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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Differences and time trends in drug treatment of atrial fibrillation in men and women and doctors' adherence to warfarin therapy recommendations

A Swedish study of prescribed drugs in primary care in 2002 and 2007

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Abstract
Background Little is known about prescription trends in atrial fibrillation (AF) in primary health care in Sweden.
Objective The aim was to study time trends in pharmacotherapy, in men and women with AF. We also aimed at studying doctors' adherence to CHADS2 for prescribing warfarin. CHADS2 assesses stroke risk by presence of known risk factors, i.e., congestive heart failure, hypertension, age >75 years, diabetes, previous stroke and transient ischemic attack.
Methods Data were obtained from primary health care records that contained individual clinical data. In total, 371,036 patients were included in the sample from 2002, and 424,329 patients were included in the sample from 2007. The study population consisted of individuals aged 45+ years who were diagnosed with AF in 2002 (1,330 men and 1,096 women) and 2007 (2,748 men and 2,234 women). The pharmacotherapies prescribed in 2002 and 2007 were analyzed separately in men and women. Logistic regression was used to calculate the association between the CHADS2 score and prescribed warfarin treatment.
Results Selective beta-blockers, anti-coagulant therapy and lipid-lowering drugs were prescribed more frequently in 2007 than in 2002. In 2007, antithrombotic and RAS-blocking agents were prescribed more frequently to men, whereas beta-1 selective beta-blockers were prescribed more frequently to women. There was no consistent association between the CHADS2 score and prescribed warfarin treatment.
Conclusions Pharmacotherapy of AF has improved over time, though CHADS2 guidelines need to be implemented systematically in primary health care in Sweden to decrease the risk of stroke and improve quality of life in patients with AF.

Keywords Atrial fibrillation · Pharmacotherapy · Gender · Warfarin · CHADS2 · Sweden

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Introduction

Atrial fibrillation (AF) is common; the prevalence is approximately 1 % in the population [1–3]. AF prevalence increases with age, with the median age at onset being 75 years. Although overall mortality in the general

population is lower in women than in men, mortality due to AF is shown to be higher among women [1, 3]. This may be due to sex-dependent differences, for example, higher mean age at onset [4] and higher risk of stroke in women with AF [5]. Studies have also suggested that there may be differences in the drug therapies given to men and women [6–8].

The main goal of drug therapy is to prevent stroke in AF patients. There are specific guidelines governing stroke prevention. A widely known tool for predicting stroke risk in patients with AF is CHADS2, which is used to determine whether and when warfarin therapy should be prescribed based on the presence of more than one risk factor (congestive heart failure, hypertension, age >75 years, diabetes and stroke) [9–12]. Age has been shown to be the most important factor for survival in AF, followed by congestive heart failure, previous stroke and diabetes [13]. We have not found any studies on how CHADS2 guidelines are followed in primary health care to treat AF patients. Most studies on AF have been based on patient data from hospital records. However, most patients undergoing AF pharmacotherapy attend primary health care centres and are treated by family medicine specialists; therefore, the findings from previous AF studies may not be representative of AF patients in general. In the 1990's, a study to estimate trends in the prescription of drugs to patients with AF in Swedish primary care was undertaken[14]. Data were collected at baseline and after five years. The main trends observed were increased use of sotalol and antithrombotic agents, as well as an increased mean dose of aspirin.

We hypothesized that these trends have continued, and that the CHADS2 score predicts prescribed warfarin treatment in AF patients. Therefore, the overall aim of this study was to analyze time trends in pharmacotherapy in men and women with AF, and whether the CHADS2 score may be associated with prescribed warfarin treatment in men and women with AF.

Methods

Patient data

This study was based on patient data from 75 primary health care centers (PHCCs) in Sweden. Men and women who visited any of the 75 PHCCs between 2001 and 2008 were included in a database (n=1,098,420). Two different patient samples were drawn from this database, one containing all patients from 2002 (371,036), and the other containing all patients from 2007 (424,329). We used *Extractor* software (http://www.slso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx, accessed September 19, 2010), to access patient files electronically. The files were transferred by authorized personnel to Statistics Sweden, where the patients' unique 10-digit national identification numbers were replaced with random serial numbers to ensure anonymity.

