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Effects of cardiovascular pharmacotherapies on incident dementia in patients with atrial fibrillation: A cohort study of all patients above 45 years diagnosed with AF in hospitals in Sweden

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ABSTRACT

Background: Patients with atrial fibrillation (AF) have an increased dementia risk dementia. We aimed to study the effect of antihypertensive drugs on dementia in AF patients.
Methods: Included patients were ≥45 years diagnosed with AF in Swedish National Patient Register (n = 160,251; 89,723 men and 70,528 women) and alive on January 1, 2007. We excluded patients with dementia before onset of AF. Cox regression was used (hazard ratios, HRs, and 99% confidence interval, CI) with adjustments for sex, age, socioeconomic factors and co-morbidities, using incident dementia diagnosis until December 31, 2015 as outcome. Cardiovascular pharmacotherapies were obtained from the Swedish Prescribed Drug Register.
Results: Incident dementia occurred in 9532 patients (5.9%), 4669 men (5.2%) and 4863 women (6.9%). ARBs were associated with lower risk for all patients (HR 0.87, 99% CI 0.78–0.98), especially in the ages 65–84 years of age (HR 0.87, 99% CI 0.76–0.99). Loop-diuretics were associated with higher risk for all dementia among patients 65–84 years of age (HR 1.16, 99% CI 1.00–1.35), and in the sub-group of other causes of dementia than Alzheimer Disease (AD) and vascular dementia (VaD) (HR 1.14, 99% CI 1.00–1.30), but with a lower risk in the sub-group of AD and VaD (HR 0.81, 99% CI 0.68–0.95).
Conclusion: ARBs were associated with a decreased incidence of dementia, and loop diuretics with a higher risk in general but lower risk in the AD and VaD sub-group. ARBs could have specific advantages in prevention of dementia, but the results need confirmation in further studies.

1. Introduction

Dementia risk among older adults is influenced by prevalent cerebrovascular and cardiovascular risk factors [1]. There is evidence that regular physical activity, and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) decreases the risk of cognitive decline, and may reduce the risk of dementia [2]. Potentially modifiable risk factors are estimated to contribute to 35% of dementia cases [3].

Regarding atrial fibrillation (AF) and dementia, a recently published study concluded, that "AF is associated with accelerated cognitive decline and higher risk of dementia even at ages when AF incidence is low" [4]. AF is the most common arrhythmia worldwide, with a prevalence of 2% in Sweden [5]. Patients with AF are typically older than the general population, and have more prescribed cardiovascular pharmacotherapies, including antihypertensive drugs (AH) drugs, than other older individuals.

However, there are conflicting results the possible role of hypertension in relation to incident dementia. Good blood pressure control is associated with a lower risk of dementia [6], while low blood pressure later in life could lead to a higher risk [6,7]. In earlier studies among AF patients, hypertension has been associated with a decreased dementia risk [8,9], possibly an effect of AH treatment.

Regarding specific AH medications, there are also contradictive results, but these conflicting results in randomized controlled trials and meta-analyses could be due to methodological considerations [10]. A Cochrane report concluded, that there are no convincing evidence that AH medication may prevent dementia [11]. Despite this conclusion, specific antihypertensive compounds may have neuroprotective properties reducing the risk of AD [12]. Diuretics are found to prevent

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dementia in general and also AD specifically in several reviews [13], especially true for potassium-sparing diuretics [14,15]. CCBs are shown to be protective in some reviews [10]. RAS-blockers have also been found to be preventive in several studies or reviews [16–19], also specifically in diabetes [20], and many components in the RAS system are altered in AD [16]. In contrast, one review only found central acting ACE-inhibitors to be protective, while peripheral acting ACE-inhibitors showed an increased risk [19]. As regards to ARBs, one review found that ARBs, in contrast to the other main AH groups, can improve cognitive functions among elderly [21], while another found no protective effect [19].

However, the effect by AHs on dementia risk may differ in specific disease groups, such as atrial fibrillation patients. In an earlier smaller study on AF patients in Swedish primary care, we found a combination of a RAS-blocker and a thiazide was associated with a lower risk of dementia [22].

