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Antihypertensive drugs and relevant cardiovascular pharmacotherapies and the risk of incident dementia in patients with atrial fibrillation

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Abstract

BACKGROUND: Atrial fibrillation (AF) and dementia are predominant among the elderly; patients with AF have an increased dementia risk. We aimed to study if prescribed antihypertensive drugs and cardiovascular pharmacotherapies are associated with a lower relative risk of dementia.

METHODS: All included patients were ≥45 years and diagnosed with AF in primary care; 12,096 (6,580 men and 5,516 women) in Sweden. We excluded patients with a dementia diagnosis before onset of AF. Cox regression was used (hazard ratios, HRs, and 95% confidence interval, CI) with adjustments for sex, age, socioeconomic factors and co-morbidities.

RESULTS: Incident dementia occurred in 750 patients (6.2%) during an average of 5.6 years of follow-up (a total of 69,214 person-years). Patients prescribed thiazides HR 0.81 (95% CI 0.66–0.99) and warfarin HR 0.78 (95% CI 0.66–0.92) had a lower risk of dementia than patients without these drugs. The use of 1–4 of the different antihypertensive drug classes (thiazides, beta blocker, vessel active calcium channel blockers or renin angiotensin aldosterone (RAAS) blockers) were associated with a reduction of incident dementia; HR 0.80 (95% CI 0.64–1.00) for one to two

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Conflict of interest

The authors have no conflict of interest to disclose.

drugs, and HR 0.63 (95% CI 0.46–0.84) for three or four drugs, versus having no prescribed antihypertensive drugs. The combination of a RAAS-blocker and a thiazide was significant, HR 0.70 (95% CI 0.53–0.92), versus not having that particular combination prescribed, while RAAS-blockers or thiazides separately were not significant.

CONCLUSION: Prescribed antihypertensive drugs, including thiazide/RAAS-blocker combination therapy and use of warfarin, were associated with a decreased incidence of dementia.

Keywords

Atrial fibrillation; dementia; antihypertensive drugs; hypertension

1. Introduction

The dementia risk among older adults seems to be influenced by prevalent cerebrovascular and cardiovascular risk factors [1]. Atrial fibrillation (AF) is the most common arrhythmia worldwide, with a prevalence of 2% in Sweden [2]. Patients with AF are typically older than the general population and are prescribed more antihypertensive drugs and other cardiovascular pharmacotherapies than other older individuals; these patients may therefore be a suitable population to study associations between relevant pharmacotherapies and dementia.

Provided that the relevant risk factors are known, dementia risk can be reduced. A summary of the evidence on modifiable risk factors for cognitive decline and dementia concluded that there seems to be sufficiently strong evidence to conclude that regular physical activity, and also management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) decreases the risk of cognitive decline and may reduce the risk of dementia [3]. Specific cardiovascular drug classes, which are needed anyway, could thus be a good addition to existing forms of treatment. In an earlier study we found hypertension among female AF patients to be associated with a decreased risk of dementia [4], possibly an effect of antihypertensive treatment. Another study found that use of antihypertensive medication preserved cognitive function in older Afro-American adults [5]. Besides, a review on the use of antihypertensive medication concluded, the antihypertensive drugs could decrease risk of the development any dementia, but more specifically vascular dementia [6]. Furthermore, it was concluded in a review from The Swedish Council on Health Technology Assessment in Health Care (SBU) that there is moderately strong evidence that good control of blood pressure in middle age reduces the risk of later onset of dementia, and that treatment with antihypertensive drugs reduces the risk of developing stroke-related dementia later in life [7]. However, results from studies as summarized in reviews and meta-analyses have been somewhat conflicting. One review of observational and RCT studies concluded that “antihypertensive drugs, in particular calcium channel blockers and renin–angiotensin system blockers, may be beneficial in preventing cognitive decline and dementia”, but that “randomized controlled trials and meta-analyses have sometimes produced conflicting results, but these are probably due to methodological considerations” [8]. Another review concluded that calcium receptor blockers, diuretics and ACE inhibitors reduce the risk of dementia but, in the majority of studies, that only ACE inhibitors and diuretics significantly reduced the risk for and progression of dementia [9]. A more recent review suggested that

