regression models, adjusted for the propensity score in Model A with the addition of antithrombotic drugs, digitalis, loop diuretics and statins. Men and women were analyzed separately. The same association was analyzed in multivariable Cox regression models of the population as a whole adjusted for all the variables listed above, including sex.

A *P*-value for two-sided tests of < 0.01 was considered to be statistically significant owing to the multiple comparisons between men and women. A *P*-value of < 0.05 was considered statistically significant in the Cox regression analyses.

Stata 11.2 software (College Station, TX, USA) was used to perform all calculations.

RESULTS

The mean follow-up time was 3.4 years (s.d. 2.1). The regression models were based on a total of 19 283 person-years at risk. Table 1 shows the characteristics of the 2809 men and 2793 women included in the study. A total of 212 men and 278 women died during follow-up (7.6% vs. 10.0%; $P<0.001$). Using these figures in our power calculations, we found that we had enough power to detect HRs > 1.5 or < 0.67 in both men and women.

Table 1 Characteristics of patients aged ≥ 45 years with diagnosed atrial fibrillation and hypertension ($n = 5602$) attending 75 primary health-care centers in Sweden between 1 January 2001 and 31 December 2007

	Men		Women		Sex difference	
	All n (%)	Dead n (%)	All n (%)	Dead n (%)	All P-value	Dead P-value
Number of patients	2809	212 (7.6)	2793	278 (10.0)		0.001
Age (years), mean (s.d.)	72.3 (9.2)		77.2 (8.6)		<0.001	
<i>Age (years) < 0.001</i>						
45–54	103 (3.7)	2 (1.9)	33 (1.2)	0 (0.0)		0.57
55–64	495 (17.6)	12 (2.4)	223 (8.0)	4 (1.8)		0.60
65–74	963 (34.3)	42 (4.4)	642 (23.0)	22 (3.4)		0.35
75–79	571 (20.3)	54 (9.5)	641 (23.0)	50 (7.8)		0.30
80–84	459 (16.3)	57 (12.4)	708 (25.4)	85 (12.0)		0.83
85+	218 (7.8)	45 (20.6)	546 (20.0)	117 (21.4)		0.81
<i>Educational level</i>						
Compulsory school	1123 (41.7)	90 (8.0)	1403 (55.8)	140 (10.0)	<0.001	0.088
Secondary school	1020 (37.8)	67 (6.6)	787 (31.3)	49 (6.2)		0.77
College/university	553 (20.5)	30 (5.4)	323 (12.9)	11 (3.4)		0.17
<i>Marital status</i>						
Married	1712 (61.1)	122 (7.1)	850 (30.5)	69 (8.1)	<0.001	0.37
Unmarried	247 (8.8)	11 (4.5)	190 (6.8)	14 (7.4)		0.19
Divorced	420 (15.0)	30 (7.1)	377 (13.5)	32 (8.5)		0.48
Widowed	423 (15.1)	46 (10.9)	1369 (49.1)	161 (11.8)		0.62
<i>Diagnosis</i>						
Coronary heart disease	596 (21.2)	55 (9.2)	623 (22.3)	83 (13.3)	0.32	0.024
Heart failure	403 (14.4)	49 (12.2)	491 (17.6)	81 (16.5)	0.001	0.067
Cerebrovascular disease	371 (13.2)	23 (6.2)	351 (12.6)	46 (13.1)	0.47	0.002
Diabetes mellitus	789 (28.1)	53 (6.7)	677 (24.2)	70 (10.3)	0.001	0.013

Those who died during the follow-up period are shown separately, as well as being included in the whole study sample.

Men were significantly younger and more highly educated than were women. More women were widows than men were widowers. Heart failure was more common among women than among men (17.6% vs. 14.4%, $P < 0.001$), whereas diabetes was more common among men than among women (28.1% vs. 24.2%) (Table 1).

Table 2 shows prescription rates of pharmacotherapies (with Anatomic Therapeutic Chemical codes) in men and women. Women were more frequently prescribed antiplatelets, digitalis, loop diuretics, thiazides, potassium-saving agents and aldosterone antagonists than were men, whereas men were more frequently prescribed anticoagulant agents, RAS-blocking agents, ACE inhibitors, lipid-lowering drugs and statins than were women.