As regards statins and risk of incident dementia, there are also conflicting results, with a Cochrane review reporting no preventive effect when given in late life [23], while another review concluded that statin use could reduce dementia risk [24], and yet another study from the US finding statins to be associated with a lower AD risk [25].

Our aims were to study the associations in a national Swedish cohort of AF patients between AH drugs and incident dementia. 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 AF, especially among those with other cardiovascular disorders.

2. Methods

2.1. Design

The study used data from the National Patient Register (NPR) based on hospital diagnoses in Sweden to identify patients with AF, with data on in-patient diagnoses from 1998, and also on out-patients from 2001. Data were linked with other Swedish registers, i.e. the Swedish Prescribed Drug Register [26,27], the Total Population Register, and the Swedish Cause of Death Register, which contains individual-level data on age, sex, educational level, cause of death and hospital diagnosis for all residents registered in Sweden.

2.2. Study population

We 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 the Swedish National Patient Register (NPR) January 1, 1998 until December 31, 2006, and aged 45 years or above and alive on January 1, 2007, until hospitalization/out-patient treatment of dementia, death, emigration or the end of the study period on December 31, 2015, whichever came first.

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 2006 [26,27]. 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 RAS-blocking agent combined with a thiazide thus being recorded into two separate groups. We recorded the following drugs (ATC-codes in Supplementary files): warfarin; diuretic drugs including thiazides or related agents; loop diuretics or aldosterone antagonists; beta blockers with beta-1-selective agents and non-selective agents; CCBs with heart-active agents and vessel-active agents; and RAS-blocking agents with ACE inhibitors and angiotensin receptor blocking (ARB) agents.

2.4. Outcome variable

New diagnosis of dementia during January 1, 2007 and December 31, 2015 (ICD 10-codes in Supplementary files), with dementia classified into Alzheimer's disease (AD) (n = 7,413, 24.4%) and Vascular dementia (VaD) (n = 7,612, 25.2%) in one sub-group (n = 15,025, 49.5%), and Other dementia diseases (n = 15,307, 50.5%) in the other.

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 NPR among the individuals in the study population at baseline (ICD 10-codes in Supplementary files): hypertension; coronary heart disease (CHD); congestive heart failure (CHF); stroke; obesity; diabetes mellitus; COPD; depression; anxiety disorders; and alcoholism and related disorders.

2.7. Statistical analyses

Characteristics of patients divided into those with and without incident dementia were shown with numbers and percentages, and difference by Chi-Square analysis. A two-sided p-value of <0.01 was considered statistically significant for variables in the Cox regression (with 99% confidence intervals) for the main outcomes, while a p-value of <0.05 was used for sensitivity analyses.

Cox regression analysis was performed, with estimation of hazard ratios (HRs) using time to the first hospital diagnosis of dementia as outcome, and excluding those with a dementia diagnosis before the first registered AF diagnosis. We adjusted for age, socioeconomic factors (educational level, marital status and NSES), non-cardiovascular co-morbidity (obesity, diabetes, COPD, depression and anxiety), cardiovascular co-morbidities (hypertension, myocardial infarction, and all studied AH drugs (loop diuretics, thiazides, potassium-saving agents, beta blockers divided into beta-1-selective and non-selective agents, calcium blockers divided into heart active and vessel active agents, ACE inhibitors, ARBs, statins anticoagulants). We also studied drug combinations

specifically (ACE inhibitors and ARBs combined with thiazides or CCBs). We subdivided into age-groups, and categories of dementia diagnoses. Furthermore, we performed a sensitivity analysis, including only patients with a recorded AF diagnosis during 2005 and 2006, with a Cox regression analysis adjusted in the same way as the original analysis in men and women. Proportional hazards assumption was met for all models.