angiotensin II receptor blockers (ARBs) can improve cognitive functions in the elderly while diuretics, beta blockers, calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors do not [10]. Another study, more specifically among patients with diabetes, showed that antihypertensive medications, especially ACE inhibitors and ARBs were associated with a reduced risk of dementia [11]. However, there is a lack of studies on the effect of antihypertensive drugs in patients with AF concerning the development of dementia.

Furthermore, anticoagulant treatment is of interest as anticoagulants are not only effective in preventing ischemic stroke among patients with AF [12] and have been shown to also decrease the risk of dementia [13]. However, underuse of anticoagulant treatment is more common in older patients with AF with dementia than in patients with AF without dementia [14].

Our aims were to study the associations in primary health care in Sweden between prescribed antihypertensive drugs and other relevant cardiovascular pharmacotherapies and dementia among men and women with AF. We hypothesized that some of these commonly used pharmacotherapies could affect the risk of incident dementia and potentially be used to reduce the risk of dementia in preventive efforts in patients with cardiovascular disorders.

2. Methods

2.1 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.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 was created containing clinical data and information on socioeconomic status on the individuals (n=1,098,420) registered at the 75 PHCCs. The investigation conforms with the principles outlined in the Declaration of Helsinki. Ethical approvals were obtained from the regional boards at Karolinska Institutet and the University of Lund.

2.2 Study population

The study included all patients with diagnosed AF, 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 at the PHCCs. The following cardiovascular related disorders were used as covariates: hypertension, coronary heart disease (CHD), congestive heart failure (CHF), cerebrovascular diseases (CVD), obesity, diabetes mellitus, depression and COPD (for specific codes, see below). The study included a total of 12,096

patients (6,580 men and 5,516 women), aged 45 years or older at the time of AF diagnosis, with patients with an earlier dementia excluded (n=187), and who visited any of the 75 participating PHCCs from January 1, 2001, until December 31, 2007, with data on neighborhood socioeconomic status (NSES) available.

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 it started, until 31 December 2010 [15, 16]. Substances were recorded, which meant that medical drugs could be single-substance drugs, or combined medical drugs with the substances recorded separately, e.g. a RAAS-blocking agent combined with a thiazide thus being recorded into two separate groups. Warfarin (B01AA03) and 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 RAAS-blocking agents with ACE inhibitors (C09AA and C09BA) and angiotensin receptor blocking (ARB) agents (C09CA, C09DA and C09DB).

2.4 Outcome variable

For Cox regression: time from first AF diagnosis to first hospital diagnosis of dementia (with the following groups: F00 Alzheimer's disease, F01 Vascular dementia, F02 Other dementia diseases, F03 Unspecified dementia, F10.7A Alcohol-related dementia, G30 Alzheimer) (until December 31, 2010).

2.5 Demographic and socioeconomic 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), with missing data from 1,041 individuals.

Marital status was classified as married, unmarried, divorced or widowed, with missing data from 50 individuals.

Neighborhood socioeconomic status (NSES) 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 NSES or high deprivation), and within one SD of the mean (middle NSES or deprivation). The neighborhood index was 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 NSES or low deprivation level), more than one SD above the mean (low NSES or high deprivation level), and within one SD of the mean (moderate NSES or moderate deprivation level).

2.6 Co-morbidities

We identified the following cardiovascular co-morbidities from the EPRs among the individuals in the study population: hypertension (I10–I15); coronary heart disease (CHD; I20–I25), also including registered hospitalizations for myocardial infarction from the NPR; congestive heart failure (CHF; I50 or I110), also including hospitalizations for CHF from the NPR; cerebrovascular diseases (CVD; I60–I69), also including registered hospitalizations for ischemic or hemorrhagic stroke from the NPR; diabetes mellitus (E10–E14); obesity (E65–E68); COPD (J40–J47); depression (F32–F34, F38–F39); and anxiety disorders (F40–F41).