Patient data were cross-referenced to national Swedish population-based registers [15–17]. These contain individual-level information on the age, gender, education and marital status of everyone residing in Sweden, including the patients in our study samples. Thus, it was possible to link clinical data from the 75 PHCCs to sociodemographic data from population registers, provided to us by Statistics Sweden, the Swedish Government-owned statistics bureau [18]. The data in this large dataset were organized and analyzed using SAS software (SAS, Version 9.1. Cary, NC, USA.). Information on drugs prescribed to the AF patients was obtained from patient records and was organized according to the Anatomic Therapeutic Chemical (ATC) Classification. Table 1 shows a list of the drugs.

The inclusion criteria for selecting patients was that they were diagnosed with AF, which was defined as the presence of ICD-10 code I48, included in the 10th version of the WHO's International Classification of Diseases. Overall, we collected pharmacotherapy data for 7,408 AF patients. Of those, 1,330 men and 1,096 women were diagnosed with AF in 2002, and 2,748 men and 2,234 women were diagnosed with AF in 2007. The two different data sets should be viewed as two separate cross-sectional studies. Of the 7,408 patients, 984 were included in both samples. The remaining patients were included only once.

ICD-10 codes for common AF cardiometabolic comorbidities were identified in patient records, and used to analyze differences between men and women. These comorbidities were: AF-related hypertension (I10–15), coronary heart disease (CHD; I20–25), cardiac heart failure (I50 and I110), non-rheumatic valvular diseases (I34–38), cardiomyopathy (I42), cerebrovascular diseases (I60–69) including intracranial bleeding (I60–62), peripheral embolism (I74) and diabetes mellitus (E10–14). No diagnosis of rheumatic valvular diseases (I05–08) was recorded.

Individual sociodemographic variables

Gender: Man or Woman.

Age: AF patients were divided into five age sub-groups: 45–54, 55–64, 65–74, 75–84 and 85+ years. Patients under 45 years of age were excluded since they were too few for statistical analysis.

Educational attainment: Classified into three levels: ≤9 years (compulsory schooling or less), 10–12 years (some/completed secondary school education) and >12 years (college and/or university education).

Marital status: Classified as married, unmarried, divorced or widowed.

Table 1 Pharmacological drugs in patients with atrial fibrillation, by Anatomic Therapeutic Chemical (ATC) Classification

ATC group coding		Specific group		Specific subgroup or agent	
B01A	Anti-thrombotic agents	B01AA	Anticoagulant agents	B01AA03	Warfarin
		B01AB	Heparin and related agents		
		B01AC	Antiplatelet agents		
C01	Heart-active drugs	C01A	Digitalis		
		C01B	Specific anti-arrhythmic agents	C01BA01	Quinidine
				C01BA03	Disopyramide
				C01BC03	Propafenone
				C01BC04	Flecainide
				C01BD01	Amiodarone
		C01D	Nitrates		
C03	Diuretic agents	C03A, C03B	Thiazides and related agents		
		C03E, C09B C09DA	Thiazides and related agents, in combinations		
		C03C	Loop diuretics		
		C03D	Potassium-saving diuretics	C03DA	Aldosterone inhibitors
				C03DB	Amiloride
				C03E	Amiloride, in combinations
C07	Beta-blockers	C07AB	Beta-1-selective agents		
		C07F	Beta-1-selective agents, in combinations		
		C07AA	Non-selective beta-blockers	C07AA07	Sotalol
		C07AG	Non-selective beta-blockers, in combinations of alpha- and beta-blockers		
C08	Calcium antagonists	C08C	Vessel-selective agents		
		C09DB	Vessel-selective agents, in combinations		
		C08DB	Heart-active agents		
C09	RAS-blockers	C09A	ACE inhibitors		
		C09B	ACE inhibitors, in combinations		
		C09C	Angiotensin receptor blocker		
		C09D	Angiotensin receptor blocker, in combinations		
C10A	Lipid-lowering drugs	C10AA	Statins		

CHADS2 score

A high CHADS2 score corresponds to a higher risk of stroke, while a low CHADS2 score corresponds to a lower risk of stroke. Well known risk factors for stroke in patients with AF are congestive heart failure, hypertension, age >75 years, diabetes, previous stroke and transient ischemic attack [9–12]. Each factor is given one point, except for stroke, which is given two points. CHADS2 scores range from 0–6, with a score of 0 indicating that none of the above factors are present and that the risk of bleeding with pharmacotherapy is higher than the risk of stroke. In patients with a CHADS2 score of 2 or more, the benefits of warfarin therapy outweigh the risk of bleeding. Intermediate stroke risk is classified by a score of 1. The association between CHADS2 score and survival after stroke in AF patients was previously analyzed by Henriksson et al., using ICD-codes in the Swedish Hospital Discharge Register [13]. Here, we used these codes in the same fashion to calculate CHADS2 scores for each AF patient.