Tables 3a and b show Cox regression models for men and women, respectively, stratified by age (< 80 and ≥ 80 years). After adjustments for a comprehensive propensity score including all pharmacotherapies, we found that prescription of anticoagulants and statins were associated with lower mortality in men aged < 80 years, whereas prescription of ARBs were associated with lower mortality in men aged ≥ 80 years. When men of all ages were analyzed, anticoagulants were associated with lower mortality in comparison with no treatment, as well as in comparison with antiplatelets. Thiazides and statins were also associated with lower mortality in models of men in all ages. Prescription of thiazides and loop diuretics was associated with higher mortality and statins were associated with lower mortality in women aged < 80 years after adjustment for a propensity score including all pharmacotherapies. No significant associations between

prescribed pharmacotherapies and mortality were observed in women aged ≥ 80 years. ARBs and statins were associated with lower mortality and loop diuretics with higher mortality when women of all ages were analyzed.

In the full model, in which men and women were analyzed together, individuals aged < 80 years prescribed anticoagulants vs. antiplatelets had HR 0.65 (95% CI: 0.47–0.90), loop diuretics an HR of 1.53 (95% CI: 1.07–2.20), ARBs of 0.56 (95% CI: 0.34–0.93) and statins of 0.44 (95% CI: 0.30–0.65). In individuals aged ≥ 80 years, ARBs had HR of 0.60 (95% CI: 0.37–0.99) and ARBs vs. ACE inhibitors 0.58 (95% CI: 0.36–0.93) (data not shown in tables).

In the full regression model of the whole study sample adjusted for sex and all other covariates, individuals prescribed anticoagulants vs. no treatment had HR 0.67 (95% CI: 0.45–0.99), anticoagulants vs. antiplatelets 0.78 (95% CI: 0.62–0.97) and non-selective β -blockers vs. β_1 -selective β -blockers 0.62 (95% CI: 0.41–0.95). Furthermore, individuals prescribed loop diuretics had an HR of 1.42 (95% CI: 1.10–1.82), ARBs of 0.59 (95% CI: 0.41–0.83), ARBs vs. ACE inhibitors 0.70 (95% CI: 0.50–0.97), ARBs combined with thiazides 0.62 (95% CI: 0.39–0.98) and statins of 0.64 (95% CI: 0.49–0.83) (data not shown in tables).

The fully adjusted models of the effect of the number of different antihypertensive drugs prescribed are shown in Table 4. In the sex-adjusted model of the whole study sample, using 0–1 prescribed hypertensive drugs as the reference, a general trend was observed ($P = 0.005$) whereby the higher the number of antihypertensive drugs

Table 2 Cardiovascular pharmacotherapies prescribed to patients aged ≥ 45 years with diagnosed atrial fibrillation and hypertension ($n = 5602$) attending 75 primary health-care centers in Sweden between 1 January 2001 and 31 December 2007

	Men, n (%)	Women, n (%)	Sex difference, P-value
<i>All antithrombotic agents (B01A)</i>	2560 (91.1)	2502 (89.6)	0.049
Anticoagulant agents (B01AA)	1667 (59.3)	1400 (50.1)	<0.001
Antiplatelet agents (B01AC)	1722 (61.3)	1847 (66.1)	<0.001
Aspirin (B01AC6, B01AC30)	1678 (59.7)	1805 (64.6)	<0.001
Digitalis (C01A)	778 (27.7)	1104 (39.5)	<0.001
Specific antiarrhythmic agents (C01B)	104 (3.7)	73 (2.6)	0.020
<i>Any diuretic treatment (C03)</i>	2021 (72.0)	2324 (83.2)	<0.001
Loop diuretics (C03C)	1335 (47.5)	1600 (57.3)	<0.001
Thiazides (C03A, C03B, C03E, C09B C09DA)	1177 (39.8)	1296 (46.4)	<0.001
Any potassium-saving agent (C03D)	797 (28.4)	1085 (38.9)	<0.001
Aldosterone antagonists (C03DA)	382 (13.6)	469 (16.8)	0.001
<i>All β-blockers (C07)</i>	2274 (81.0)	2307 (82.6)	0.11
β 1-Selective agents (C07AB, C07F)	2046 (72.8)	2100 (75.2)	0.045
All non-selective β -blockers (C07AA)	547 (19.5)	553 (19.8)	0.76
<i>Ca-blocking agents (C08)</i>	1363 (48.5)	1358 (48.6)	0.94
Vessel selective Ca blockers (C08C, C09DB)	1210 (43.1)	1137 (40.7)	0.073
Heart-active Ca blockers (C08D)	210 (7.5)	305 (10.9)	<0.001
<i>RAS-blocking agents (C09)</i>	1992 (70.9)	1728 (61.9)	<0.001
ACE inhibitors (C09A, C09B)	1516 (54.0)	1241 (44.4)	<0.001
ARBs (C09C, C09D)	827 (29.4)	814 (29.1)	0.81
<i>All lipid-lowering drugs (C10A)</i>	1094 (40.0)	913 (32.7)	<0.001
Statins (C10AA)	1068 (38.0)	894 (32.0)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; RAS, renin-angiotensin system.
RAS-blocking agents include both ACE inhibitors and ARBs.