2.7 Statistical analyses

Differences in means and distributions between individuals with or without dementia were compared by Student's *t*-test, chi-square analysis and Fisher's exact test. Age-adjustments were performed with logistic regression, and for marital status and socioeconomic factors by ANCOVA.

For patients with incident dementia, excluding those with a dementia diagnosis before the first registered AF diagnosis, follow-up analyses were performed by using Cox regression estimating hazard ratios (HRs) with 95% confidence intervals (CIs); time to the first hospital diagnosis of dementia was used as the outcome. The regression models were also tested for possible interactions, and a significant interaction was found between age and marital status. We used four models; in the first two the pharmacotherapies were tested separately; in Model 1 with adjustment for age and sex; and in Model 2 also for socioeconomic factors (educational level, marital status and NSES). Additional adjustments for non-cardiovascular co-morbidity (obesity, diabetes, COPD, depression and anxiety), and cardiovascular co-morbidities (hypertension, myocardial infarction, CHF and cerebrovascular diseases) were added in Model 4. In the full models, we also analyzed the association between the number of the most common classes of antihypertensive drugs (thiazides, beta blockers, vessel active calcium blockers and RAAS-blockers) with incident dementia, and the association between RAAS-blockers and thiazides and incident dementia.

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 Cox regression. All analyses were performed in STATA 11.2.

3. Results

Baseline characteristics

In Table 1 the characteristics of the entire study population consisting of patients with AF, n=12,096 patients (6,580 men and 5,516 women) are shown, stratified into those with a diagnosis of dementia (yes/no) during follow-up. The prescribed drugs for patients with or without incident dementia are shown in Table 2.

Follow-up

In total, 750 patients (6.2%) were diagnosed with dementia during the follow-up of whom 322 were men (4.9%) and 428 were women (7.8%). The mean follow-up time until first hospital diagnosis of dementia in those without previous dementia was 5.6 years (standard deviation 2.5). Patients were followed for a total of 69,214 person-years: 38,184 person-years for men and 31,030 person-years for women.

The relative risk of dementia

The relative risks of a first hospital diagnosis for dementia are shown in Table 3. Warfarin and thiazides were consistently associated with a lower risk (HR) of incident dementia across the models. ACE inhibitors and the combined group RAAS-blockers were associated with a lower risk in the two first models, but not when adjusting for co-morbidity, and the combined group of all beta blockers was only associated with a lower risk in Model 2, which was adjusted for sex, age and socioeconomic factors. Table 4 shows the results from the analyses of the four most important antihypertensive drug classes (thiazides, beta blockers, vessel active calcium blockers and RAAS-blockers) and their association with incident dementia; the associations between RAAS-blockers and thiazides alone and combined with incident dementia are also shown. Using one or two of the four classes of antihypertensive drugs was associated with a 20% lower relative risk, and three or four classes a 37% lower relative risk of incident dementia. Analyses of the relation between RAAS-blockers and thiazides showed that only these two drugs combined show a lower risk of dementia.

For the sensitivity analysis we excluded the lowest and highest quartiles of ages for patients developing dementia (patients < 77 and > 85 years of age). Fully adjusted estimates for thiazides were non-significant but the combination of a thiazide and a RAAS-blocker was still significant (HR 0.67, 95% CI 0.48–0.94), and vessel active calcium channel blockers were also significant (HR 0.73, 95% CI 0.56–0.98).

4. Discussion

The main findings of this observational study were that warfarin and thiazides were associated with a significantly lower risk of incident dementia, which was defined as a first hospital diagnosis of dementia. However, further analyses showed that only the combination between thiazides and a RAAS blocking agent was associated with a significantly lower relative risk - not thiazides without the combination with a RAAS-blocker. The number of the four most important antihypertensive drugs was also significant, and three or four antihypertensive drugs were associated with a 37% relative risk reduction, while one or two

of the drugs from these classes showed a borderline significance of just below p 0.05; when compared to those without prescribed antihypertensive drugs.