Statistical analysis

P-values for the differences in age and socioeconomic factors between the two cross-sectional samples, and between men and women in the same sample, were analyzed by *t*-test

(mean age) and chi-square test (frequencies). Because comorbidities and AF prevalence increase with age, we used logistic regression to age-adjust the p-values for comorbidities and prescribed drugs. Logistic regression models using warfarin treatment as the dependent variable were used to calculate odds ratios (ORs) to assess adherence with CHADS2 therapy recommendations. The models were adjusted for age, valvular disease and marital status.

The two-sided significance level was set to 0.01, with the exception of the ORs for warfarin treatment, for which 95 % confidence intervals (CIs) were calculated.

Ethical considerations

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

Results

The characteristics of all AF patients aged 45 years or over are shown in Table 2. We made comparisons in age, socioeconomic factors and comorbidities between patient samples from 2002 and 2007, and between men and women in the same sample. On average, patients in the sample from 2007 were about 3 years older than those in the sample from 2002 ($p<0.001$). This can partly be explained by the presence of the same individuals in both samples. There was also a general trend towards more diagnosed comorbidities in 2007 than in 2002. More women were diagnosed with heart failure and hypertension than were men. Also, women with AF were significantly older than men ($p<0.001$).

Tables 3 and 4 show the age-adjusted drug prescription patterns for the AF patients. In men, prescription rates of antithrombotic agents, warfarin, diuretics (thiazides, loop diuretics and potassium saving-agents), RAS-blocking agents, vessel-active Ca-blocking agents and lipid-lowering drugs (statins), were significantly higher in 2007 than in 2002 ($p<0.001$), as were prescription rates of beta-1-selective beta-blockers ($p<0.001$). In contrast, prescription rates of verapamil, non-selective beta-blockers (mostly sotalol) and digitalis were significantly lower for men in 2007 than in 2002 ($p<0.001$).

In women, prescription rates of antithrombotic agents, warfarin, diuretics (mostly thiazides), RAS-blocking agents, lipid lowering drugs (statins) and beta-1 selective beta-blockers were significantly higher in 2007 than in 2002. In contrast, prescription rates of antiplatelet agents, verapamil and sotalol were significantly lower for women in 2007 than in 2002 ($p<0.001$).

We observed several differences between men and women with regard to drugs they were prescribed in 2002. Many of these differences were also present in 2007. For example, warfarin was prescribed to men more often than women, while women were prescribed diuretics more often than were men. In addition, new trends emerged in 2007, with more antithrombotic and RAS-blocking agents being prescribed to men, and more beta-1 selective beta-blockers being prescribed to women.

The prescription of any anti-arrhythmic agents was higher in 2007 than in 2002, largely due to an increase in the prescription of beta-1-selective beta-blockers. Rates of prescriptions of non-selective beta-blockers (mostly sotalol) and digitalis were lower in 2007 than in 2002, in both men and women.

Table 5 shows logistic regression models with prescription of warfarin treatment as the dependent variable. We found no association between CHADS2 scores and warfarin treatment, except in 2007 in men with CHADS2 scores of 2-6. Their OR was 1.36 (95 % CI 1.08-1.73). In addition, men 55-74 years of age were more likely to be prescribed warfarin, and men and women above 85 years of age were less likely to be prescribed warfarin. AF patients with valvular disease had greater odds of receiving warfarin treatment. In 2007, divorced and widowed men, as well as unmarried women, were less likely to receive warfarin treatment.

Discussion

In this study, more AF patients were prescribed beta-1-selective beta-blockers and blood lipid lowering drugs in 2007 than in 2002, whereas fewer AF patients were prescribed sotalol and digitalis in 2007 than in 2002. In addition, we observed no consistent association between CHADS2 scores and prescribed warfarin except in men with CHADS2 score of 2-6 in 2007.