prescribed the lower the mortality rate. Interestingly, individuals prescribed 4–5 antihypertensive drugs had an HR of 0.62 (95% CI: 0.45–0.86) (Table 4).

DISCUSSION

In this study of a large number of patients with both AF and hypertension in which over 19 000 patient-years of risk were analyzed, none of the main antihypertensive drug classes prescribed was associated with either an increased or decreased risk in all subgroups. Nevertheless, a general trend was observed whereby the higher the number of antihypertensive drugs prescribed the lower the mortality rate. Prescription of statins was associated with lower mortality in men and women aged <80 years, whereas prescription of loop diuretics and thiazides was associated with higher mortality in women aged <80 years. Across the whole study population, prescription of loop diuretics was associated with high mortality, whereas prescription of anticoagulants, non-selective β -blockers, ARBs and statins was associated with lower mortality.

Prescription of a high number of antihypertensive drugs to AF patients with hypertension tended to result in lower mortality, suggesting that the more antihypertensive drugs administered, the better the protective effect they exert in controlling hypertension. This overall protective effect of multiple antihypertensive drugs could be explained by the poor blood pressure control in Sweden,^{20,21} similar to other countries,^{22–25} and that the blood pressure control may be better in those with multiple antihypertensive drugs. This is consistent

with meta-analyses where all main antihypertensive drug classes were shown to be equally beneficial.^{3–5} A conclusion of these meta-analyses was that control of blood pressure was of greater importance than prescription of antihypertensive drugs of any specific class and our findings suggest that this may hold true for AF patients with hypertension as well. It is also possible that the protective effects of prescribed RAS blockers, and more specifically ARBs, in the current study could be due to their well-documented positive effects on heart function.²⁶ A gender difference could also be in place, as a mortality risk reduction of ARB compared with ACE inhibitors have been shown in women but not in men with heart failure.²⁷ Having said that, ARBs are often prescribed in combined formulations with low-dose thiazides, which have previously been shown to delay the onset of heart failure in AF patients better than other antihypertensive drugs.^{28,29} This could also be the explanation to the lower mortality seen in men with thiazides.

The higher mortality in women aged >80 years prescribed either loop diuretics (or possibly also thiazides) in the current study may be explained by these women having symptomatic heart failure, which would imply a potential confounding by indication.^{30,31} Mortality among AF patients has been shown to increase greatly in individuals with concomitant heart failure.¹⁶ When thiazides are prescribed alone, higher doses are often used, which could result in low potassium levels.