In a recently published study it was concluded that “AF is associated with accelerated cognitive decline and higher risk of dementia even at ages when AF incidence is low” [17]. Identifying medical drugs with a possible preventive effect on dementia development is thus of great importance.

The result of warfarin being associated with a significantly lower dementia risk is in-line with earlier findings as anticoagulant treatment has been shown to decrease the risk of dementia among patients with AF [13]. Furthermore, the fact that underuse of anticoagulant drugs is more common among patients with AF and dementia than among patients with AF without dementia [14].

Regarding effects of antihypertensive drugs, earlier studies have found somewhat conflicting results but many classes of antihypertensive drugs have been associated with a dementia preventive effect, such as diuretics [9, 18], calcium channel blockers [8, 9], and RAAS-blockers [8], including ACE inhibitors [9], and ARBs [10]. Our results showing that the use of multiple antihypertensive drugs are associated with a lower relative risk of dementia concur with findings from a review, concluding that there is evidence that good control of blood pressure in middle age reduces the risk of later onset of dementia, and that treatment with antihypertensive drugs reduces the risk of developing stroke-related dementia later [7]. When compared with those without prescribed antihypertensive drugs, we found a reduction of incident dementia of 20% when using one or two out of the four most important classes of antihypertensive drugs, and 37% when using three or four out of these classes. An Italian study found a high rate of suboptimal drug prescription among elderly patients, thus supporting our findings [19]. However, thiazides was the only drug with a consistently lower risk but only when combined with a RAAS-blocker. We divided diuretic drugs into thiazides, loop diuretics and aldosterone antagonists, as the latter two are mostly used in patients with CHF; we did not see a protective effect by these two classes of diuretic drugs. By contrast, we found loop diuretics to be associated with a higher dementia risk but only in the full model. This finding could be the result of association with more fragile individuals or possibly an artefact.

Although we found an increased number of antihypertensive medications to be associated with a lower risk of incident dementia among AF patients, there are also problems with polypharmacy. The risk of side-effects and drug interactions are likely more common in patients with many prescribed drugs. The complexity and the practical handling of many drugs is also more complex for the prescriber, healthcare, pharmacists and patients. Thus, the benefits of treatment must be weighed against the risks of polypharmacy. In addition, in the earlier cited review it was concluded that too low blood pressure may be predictive of clinical dementia and AD as well among subjects aged 75 years and older, even if the evidence is limited [7]. Another topic of importance is the possibility of arterial stiffness among elderly as pulse wave velocity (PWV) does not seem to be a surrogate for blood pressure itself [20], and that not only blood pressure but also higher PWV and hypotension together with cerebral microvascular damage are predictive for poorer cognitive function

[21]. However, the topic of arterial stiffness and possible hypotension goes beyond the scope of our study as we did not have access to data regarding blood pressure or PWV.

There are several limitations of this study. The study sample is a subgroup of the AF population, i.e. patients with AF without dementia registered in primary health care at baseline. In another study, it was found that 36% of all registered patients with AF in Stockholm County were not registered with a diagnosis in primary health care [2]. Results cannot be generalized to all patients with AF or patients with dementia or to patients in other settings. The findings may have been subject to confounding by indication and to survival bias [22], however, we adjusted for registered co-morbidities to limit these effects. We did not have access to blood pressure levels. AF is sometimes difficult to diagnose and can be missed for a number of years. We only had access to dementia diagnosis, and it mostly had a long prodromal period before a diagnosis was set. Regarding dementia diagnoses in registers, these are not validated, and besides the patterns of different dementia types we found did not correspond well to the generally accepted distributions, hence why we decided not to divide into specific types of dementia, as we consider that this could be misleading. Furthermore, cognitive performance at baseline is a possible confounder. We had no access to type of AF, i.e. whether classified as paroxysmal, persistent or permanent, and could not classify heart rhythm into sinus rhythm or fibrillation rhythm. All of these mentioned factors could have affected the results and yielded discrepant findings. However, we believe that the effects of the prescribed drugs on the development of dementia is more likely to be a general effect than specific to patients with AF in primary care, and thus of relevance for patients with the need for antihypertensive drugs and cardiovascular pharmacotherapies in general.