These findings were consistent with those of studies showing that uncontrolled diagnosed hypertension and dyslipidaemia are common in Sweden [19, 20], which may explain the lack of association between CHADS2 score and anticoagulant therapy observed in this study. Having said that, our findings are indicative of a low adherence of doctors to treatment recommendations, which suggests either low awareness or "clinical inertia," as previously discussed by Pimenta and Stowasser [21]. In addition, fear of side effects among doctors and patients could also provide an alternative explanation, and so could the fact that warfarin is most often prescribed by doctors at hospitals while treatment monitoring is largely carried out by primary care physicians and nurses. Low persistence to warfarin therapy may also be a contributing factor. A recent study showed that persistence with warfarin therapy prescribed at discharge after stroke was low [22], and that only 45 % of stroke patients were still collecting their warfarin

Table 2 Data on subjects aged 45+ years with a diagnosis of atrial fibrillation in primary care, from 31 December 2002 (*N*=2,426) and 31 December 2007 (*N*=4,982)

	Men			Women			Men vs. Women	
	2002 *n*=1,330	2007 *n*=2,748	*p*	2002 *n*=1,096	2007 *n*=2,234	*p*	2002 *p*	2007 *p*
Age (years), mean (SD)	71.4 (9.3)	74.2 (9.9)	<0.001	76.0 (8.4)	79.1 (8.8)	<0.001	<0.001	<0.001
Age group (years)			<0.001			<0.001	<0.001	<0.001
	n (%)	*n* (%)		*n* (%)	*n* (%)			
45-54	70 (5.3)	93 (3.4)		21 (1.9)	16 (0.7)			
55-64	240 (18.1)	416 (15.1)		82 (7.5)	157 (7.0)			
65-74	462 (34.7)	773 (28.1)		315 (28.7)	422 (18.9)			
75-84	496 (37.3)	1033 (37.6)		529 (48.3)	977 (43.7)			
85+	62 (4.7)	433 (15.8)		149 (13.6)	662 (29.6)			
Marital status			0.018			0.021	<0.001	<0.001
Married	872 (65.6)	1685 (61.4)		396 (36.2)	714 (32.0)			
Unmarried	119 (9.0)	260 (9.5)		84 (7.7)	144 (6.5)			
Divorced	199 (15.0)	425 (15.5)		141 (12.9)	338 (15.1)			
Widowed	139 (10.5)	374 (13.6)		474 (43.3)	1037 (46.4)			
Educational level			0.024			0.82	<0.001	<0.001
Compulsory school	543 (42.0)	1009 (38.2)		508 (51.3)	1027 (50.1)			
Secondary school	489 (37.9)	1012 (38.4)		336 (33.9)	711 (34.7)			
College/university	260 (20.1)	618 (23.4)		146 (14.8)	312 (15.2)			
AF-related disease								
Hypertension	339 (24.8)	828 (30.1)	0.002	317 (28.9)	759 (34.0)	0.003	0.023	0.004
Coronary heart disease	142 (10.7)	279 (10.2)	0.61	113 (10.3)	208 (9.3)	0.36	0.77	0.32
Heart failure	166 (12.5)	470 (17.1)	<0.001	185 (16.9)	488 (21.8)	0.001	0.002	<0.001
Valvular disease	33 (2.5)	83 (3.0)	0.33	32 (2.9)	70 (3.1)	0.74	0.51	0.82
Cardiomyopathy	10 (0.8)	13 (0.5)	0.27	0 (0)	7 (0.3)	0.10	0.003	0.38
Cerebrovascular disease	78 (5.9)	186 (6.8)	0.27	57 (5.2)	133 (6.0)	0.38	0.48	0.24
Intracranial bleeding	1 (0.1)	4 (0.2)	1.00	1 (0.1)	1 (0.0)	0.55	0.64	0.39
Peripheral embolism	1 (0.1)	1 (0.0)	0.55	0 (0)	5 (0.2)	0.18	0.59	0.10
Diabetes mellitus	200 (15.1)	491 (17.8)	0.024	136 (12.4)	353 (15.8)	0.009	0.062	0.053

P-values for the differences between 2007 and 2002 and between men and women were analyzed by *t*-test (mean age) and chi-square test (frequencies)

prescriptions after 2 years. Persistence with warfarin therapy in AF patients has not been analyzed in detail to date.