In an earlier study, we showed that a greater proportion of AF patients were prescribed statins and fewer non-selective β -blockers in

Table 3a Cox regression models for men ($n=2809$) aged 45–104 years with atrial fibrillation and hypertension attending the 75 primary health-care centers for a period of 1–7 years, stratified by age: 45–79 years ($n=2132$) and 80–104 years ($n=677$)

	Men aged <80 years		Men aged ≥80 years		Men all ages	
	Model A	Model B	Model A	Model B	Model A	Model B
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
<i>Antithrombotic drugs</i>						
Antiplatelet agents vs. no treatment	1.10 (0.54–2.19)	1.29 (0.62–2.68)	0.47 (0.21–1.02)	0.44 (0.19–1.04)	0.76 (0.45–1.26)	0.83 (0.49–1.42)
Anticoagulant agents vs. no treatment	0.53 (0.27–1.03)	0.70 (0.33–1.45)	0.40 (0.19–0.88)	0.42 (0.17–1.04)	0.44 (0.26–0.72)	0.54 (0.31–0.93)
Anticoagulants vs. antiplatelets	0.61 (0.41–0.92)	0.59 (0.39–0.90)	0.82 (0.50–1.35)	0.78 (0.47–1.29)	0.70 (0.51–0.96)	0.66 (0.48–0.92)
Digitalis	1.35 (0.91–2.02)	1.27 (0.85–1.91)	1.13 (0.71–1.79)	1.06 (0.66–1.70)	1.29 (0.95–1.74)	1.22 (0.90–1.64)
Thiazides	0.61 (0.40–0.92)	0.70 (0.45–1.07)	0.60 (0.36–0.98)	0.69 (0.41–1.15)	0.62 (0.45–0.85)	0.69 (0.50–0.95)
Loop diuretics	1.31 (0.86–2.01)	1.25 (0.79–1.96)	1.52 (0.92–2.51)	1.52 (0.89–2.62)	1.39 (1.01–1.93)	1.33 (0.93–1.88)
Aldosterone antagonists	1.52 (0.93–2.46)	1.51 (0.90–2.51)	1.17 (0.66–2.08)	1.01 (0.56–1.83)	1.40 (0.96–2.02)	1.32 (0.90–1.95)
<i>β-Blockers</i>						
β1-Selective vs. no treatment	0.93 (0.58–1.50)	1.09 (0.66–1.78)	1.01 (0.60–1.70)	1.09 (0.64–1.85)	0.99 (0.69–1.40)	1.12 (0.77–1.59)
Non-selective vs. no treatment	0.62 (0.27–1.38)	0.83 (0.35–1.89)	0.47 (0.14–1.64)	0.53 (0.15–1.88)	0.55 (0.28–1.08)	0.68 (0.34–1.36)
Non-selective vs. β1-selective	0.69 (0.33–1.44)	0.67 (0.32–1.40)	0.42 (0.13–1.37)	0.39 (0.12–1.25)	0.57 (0.32–1.05)	0.54 (0.29–1.01)
<i>RAS-blocking agents</i>						
ACE inhibitors vs. no treatment	0.70 (0.45–1.10)	0.72 (0.45–1.15)	1.19 (0.69–2.06)	1.13 (0.69–1.98)	0.85 (0.60–1.20)	0.89 (0.62–1.27)
ARBs vs. no treatment	0.66 (0.36–1.20)	0.73 (0.39–1.36)	0.44 (0.19–1.05)	0.38 (0.16–0.91)	0.60 (0.37–0.97)	0.63 (0.38–1.04)
ARBs vs. ACE inhibitors	1.14 (0.66–1.98)	1.13 (0.65–1.96)	0.47 (0.21–1.05)	0.46 (0.20–1.04)	0.83 (0.53–1.30)	0.84 (0.53–1.32)
ACE inhibitor + thiazide vs. no treatment	0.70 (0.41–1.22)	0.78 (0.44–1.35)	0.48 (0.15–1.52)	0.53 (0.16–1.69)	0.64 (0.39–1.05)	0.70 (0.42–1.14)
ARB + thiazide vs. no treatment	0.69 (0.30–1.58)	0.64 (0.28–1.48)	0.74 (0.27–2.04)	0.61 (0.21–1.72)	0.70 (0.37–1.32)	0.68 (0.36–1.30)
ARB + thiazide vs. ACE inhibitor + thiazide	1.39 (0.54–3.58)	1.28 (0.49–3.35)	1.21 (0.35–4.19)	0.84 (0.21–3.39)	1.40 (0.66–2.97)	1.27 (0.59–2.72)
<i>Calcium receptor-blocking agents</i>						
Vessel selective vs. no treatment	0.79 (0.53–1.18)	0.89 (0.59–1.35)	0.86 (0.54–1.37)	0.86 (0.53–1.38)	0.80 (0.59–1.09)	0.87 (0.64–1.19)
Heart active vs. no treatment	0.81 (0.35–1.89)	0.90 (0.38–2.12)	0.41 (0.10–1.71)	0.37 (0.08–1.75)	0.64 (0.31–1.32)	0.70 (0.34–1.45)
Heart active vs. vessel selective	1.13 (0.48–2.67)	0.92 (0.37–2.27)	0.49 (0.12–2.05)	0.52 (0.11–2.39)	0.85 (0.41–1.78)	0.74 (0.34–1.58)
Statins	0.46 (0.29–0.73)	0.52 (0.33–0.83)	1.13 (0.65–1.96)	1.23 (0.70–2.16)	0.59 (0.41–0.85)	0.66 (0.46–0.95)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cerebrovascular disease; HR, hazard ratio; RAS, renin-angiotensin system.