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 health 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 health care, we found a number of antihypertensive drugs to be associated with a lower dementia risk. Besides, among the specific classes, thiazides were associated with a lower dementia risk, but only in combination with a RAAS blocking agent. Thus, this emphasizes the positive effect of the combination of RAAS-blockers and thiazides also in the primary care setting among AF patients. We believe that these findings should be confirmed in clinical trials but that they could be considered when choosing pharmacotherapy in patients with a high risk of dementia.

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Highlights

- The present study explores the impact of the different classes of antihypertensive drugs on the connection between atrial fibrillation and incident dementia
- Thiazides were associated with a lower risk of incident dementia among patients with atrial fibrillation
- Thiazides to be significantly associated with reduced risk of dementia only in combination with RAAS-blocker treatment
- Use of 3–4 antihypertensive drugs were associated with a further decreased risk compared to 1–2 drugs

Baseline characteristics for patients aged 45 years with diagnoses of AF (n=12,096 patients, 6,580 men and 5,516 women), and with or without incident dementia in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007

Table 1

	All N=12,096	No dementia N=11,346	Dementia N=750	Difference Age-adjusted
	Numbers (%)	Numbers (%)	Numbers (%)	<i>p-values</i>
Number of deaths	3,812 (31.5)	3,354 (29.6)	458 (61.1)	
Age (years), mean (SD)	72.3 (10.1)	73.9 (10.1)	80.1 (6.5)	<0.001
Age groups (years)				<0.001
45–54	474 (3.9)	474 (4.2)	0 (0.0)	
55–64	1,741 (14.4)	1,722 (15.2)	19 (2.5)	
65–74	3,297 (27.3)	3,196 (28.2)	101 (13.5)	
75–79	2,392 (19.8)	2,205 (19.4)	187 (24.9)	
80–84	2,394 (19.8)	2,144 (18.9)	250 (33.3)	
85	1,798 (14.9)	1,605 (14.2)	193 (25.7)	
Educational level				0.55
Compulsory schooling	4,999 (45.1)	4,671 (44.8)	328 (49.9)	
Secondary schooling	3,951 (35.6)	3,734 (35.8)	217 (33.0)	
College and/or university studies	2,142 (19.3)	2,029 (19.5)	113 (17.2)	
Marital status				0.046
Married	5,552 (46.1)	5,269 (46.6)	283 (37.8)	
Unmarried	1,020 (8.5)	979 (8.7)	41 (5.5)	
Divorced	1,789 (14.9)	1,704 (15.1)	85 (11.4)	
Widowed	3,688 (30.6)	3,348 (29.6)	340 (45.4)	
Neighborhood SES				0.98
High	4,538 (37.5)	4,221 (37.2)	317 (42.3)	
Middle	5,710 (47.2)	5,365 (47.3)	345 (46.0)	
Low	1,848 (15.3)	1,760 (15.5)	88 (11.7)	
Diagnosis				
Hypertension	5,387 (44.5)	5,081 (44.8)	306 (40.8)	0.044
Coronary heart disease	3,180 (26.3)	2,951 (26.0)	229 (30.5)	0.75
Congestive heart failure	5,570 (46.1)	5,113 (45.1)	457 (60.9)	<0.001

	All N=12,096	No dementia N=11,346	Dementia N=750	Difference Age-adjusted <i>p-values</i>
	Numbers (%)	Numbers (%)	Numbers (%)	
Cerebrovascular diseases	2,514 (20.8)	2,286 (20.2)	228 (30.4)	<0.001
Obesity	612 (5.1)	599 (5.3)	13 (1.7)	0.042
Diabetes mellitus	2,334 (19.3)	2,175 (19.2)	159 (21.2)	0.013
COPD	1,401 (11.6)	1,314 (11.6)	87 (11.6)	0.94
Depression	1,017 (8.4)	919 (8.1)	98 (13.1)	<0.001
Anxiety	485 (4.0)	441 (3.9)	44 (5.9)	0.011

Information on educational level (1,104) and marital status (n=17) is missing for some individuals.