The main time trends in pharmacotherapy for AF during the 1990's in Sweden were high prescription rates of sotalol and antithrombotic agents, as well as an increased mean dose of aspirin [14]. While we observed a decrease in sotalol prescriptions, we had no data on the dose of aspirin prescribed to the AF patients in this study. The trend of prescribing beta-1-selective beta-blockers, anticoagulant therapy and lipid-lowering drugs more frequently in 2007 than in 2002 observed here is interesting, and highlights the need for studies on how these drugs influence survival and comorbidities in patients with AF. In the present study, fewer than 30 % of AF patients were prescribed digitalis. Interestingly, prescription of digitalis has continued to decrease since the 1990's, when digitalis was prescribed to around 60 % of AF patients in primary health care [14].

The specific anti-arrhythmic drugs are not widely prescribed in primary health care in Sweden, which may explain the similarities in their prescription frequency between men and women in this study. Men tend to develop AF five years earlier than women [23], and women have a higher risk of bradycardia and anti-arrhythmic drug-related torsades de pointes [1], both of may partly explain differences in risk between men and women with AF.

There are distinct problems with different types of anti-arrhythmic drugs, which may explain why fewer AF patients were prescribed specific anti-arrhythmic drugs in this study. For example, class 1 C agents (flecainamide and propaphenone) are contraindicated for patients with coronary heart disease, because of their negative inotropic and

Table 3 Drug prescriptions (except for drugs with anti-arrhythmic properties) for subjects aged 45+ years with a diagnosis of atrial fibrillation in primary care, according to data from 31 December 2002 (*N*= 2,426) and 31 December 2007 (*N*=4,982)

Drug treatment	Men			Women			Men vs. Women	
	2002 *n*=1,330	2007 *n*=2,748	*p*	2002 *n*=1,096	2007 *n*=2,234	*p*	2002 *P*	2007 *p*
	n (%)	*n* (%)		*n* (%)	*n* (%)			
All anti-thrombotic agents	893 (67.1)	2154 (78.4)	<0.001	730 (66.6)	1682 (75.3)	<0.001	0.13	0.001
Warfarin	498 (37.4)	1437 (53.3)	<0.001	347 (31.7)	1036 (46.4)	<0.001	0.015	0.014
Antiplatelet agents	463 (34.8)	882 (32.1)	0.084	436 (39.8)	756 (33.8)	0.001	0.47	0.45
Aspirin	441 (33.2)	854 (31.1)	0.18	422 (38.5)	728 (32.6)	0.001	0.31	0.43
Nitrates	188 (14.1)	388 (14.1)	0.99	196 (17.9)	414 (18.5)	0.65	0.49	0.10
All diuretics	478 (35.9)	1238 (45.1)	<0.001	555 (50.6)	1313 (58.8)	<0.001	<0.001	<0.001
Thiazides	135 (10.2)	441 (16.1)	<0.001	137 (12.5)	412 (18.4)	<0.001	0.19	0.063
Loop-diuretics	341 (25.6)	853 (31.1)	<0.001	418 (38.1)	941 (42.1)	0.028	<0.001	<0.001
Potassium-saving agents	126 (9.5)	369 (13.4)	<0.001	187 (17.1)	450 (20.1)	0.034	<0.001	<0.001
Vessel-active Ca-blocking agents	122 (9.2)	421 (15.3)	<0.001	115 (10.5)	357 (16.0)	<0.001	0.34	0.46
RAS-blocking agents	368 (27.7)	1213 (44.1)	<0.001	283 (25.8)	890 (39.8)	<0.001	0.14	0.001
All lipid-lowering drugs	218 (16.4)	761 (27.7)	<0.001	145 (13.2)	488 (21.8)	<0.001	0.26	0.002
Statins	216 (16.2)	750 (27.3)	<0.001	138 (12.6)	476 (21.3)	<0.001	0.15	0.001

The age-adjusted p-values for the odds ratio of having each drug type in 2007 using 2002 as reference, and for women using men as reference in 2002 and in 2007, was calculated was calculated by means of logistic regression

pro-arrhythmic effects [24]. Similarly, patients with chronic heart failure or ventricular hypertrophy should avoid sotalol, due to their increased risk of QT prolongation and pro-arrhythmia [24]. Amiodarone has been shown to maintain sinus rhythm after cardioversion, but its chronic use is limited by its side effects, including bradycardia and liver toxicity [24]. Standard beta-blockers are modestly efficacious in maintaining sinus rhythm, but should be prescribed

Table 4 Prescription of drugs with anti-arrhythmic properties in subjects aged 45+ years with a diagnosis of atrial fibrillation in primary care according to data from 31 December 2002 (*N*= 2,426) and 31 December 2007 (*N*=4,982)