3. Results

3.1. Baseline characteristics

In total we included 160,251 (89,723 men and 70,528 women) patients ≥ 45 years diagnosed with AF. Incident dementia occurred in 9532 patients (5.9%), 4669 men (5.2%) and 4863 women (6.9%). In the sensitivity analyses, when excluding individuals with an AF diagnosis before 2005, similar results were yielded as in the main analysis (Supplementary Table S1). In the lowest age-group, i.e. 45–64 years of age, the number of incident dementia cases was low, 224 out of 26,951 patients, 0.8% (Supplementary Table S2). Mean follow-up, from January 1, 2007, was 5.4 years overall, for patients 45–64 years of age 7.4 years, 65–84 years of age 5.7 years, and 85 years of age and above 3.0 years. Mean follow-up was for cases with dementia 3.4 years and without dementia 5.4 years (see Table 1).

Results from the Cox regression analyses for patients for all dementia cases as well as by age-groups are shown in Table 2. Significantly lower HRs were found for ARBs for all dementia in all ages and in the age-group 65–84 years of age. Significantly higher HRs were found for all dementia for loop-diuretics for the age-group 65–84 years of age. When looking at sub-groups (Table 3), loop diuretics showed lower HR in the sub-group of AD and VaD, but higher HR in the sub-group of other causes of dementia. When looking at AD and VaD separately, no significant results at all was found (Supplementary Table S3). We also studied combined medications, i.e. ACE-inhibitors or ARBs combined

Table 1
Characteristics for patients aged at least 45 years with diagnosed atrial fibrillation (1998–2006) and for those with newly diagnosed dementia (2007–2015) in Sweden.

	Total population		Dementia events		Without dementia		
	No.	%	No.	%	No.	%	*P*-value[a]
Total population	160,251		9532		150,719		
Cardiovascular medication	148,511	92.7	8947	93.9	139,564	92.6	<0.001
a. Loop diuretics (C03C)	11,135	6.9	709	7.4	10,426	6.9	0.0526
b. Thiazides (C03A, C03B, C03E, C09B C09DA)	6372	4.0	404	4.2	5968	4.0	0.1769
c. Potassium-saving agents (C03D)	3534	2.2	220	2.3	3314	2.2	0.4813
d. Beta-1-selective beta-blockers (C07AB and C07FB)	41,720	26.0	2526	26.5	39,194	26.0	0.2850
e. Non-selective beta-blockers (C07AA and C07AG)	8466	5.3	470	4.9	7996	5.3	0.1130
f. Heart-active calcium channel blockers (C08DA)	1941	1.2	111	1.2	1830	1.2	0.6672
g. Vessel-active calcium channel blockers (C08CA and C08DB)	12,348	7.7	809	8.5	11,539	7.7	0.0032
h. ACE inhibitors (C09AA and C09BA)	27,520	17.2	1585	16.6	25,935	17.2	0.1458
i. ARBs (C09CA, C09DA and C09DB)	10,170	6.3	535	5.6	9635	6.4	0.0025
j. Statins (C10AA)	18,992	11.9	1152	12.1	17,840	11.8	0.4657
K. Anticoagulants (B01AA)	9151	5.7	576	6.0	8575	5.7	0.1493
Subtypes of dementia							
Alzheimer's disease			2500	26.2			
Vascular dementia			2250	23.6			
Other dementia diseases			4782	50.2			
Gender							<0.001
Males	89,723	56.0	4669	49.0	85,054	56.4	
Females	70,528	44.0	4863	51.0	65,665	43.6	
Age (years)							<0.001
45-64	27,175	17.0	224	2.3	26,951	17.9	
65-84	94,736	59.1	6560	68.8	88,176	58.5	
85+	38,340	23.9	2748	28.8	35,592	23.6	
Educational attainment							<0.001
≤9 years	78,489	49.0	4948	51.9	73,541	48.8	
10–12 years	37,102	23.2	2144	22.5	34,958	23.2	
>12 years	44,660	27.9	2440	25.6	42,220	28.0	
Immigrant status							0.4482
Sweden	143,922	89.8	8539	89.6	135,383	89.8	
Others	16,329	10.2	993	10.4	15,336	10.2	
Marital status							<0.001
Married	87,334	54.5	4580	48.0	82,754	54.9	
Not married/Widowed/Divorced	72,917	45.5	4952	52.0	67,965	45.1	
Neighborhood deprivation							<0.001
Low	17,776	11.1	1016	10.7	16,760	11.1	
Middle	81,198	50.7	4531	47.5	76,667	50.9	
High	19,343	12.1	1170	12.3	18,173	12.1	
Unknown	41,934	26.2	2815	29.5	39,119	26.0	
Hospital diagnosis							
Hypertension	45,553	28.4	2736	28.7	42,817	28.4	0.5360
CHD	44,532	27.8	2779	29.2	41,753	27.7	0.0021
Heart failure	41,898	26.1	2432	25.5	39,466	26.2	0.1482
Stroke	26,227	16.4	1869	19.6	24,358	16.2	<0.001
Obesity	1519	0.9	33	0.3	1486	1.0	<0.001
Diabetes	18,313	11.4	1049	11.0	17,264	11.5	0.1811
COPD	11,397	7.1	588	6.2	10,809	7.2	<0.001
Depression	3646	2.3	341	3.6	3305	2.2	<0.001
Anxiety	2255	1.4	161	1.7	2094	1.4	0.0160
Alcoholism and related disorders	2903	1.8	182	1.9	2721	1.8	0.4603

CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; ARBs: Angiotensin receptor blocking (ARB) agents.
[a] *P*-value was calculated based on Chi-square test.

Table 2
The relative risk of incident dementia in patients with atrial fibrillation prescribed different cardiovascular pharmacotherapies (with 99% confidence intervals).

	All			45–64 years			65–84 years			85 + years		
	HR	99% CI		HR	99% CI		HR	99% CI		HR	99% CI	
All medication	1.01	0.90	1.13	1.00	0.57	1.76	0.94	0.81	1.08	0.79	0.65	0.95
a. Loop diuretics	0.98	0.89	1.09	0.42	0.07	2.65	1.16	1.00	1.35	1.12	0.97	1.29
b. Thiazides	0.99	0.86	1.12	0.48	0.13	1.76	0.98	0.84	1.16	1.00	0.79	1.27
c. Potassium-saving agents	0.94	0.79	1.12	0.86	0.14	5.41	0.90	0.70	1.14	1.08	0.83	1.40
d. Beta-1-selective beta-blockers	1.01	0.96	1.08	1.25	0.86	1.81	1.02	0.95	1.10	0.98	0.87	1.10
e. Non-selective beta-blockers	0.95	0.84	1.08	1.30	0.69	2.46	0.92	0.79	1.06	0.95	0.75	1.21
f. Heart-active calcium channel blockers	0.94	0.73	1.20	1.29	0.35	4.82	0.96	0.71	1.30	0.86	0.54	1.36
g. Vessel-active calcium channel blockers	1.04	0.94	1.14	1.17	0.61	2.24	1.06	0.95	1.19	0.92	0.76	1.11
h. ACE inhibitors	1.01	0.94	1.08	1.14	0.70	1.84	0.97	0.89	1.06	0.96	0.84	1.11
i. ARBs	0.87	0.78	0.98	0.47	0.17	1.27	0.87	0.76	0.99	0.84	0.67	1.06
j. Statins	1.05	0.97	1.14	0.73	0.41	1.29	1.01	0.92	1.11	0.92	0.75	1.13
K. Anticoagulants	1.04	0.93	1.16	0.61	0.23	1.66	0.97	0.85	1.11	1.07	0.86	1.33

Full adjusted model; HR: Hazards ratios; CI: Confidence intervals.
In the full model, we adjusted for age, region of Sweden, immigrant status, socioeconomic factors, co-morbidities and all drug classes.
ARBs denotes Angiotensin receptor blocking agents.

with either thiazides or CCBs, with borderline significance for ARBs in combination with CCS, HR 0.89 (95% CI 0.79–1.00) but otherwise no significant results (data not shown).