Prescription data for patients aged 45 years with diagnoses of AF and dementia ($n=12,096$) in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007

Table 2

	All N=12,096	No dementia N=11,346	Dementia N=750	Difference Age-adjusted
Warfarin (B01AA03)	6,374 (52.7)	6,058 (53.4)	316 (42.1)	0.027
Digitalis (C01A)	4,261 (35.2)	3,916 (34.5)	345 (46.0)	<0.001
Thiazides (C03A, C03B, C03E, C09B C09DA)	2,911 (24.1)	2,753 (24.3)	158 (21.1)	0.011
Loop diuretics (C03C)	5,952 (49.2)	5,449 (48.5)	453 (60.4)	0.055
Aldosterone antagonists (C03DA)	1,773 (15.7)	1,655 (14.6)	118 (15.7)	0.50
All beta blockers (C07)	8,594 (71.1)	8,108 (71.5)	486 (64.8)	0.13
Beta1-selective agents (C07AB, C07F)	7,598 (62.8)	7,170 (63.2)	428 (57.1)	0.059
Non-selective beta blockers (C07AA)	2,232 (18.5)	2,110 (18.6)	122 (16.3)	0.47
Calcium channel blockers (C08)	3,663 (30.3)	3,425 (30.2)	238 (31.7)	0.32
Heart active (C08D)	1,089 (9.0)	1,000 (8.8)	89 (11.9)	0.003
Vessel selective (C08C, C09DB)	2,746 (22.7)	2,598 (22.8)	157 (20.9)	0.25
RAAS-blocking agents (C09)	5,846 (48.3)	5,528 (48.7)	318 (42.4)	0.007
ACE inhibitors (C09A, C09B)	4,485 (37.1)	4,246 (37.4)	239 (31.8)	0.006
ARB (C09C, C09D)	2,251 (18.6)	2,128 (18.8)	123 (16.4)	0.42
Statins (C10AA)	3,363 (27.8)	3,200 (28.2)	163 (21.7)	0.45

Cox regression models for patients ($n=12,096$) aged 45–104 years with AF and newly diagnosed dementia attending the 75 PHCCs between July 1st 2005 and December 31st 2007.

Table 3

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Warfarin	0.79 (0.68–0.92)	0.77 (0.66–0.91)	0.79 (0.67–0.93)	0.78 (0.66–0.92)
Digitalis	1.10 (0.93–1.25)	1.13 (0.96–1.32)	1.11 (0.94–1.30)	1.13 (0.96–1.33)
Thiazides	0.76 (0.64–0.91)	0.77 (0.64–0.92)	0.82 (0.68–1.00)	0.81 (0.66–0.99)
Loop diuretics	1.04 (0.89–1.20)	1.11 (0.95–1.30)	1.18 (0.98–1.41)	1.34 (1.11–1.61)
Aldosterone antagonists	0.89 (0.73–1.08)	0.92 (0.74–1.13)	0.89 (0.71–1.11)	1.01 (0.81–1.27)
Beta-1-selective blockers	0.92 (0.79–1.06)	0.86 (0.74–1.01)	-	-
Non-selective beta blockers	0.91 (0.75–1.11)	0.85 (0.69–1.04)	-	-
All beta blockers	0.90 (0.77–1.04)	0.81 (0.69–0.95)	0.89 (0.75–1.06)	0.92 (0.77–1.09)
Heart active calcium channel blockers	1.24 (1.00–1.55)	1.26 (1.00–1.59)	1.24 (0.97–1.57)	1.26 (0.99–1.60)
Vessel active calcium channel blockers	0.90 (0.75–1.07)	0.90 (0.75–1.09)	0.98 (0.81–1.19)	0.98 (0.80–1.20)
ACE inhibitors	0.80 (0.69–0.93)	0.84 (0.71–0.99)	-	-
ARB	0.90 (0.74–1.09)	0.89 (0.73–1.09)	-	-
RAAS-blockers	0.81 (0.70–0.93)	0.83 (0.71–0.97)	0.84 (0.71–1.00)	0.93 (0.78–1.11)
Statins	0.99 (0.82–1.18)	0.94 (0.78–1.13)	0.99 (0.82–1.20)	1.03 (0.85–1.25)