Model A was adjusted for a propensity score comprising age group, cardiovascular co-morbidity (diabetes, CHD, CHF and CVDs), educational level and marital status. Model B was adjusted for a propensity score including all variables in Model A and all the anti-hypertensive drugs, antithrombotics and statins (except the studied drug class). Hazard ratios (HRs) with 95% confidence intervals (95% CIs) are shown.

Statistically significant results are indicated in bold.

2007 than in 2002.³² In the current study, prescription of statins and non-selective β-blockers was associated with lower mortality, implying that the increased statin prescription rate is of benefit to patients with AF, whereas the lower rate of non-selective β-blockers may not have the same effect. The finding of a lower mortality in those prescribed statins may hold true as it has previously been shown that individuals prescribed statins have lower overall mortality than those not prescribed them.³³ There may also be other mechanisms at play. For example, statins are known to reduce low-density lipoprotein levels and cholesterol has been discussed as a risk factor for AF.³⁴ In addition, statins have been shown to have antiarrhythmic properties.³⁵

The negligible effect of prescribed antithrombotics on mortality in women could be explained by our models being adjusted for other pharmacotherapies, diagnosed comorbidities and diabetes. It could also be explained by low doctors' adherence to CHADS₂ treatment recommendations in Sweden.³² The good effect of anticoagulants vs. antiplatelets in men is in line with and supported by the current recommendation to treat AF patients at high risk of stroke with anticoagulants, for example, warfarin.^{36–38}

Limitations and strengths

Despite having adjusted for many covariates using propensity scores to stabilize the complex statistical models,³⁹ we cannot rule out the effect of residual confounding factors. In addition, patient data were extracted from primary health-care records, which may not necessarily have included details of medications prescribed by other caregivers. Besides medications, lists of diagnoses for each patient may

have been incomplete, although diagnoses of cardiovascular diseases and diabetes were likely accurately recorded in the primary care records.⁴⁰

Another limitation was the absence of CHF disease severity in the patient records. Also, the prescription of drugs in observational studies may be subject to confounding by indication.^{30,31} A further weakness of the present study was our inability to classify AF as paroxysmal, persistent or permanent. It was thus impossible to draw conclusions about which drugs were more appropriate for treating the different types of AF. Also, no information on catheter ablation procedures or Cox-Maze operations was available for the study population. Finally, we did not have access to blood pressure levels.

A key strength of this study was our ability to link patient data extracted from primary health-care records to data from national demographic and socioeconomic registers with <1% of information missing. In addition, a study of the diagnoses recorded in the electronic patient records showed that fewer than 2% of all diagnoses were missing.⁴⁰ The comprehensive nature of our data made it possible to analyze men and women with different educational levels and socioeconomic or marital statuses. In addition, the large population size (2809 men and 2793 women; over 19 000 person-years of risk) was a major strength of this study. A power calculation for Cox regression analysis revealed that with a power of over 80%, we were able to detect HRs >1.5 or <0.67 for dichotomous variables in both men and women. However, as we stratified the population by age, the power decreased for some models; it increased in models adjusted for sex.