	Men			Women			Men vs. Women	
	2002 *n*=1,330	2007 *n*=2,748	*p*	2002 *n*=1,096	2007 *n*=2,234	*p*	2002 *p*	2007 *p*
	n (%)	*n* (%)		*n* (%)	*n* (%)			
Any anti-arrhythmic agent	853 (64.1)	1945 (70.8)	<0.001	776 (70.8)	1731 (77.5)	<0.001	0.006	<0.001
Digitalis	353 (26.4)	561 (20.4)	<0.001	409 (37.3)	688 (30.8)	<0.001	<0.001	<0.001
Specific anti-arrhythmic agents	41 (3.1)	55 (2.0)	0.033	23 (2.1)	44 (2.0)	0.67	0.54	0.034
Disopyramide	21 (1.6)	20 (0.7)	0.011	16 (1.5)	23 (1.0)	0.28	0.66	0.017
Flekainamide	7 (0.5)	23 (0.8)	0.28	2 (0.2)	19 (0.9)	0.02	0.36	0.062
Amiodarone	9 (0.7)	13 (0.5)	0.41	4 (0.4)	3 (0.1)	0.23	0.51	0.14
Other anti-arrhythmic agents	4 (0.3)	0 (0)	0.011	1 (0.1)	0 (0)	0.33	0.30	1.00
Beta-blockers	605 (45.4)	1656 (60.3)	<0.001	527 (48.1)	1443 (64.6)	<0.001	0.034	<0.001
Beta-1-selective agents	409 (30.8)	1311 (47.7)	<0.001	361 (32.9)	932 (41.7)	<0.001	0.12	<0.001
Non-selective beta-blockers	222 (16.7)	253 (9.2)	<0.001	192 (17.5)	171 (7.7)	<0.001	0.22	0.29
Sotalol	189 (14.2)	192 (7.0)	<0.001	174 (15.9)	121 (5.4)	<0.001	0.045	0.16
Ca-blocking agents, heart-active	91 (6.8)	139 (5.1)	0.021	97 (8.9)	122 (5.5)	<0.001	0.19	0.43
Verapamil	70 (5.3)	76 (2.8)	<0.001	73 (6.6)	79 (3.5)	<0.001	0.36	0.14
Diltiazem	21 (1.6)	63 (2.3)	0.13	24 (2.2)	43 (1.9)	0.61	0.31	0.57

The age-adjusted p-values for the odds ratio of having each drug type in 2007 using 2002 as reference, and the age-adjusted p-values for women using men as reference in 2002 and in 2007, was calculated was calculated by means of logistic regression

Table 5 Logistic regression models of CHADS2, using prescription of warfarin treatment as the dependent variable

	Men		Women	
	2002 n=1,330	2007 n=2,748	2002 n=1,096	2007 n=2,234
Age group (years)				
45-54	1 (ref)	1 (ref)	1 (ref)	1 (ref)
55-64	1.93 (1.04-3.60)	1.67 (1.13-2.45)	1.74 (0.58-5.32)	0.92 (0.40-2.10)
65-74	2.35 (1.29-4.27)	1.91 (1.31-2.78)	2.20 (0.77-6.29)	0.97 (0.43-2.16)
75-84	1.50 (0.79-2.86)	1.26 (0.85-1.88)	1.64 (0.55-4.87)	0.68 (0.30-1.53)
85+	0.85 (0.36-2.00)	0.50 (0.31-0.80)	0.59 (0.18-1.92)	0.20 (0.08-0.46)
CHADS-2 score				
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	1.11 (0.81-1.52)	1.25 (1.00-1.56)	1.11 (0.72-1.69)	1.11 (0.82-1.51)
2-6	1.32 (0.92-1.87)	1.36 (1.08-1.73)	1.24 (0.78-1.97)	1.28 (0.93-1.77)
Valvular disease*	2.99 (1.45-6.19)	1.89 (1.18-3.02)	3.41 (1.63-7.13)	2.26 (1.35-3.80)
Marital status				
Married	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unmarried	0.77 (0.51-1.17)	0.77 (0.59-1.01)	1.23 (0.75-2.02)	0.68 (0.47-0.98)
Divorced	0.96 (0.69-1.32)	0.70 (0.57-0.87)	1.05 (0.69-1.58)	0.92 (0.70-1.20)
Widowed	0.96 (0.65-1.40)	0.72 (0.57-0.92)	0.76 (0.56-1.03)	0.86 (0.70-1.06)

The CHADS2 score is the number of concomitant stroke risk factors, excluding atrial fibrillation (congestive heart failure, hypertension, age >75 years, diabetes and previous stroke)

Data are presented as OR (95 % CI)

*Reference group: individuals without valvular disease

prior to other anti-arrhythmic drugs, to prevent paroxysmal AF because of the lower risk of drug-related pro-arrhythmia [24]. On the other hand, standard beta-blockers have antihypertensive and positive effects on patients with coronary heart disease, myocardial infarction and chronic heart failure [25].