4. Discussion

The main findings of this observational study were that ARBs were associated with a significantly lower risk of incident dementia in a national cohort of patients with AF in the age range 65–84 years, and also in the whole age span. Furthermore, higher risks were seen in patients in the ages 65–84 years age for loop diuretics, and in the sub-group of other causes of dementia, but a lower risk in the sub-group of AD and VaD.

It may be questioned to merge all dementia diagnoses together, considering the different pathophysiology. However, we are uncertain of the validity of the categorization of dementia types, including the overlapping and mixed forms between especially AD and VaD. Besides, from a clinical point of view the risk of dementia in itself is of highest concern. However, we also categorized dementia into two sub-groups, i.e. AD and VaD together in one, and other causes of dementia in the second.

In the earlier cited study conducted in Swedish primary care, the combination of a RAS-blocker and a thiazides was associated with a decreased risk of incident dementia, and also the use of medications from 3 to 4 of the different classes of AH medications (thiazides, beta blockers, CCBs and RAS-blockers) [22]. In contrast, in the present study of a national Swedish cohort, we found only ARBs to be associated with a lower risk of dementia in general.

Regarding effects of AH drugs in general, results from earlier studies have found somewhat conflicting results, to some part depending on differences in the studied population and the methodology used. Besides, the effects on dementia could also be associated with the blood pressure lowering effect in general, or with a more specific effect of the drug class.

We only found a preventive effect on dementia in general in AF by ARBs, in line with some earlier studies [17], and reviews [16–18,21]. There are also other reviews on the possible preventive effect on dementia by RAS blockers, as many components in the RAS system are altered in AD [16], and this effect could be independent of effect on blood pressure [12]. In AD it is found, that both angiotensin II, a multifunctional and potent vasoconstrictor, and angiotensin III, similarly acting, are greatly altered at the expense of other RAS signaling peptides, and this is considered to contribute to neuronal and cognitive function [16]. Although this is described for AD, these effects could possibly also be at hand for other dementia causes, furthermore as many cases could have mixed causes. One question is whether there are differences between ACE inhibitors and ARBs regarding the dementia risk. The mechanisms of action do differ, and ARBs do seem to have advantages over ACE inhibitors as regards the AD-related β amyloid pathologies, like senile plaques and cerebral amyloid angiopathy [16]. Thus, our results could support this hypothesis.

In contrast, we found loop diuretics to be associated with a higher risk of all dementia in patients aged 65–84 years of age, and also in the sub-groups of other dementia causes than AD and VaD, but a lower risk for AD and VaD combined. Earlier studies have found conflicting results regarding the association between diuretics and incident dementia, with a preventive effect shown in several reviews [13].

Table 3
The associated relative risk of dementia in patients with atrial fibrillation and different cardiovascular pharmacotherapies (with 99% confidence intervals).

	Alzheimer's disease/Vascular dementia			Other dementia diseases		
	HR	99% CI		HR	99% CI	
All medication	1.14	0.96	1.34	0.90	0.77	1.05
a. Loop diuretics	0.81	0.68	0.95	1.14	1.00	1.30
b. Thiazides	0.92	0.75	1.11	1.05	0.88	1.26
c. Potassium-saving agents	1.04	0.81	1.34	0.84	0.65	1.08
d. Beta-1-selective beta-blockers	1.02	0.93	1.11	1.01	0.93	1.10
e. Non-selective beta-blockers	1.04	0.88	1.23	0.88	0.74	1.06
f. Heart-active calcium channel blockers	0.85	0.58	1.23	1.02	0.73	1.41
g. Vessel-active calcium channel blockers	1.12	0.99	1.28	0.94	0.82	1.09
h. ACE inhibitors	1.01	0.91	1.12	1.00	0.90	1.11
i. ARBs	0.86	0.73	1.01	0.89	0.75	1.04
j. Statins	1.09	0.97	1.22	1.01	0.90	1.15
K. Anticoagulants	1.12	0.96	1.30	0.97	0.83	1.14

Full adjusted model; HR: Hazards ratios; CI: Confidence intervals.
In the full model, we adjusted for age, region of Sweden, immigrant status, socioeconomic factors, co-morbidities and all drug classes.
ARBs denotes Angiotensin receptor blocking agents.