Table 3b Cox regression models for women ($n = 2793$) aged 45–104 years with atrial fibrillation and hypertension attending the 75 primary health-care centers for a period of 1–7 years, stratified by age: 45–79 years ($n = 1539$) and 80–104 years ($n = 1254$)

	Women aged < 80 years		Women aged ≥ 80 years		Women all ages	
	Model A	Model B	Model A	Model B	Model A	Model B
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
<i>Antithrombotic drugs</i>						
Antiplatelet agents vs. no treatment	1.24 (0.43–3.58)	1.25 (0.40–3.79)	1.11 (0.63–2.05)	1.21 (0.62–2.31)	1.06 (0.63–1.80)	1.11 (0.64–1.93)
Anticoagulant agents vs. no treatment	0.88 (0.30–2.55)	0.64 (0.21–2.01)	0.93 (0.49–1.76)	0.77 (0.38–1.57)	0.91 (0.52–1.57)	0.81 (0.44–1.48)
Anticoagulants vs. antiplatelets	0.67 (0.41–1.10)	0.76 (0.45–1.26)	0.93 (0.64–1.34)	0.94 (0.65–1.37)	0.83 (0.62–1.12)	0.91 (0.67–1.23)
Digitalis	1.02 (0.62–1.69)	0.88 (0.53–1.47)	1.16 (0.82–1.64)	1.14 (0.79–1.64)	1.11 (0.83–1.48)	1.03 (0.77–1.38)
Thiazides	1.24 (0.76–2.02)	1.78 (1.07–2.95)	0.79 (0.55–1.12)	0.84 (0.58–1.22)	0.91 (0.69–1.21)	1.07 (0.80–1.45)
Loop diuretics	2.06 (1.13–3.75)	2.33 (1.25–4.37)	1.19 (0.79–1.80)	1.21 (0.77–1.89)	1.46 (1.03–2.07)	1.53 (1.05–2.20)
Aldosterone antagonists	1.27 (0.71–2.25)	1.21 (0.68–2.18)	1.05 (0.69–1.60)	1.02 (0.66–1.58)	1.19 (0.85–1.66)	1.15 (0.81–1.62)
<i>β-Blockers</i>						
β1-Selective vs. no treatment	0.87 (0.46–1.65)	0.91 (0.48–1.77)	0.87 (0.58–1.31)	0.90 (0.59–1.38)	0.85 (0.60–1.20)	0.88 (0.62–1.25)
Non-selective vs. no treatment	0.52 (0.17–1.64)	0.59 (0.38–1.94)	0.77 (0.36–1.64)	0.76 (0.35–1.64)	0.62 (0.33–1.17)	0.66 (0.34–1.25)
Non-selective vs. β1-selective	0.54 (0.19–1.50)	0.52 (0.19–1.46)	0.88 (0.44–1.76)	0.86 (0.41–1.75)	0.76 (0.43–1.35)	0.73 (0.41–1.31)
<i>RAS-blocking agents</i>						
ACE inhibitors vs. no treatment	0.70 (0.40–1.23)	0.63 (0.35–1.11)	0.99 (0.67–1.46)	1.00 (0.67–1.49)	0.88 (0.64–1.21)	0.85 (0.61–1.19)
ARBs vs. no treatment	0.43 (0.18–1.00)	0.38 (0.15–0.91)	0.66 (0.37–1.20)	0.76 (0.41–1.41)	0.53 (0.33–0.88)	0.55 (0.33–0.91)
ARBs vs. ACE inhibitors	0.60 (0.26–1.37)	0.57 (0.25–1.30)	0.65 (0.37–1.17)	0.67 (0.37–1.20)	0.60 (0.37–0.97)	0.60 (0.37–0.96)
ACE inhibitor + thiazide vs. no treatment	1.12 (0.60–2.09)	1.34 (0.71–2.53)	0.78 (0.47–1.29)	0.83 (0.50–1.37)	0.88 (0.60–1.30)	0.98 (0.66–1.44)
ARB + thiazide vs. no treatment	0.61 (0.22–1.71)	0.69 (0.25–1.94)	0.50 (0.22–1.14)	0.52 (0.23–1.18)	0.52 (0.27–0.98)	0.55 (0.29–1.05)
ARB + thiazide vs. ACE inhibitor + thiazide	0.62 (0.21–1.89)	0.60 (0.20–1.82)	0.67 (0.27–1.68)	0.63 (0.25–1.57)	0.62 (0.31–1.25)	0.59 (0.29–1.20)
<i>Calcium receptor-blocking agents</i>						
Vessel selective vs. no treatment	0.86 (0.50–1.46)	0.93 (0.54–1.59)	0.70 (0.47–1.03)	0.73 (0.49–1.09)	0.75 (0.55–1.02)	0.80 (0.58–1.10)
Heart active vs. no treatment	1.17 (0.52–2.67)	1.15 (0.49–2.59)	0.71 (0.37–1.35)	0.61 (0.32–1.19)	0.90 (0.54–1.48)	0.78 (0.47–1.32)
Heart active vs. vessel selective	1.28 (0.55–2.97)	1.59 (0.65–3.90)	1.15 (0.58–2.24)	1.05 (0.51–2.14)	1.23 (0.73–2.08)	1.16 (0.67–2.01)
Statins	0.31 (0.16–0.58)	0.33 (0.17–0.64)	0.89 (0.56–1.39)	0.96 (0.61–1.53)	0.57 (0.39–0.83)	0.61 (0.42–0.90)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cerebrovascular disease; HR, hazard ratio; RAS, renin-angiotensin system.