Models 1 adjusted for age and sex for each medication; Model 2 adjusted for age, sex, and sociodemographic status (educational level, marital status and neighborhood SES) for each medication; Models 3 for all medications and for non-cardiovascular co-morbidity (obesity, diabetes, COPD, depression and anxiety); and Model 4 also for cardiovascular co-morbidity (hypertension, myocardial infarction, CHF, CVS). Interaction terms are included (for men and women: age and educational level, and age and neighborhood SES). HRs and 95% CIs are shown. Statistically significant HRs are highlighted in bold

Table 4

Cox regression models for patients ($n=12,096$) aged 45–104 years with AF and newly diagnosed dementia attending the 75 PHCCs between July 1st 2005 and December 31st 2007, showing number of antihypertensive medications from the following groups: thiazides, beta blockers, vessel active calcium blockers and RAAS-blockers.

Number of medications	Number of patients	Model 1	Model 2	Model 3 HR (95% CI)	Model 4
0	1,973 (16.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	3,725 (30.8)	0.81 (0.66–0.99)	0.74 (0.59–0.93)	0.76 (0.60–0.95)	0.76 (0.60–0.96)
2	3,626 (30.0)	0.82 (0.66–1.00)	0.77 (0.62–0.96)	0.80 (0.63–1.01)	0.87 (0.68–1.13)
3	1,968 (16.3)	0.65 (0.50–0.84)	0.60 (0.46–0.80)	0.62 (0.46–0.82)	0.67 (0.49–0.92)
4	804 (6.7)	0.58 (0.39–0.85)	0.53 (0.36–0.79)	0.55 (0.37–0.82)	0.60 (0.39–0.92)
1–2	7,351 (60.8)	0.81 (0.68–0.98)	0.75 (0.62–0.93)	0.78 (0.63–0.96)	0.80 (0.64–1.00)
3–4	2,772 (22.9)	0.63 (0.50–0.80)	0.58 (0.45–0.75)	0.59 (0.46–0.78)	0.63 (0.46–0.84)
No RAAS-blocker or thiazides	5,283 (43.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Only RAAS-blocker	3,902 (32.3)	0.87 (0.73–1.02)	0.91 (0.76–1.09)	0.90 (0.74–1.08)	1.00 (0.83–1.22)
Only thiazides	967 (8.0)	0.87 (0.68–1.11)	0.90 (0.69–1.18)	0.95 (0.72–1.24)	0.97 (0.73–1.29)
Both RAAS-blockers and thiazides	1,944 (16.1)	0.62 (0.49–0.79)	0.64 (0.50–0.82)	0.65 (0.50–0.84)	0.70 (0.53–0.92)

Models 1 adjusted for age and sex; Model 2 adjusted for age, sex, and sociodemographic status (educational level, marital status and neighborhood SES); Models 3 for all medications and for non-cardiovascular co-morbidity (obesity, diabetes, COPD, depression and anxiety); and Model 4 also for cardiovascular co-morbidity (hypertension, myocardial infarction, CHF, CVS) Interaction terms are included (for men and women: age and educational level, and age and neighborhood SES)

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