However, loop diuretics have been associated with worsening renal function [28], and also with activation of the renal-angiotensin-aldosterone system and sympathetic nervous system [29]. Furthermore, loop diuretics and aldosterone antagonists in AF patients have been associated with an increased mortality [30]. Additionally, in contrast to earlier studies we found neither thiazides nor potassium-saving diuretics to be associated with a lower dementia risk [13–15].

We did not find an effect of anticoagulants, but analyzing this association would probably have needed another approach. In earlier studies, using different methodologies, a 20% lowering of anticoagulants is described [22,31]. However, we assumed that prescribed and dispensed on two occasions would represent a consistent treatment, but for anticoagulants this assumption might not be valid. Within the time frame only warfarin was prescribed, and not non-vitamin K antagonist oral anticoagulants (NOACs). As regards the effect by statins on dementia risk, earlier reviews have found competing results [23,24]. In the present study we found no preventive effect, in line with the results from the study from Swedish primary care [22].

There are several limitations of this study. This is an observational study based on diagnoses from hospitals, however with diagnoses from both hospitalization hospital in and out-patient care, but we did not have access to primary care diagnoses. However, in another study, it was found that 12% of all registered AF patients in Stockholm County were only registered in primary care [5]. 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 [32]. 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. Besides, the number of co-morbidities and cardiovascular drugs seems remarkably low, but these data are checked, and seems to be associated with the model we used. We adjusted for dispensed anticoagulants, but studying the effect of these drugs would have needed another approach. The Swedish Prescribed Drug Register was introduced in 2005, and data on dispensed drugs earlier than 2005 are not available. Thus, the consistency of dispensed drugs could be discussed, but we regard that recorded of dispensed drugs on two occasions was the best way to handle these data, even if some prescriptions could have been newly performed. Other models using these data would have decreased statistical power substantially. Multiple comparisons were performed, but we used 99% CI for the main outcomes to compensate for this. Another remark is that we included patients with an AF diagnosis from several years back, but in a sensitivity analysis we checked the results when excluding patients with a diagnosis earlier than the last two years, and the results were quite similar. The reason for including patients from 1998 and onwards was to obtain enough number of individuals in the cohort to get enough statistical power. Besides, as dementia is a disorder developing over many years we wanted to get enough time for this to occur. Dementia diagnoses in registers are not validated, and the distribution of dementia sub-groups did not correspond well to earlier findings. Accuracy of diagnosis of AD is difficult, and an American study found sensitivity to be 70.9–87.3%, and specificity 44.3–70.8% from Alzheimer Disease Centers [33]. Thus, the findings in the different dementia sub-groups should be interpreted with caution. 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 heart rhythm could not be classified as sinus rhythm or fibrillation rhythm.

A major strength of this study was that we were able to link clinical data from individual EPRs to data from national demographic and socio-economic registers with less than 1% of information missing. The quality of Swedish registers in general is shown to be good [26,34]. Moreover, as randomized controlled trials often exclude individuals with different co-morbidities, our findings could be more representative to the clinical practice today. Relevant comorbidities were included considering results from earlier studies [8,9].

In conclusion, in this clinical setting with a national Swedish cohort of patients with AF, we found ARBs to be associated with a lower dementia risk among all patients and also among those aged 65–84 years of age. For loop diuretics, a higher risk for all dementia was found among patients aged 65–84 years of age, and in the sub-groups for other causes, but in contrast a lower risk in the sub-group of AD and VaD. We believe that these findings should be confirmed in clinical trials, but that they could also be considered when choosing pharmacotherapy in AF patients with a high risk of dementia.

Declaration of competing interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.065.

Author contribution

PW, ACC, JS and KS designed the study, XL analyzed data, and all authors participated in the interpretation of data; PW and ACC drafted the manuscript and all other authors revised it critically for important intellectual content.

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