Model A was adjusted for a propensity score comprising age group, cardiovascular comorbidity (diabetes, CHD, CHF and CVDs), educational level and marital status. Model B was adjusted for a propensity score including all variables in Model A and all the antihypertensive drugs, antithrombotics and statins (except the studied drug class). HRs with 95% CIs are shown.

Statistically significant results are indicated in bold.

Table 4 Cox regression models for men ($n = 2809$) and women ($n = 2793$) aged 45–104 years with atrial fibrillation and hypertension attending the 75 primary health-care centers for a period of 1–7 years stratified into two age groups: 45–79 years (men, $n = 2132$; women, $n = 1539$) and 80–104 years (men, $n = 677$; women, $n = 1254$)

		Men				Women		
		All ages	< 80 years	≥ 80 years	All ages	< 80 years	≥ 80 years	All ages
n	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Number of antihypertensive drugs								
0–1	861	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2	1516	0.85 (0.63–1.14)	0.94 (0.54–1.66)	0.88 (0.46–1.69)	0.95 (0.63–1.45)	0.41 (0.19–0.91)	0.88 (0.52–1.50)	0.74 (0.48–1.13)
3	1719	0.80 (0.60–1.08)	0.92 (0.52–1.65)	0.48 (0.23–0.98)	0.76 (0.49–1.18)	0.65 (0.32–1.35)	0.94 (0.57–1.56)	0.84 (0.56–1.27)
4–5	1506	0.62 (0.45–0.86)	0.51 (0.26–1.00)	0.62 (0.29–1.30)	0.57 (0.35–0.94)	0.68 (0.33–1.41)	0.58 (0.33–1.02)	0.63 (0.40–0.98)
P-value for trend		0.005	0.079	0.063	0.021	0.55	0.096	0.075

Abbreviations: CI, confidence interval; HR, hazard ratio; RAS, renin-angiotensin system.

The relative risk associated with the total number of prescribed antihypertensive drugs (thiazides, potassium-saving diuretics, β-blockers, RAS blockers and calcium antagonists) was calculated. The models were adjusted for age group, comorbidities, educational level, marital status and prescribed drugs other than antihypertensives (antithrombotic drugs, digitalis, loop diuretics and statins). The model for the whole sample was also adjusted for sex.

Statistically significant results are indicated in bold.

Although many previous follow-up studies of AF have used hospital data for severely ill patients, the current study used data from primary care, which may better reflect the risks associated with AF in the society as a whole. In addition, randomized controlled trials often exclude individuals with comorbidities, such as AF patients with concomitant diabetes and CHF. In the current study, we were able to include these patients in the analyses. Our findings may thus be more representative of the variety of AF patients attending PHCCs today.

In conclusion, AF patients with hypertension prescribed statins had lower relative mortality risks, suggesting that statins were of great benefit to these patients. Furthermore, prescription of non-selective β-blockers and ARBs was associated with lower mortality in sex-adjusted models. This needs to be further explored in future studies of AF patients with hypertension in other types of clinical settings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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