About half of the AF patients were prescribed warfarin, a figure in agreement with data from other Western countries [26]. Warfarin has been widely considered under-prescribed [24], so the increase in warfarin prescriptions in the last two decades is encouraging [14]. Ironically, our results suggest that CHADS2 guidelines are not properly followed, and warfarin seems to be prescribed to patients without adherence to guidelines. However, warfarin can be a risky option, and safety aspects should always be considered [27]. Warfarin therapy has the highest expected net clinical benefit among patients with the highest risk of stroke, such as elderly persons [12]. In addition, women are at higher risk of AF-related thrombotic strokes [28], which is why the low prescription rate of warfarin in women is particularly unsatisfactory. It should be noted that in a revised version of the CHADS2 instrument, CHA_2DS_2-VASc [29, 30], female sex is considered a risk factor of stroke. Consequently, this makes our findings even more alarming as adherence to CHA_2DS_2-VASc is likely to be even lower than that we found for CHADS2.

Our finding that in 2007, divorced and unmarried men were less likely to be prescribed anticoagulant treatment, deserves attention and stresses the need to closely monitor single men with AF in primary health care. In a Swedish study of hypertension control, it was shown that men who did not seek health care because of the costs involved were more likely to have uncontrolled diagnosed hypertension [19]. Taken together, these findings suggest that single men may need particular attention in clinical practice.

This study has some limitations. We only had data on prescriptions in primary health care, while AF patients may have been prescribed their pharmacotherapy at hospitals. In addition, data on all diagnoses may be incomplete for each patient, though information about diagnoses of important diseases such as cardiovascular disease and diabetes would most likely be present in the patient records, and therefore included in our data set. A further limitation was that we only analyzed prescriptions of the drug classes shown in Table 1. However, these are the drugs of interest for AF. We lacked clinical data on liver function, history of anemia, comorbidities requiring surgery, and history of major bleedings, which all influence warfarin therapy decisions. Finally, we had no information on catheter ablation procedures or Cox-Maze operations.

One of the key strengths of this study was that we were able to link clinical data from individual patients to >99 % complete national sociodemographic data. Furthermore, clinical data were also highly complete, as less than 2 % of the total number of diagnoses were missing in the primary health care center records [31]. The comprehensive nature of our data made it possible to analyze data for men and women across all educational backgrounds and marital status classification groups. Finally, a major strength of this study was its use of primary health care data, which may

reflect AF in the population better than hospital data, as hospital data may be biased toward more severe cases and/or younger patients with AF.

Conclusions

Overall, pharmacotherapy for patients with AF in primary health care seems to have improved over time. There is a clear trend towards prescribing warfarin and lipid-lowering drugs more frequently, which is likely to reduce overall mortality among patients with AF in Sweden. However, women in this study werepresprescribed warfarin less often. Also, there was no consistent association between CHADS2 scores and prescribed warfarin treatment. Thus, enhanced awareness of stroke risk and adherence to CHADS2 are needed in primary health care in Sweden to reduce stroke and improve quality of life among patients with AF.

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References

1. Michelena HI, Powell BD, Brady PA, Friedman PA, Ezekowitz MD (2010) Gender in atrial fibrillation: ten years later. Gend Med 7(3):206–217. doi:10.1016/j.genm.2010.06.001
2. Wandell PE (2001) A survey of subjects with present or previous atrial fibrillation in a Swedish community. Scand J Prim Health Care 19(1):20–24
3. Volgman AS, Manankil MF, Mookherjee D, Trohman RG (2009) Women with atrial fibrillation: greater risk, less attention. Gend Med 6(3):419–432. doi:10.1016/j.genm.2009.09.008
4. Naccarelli GV, Varker H, Lin J, Schulman KL (2009) Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol 104(11):1534–1539. doi:10.1016/j.amjcard.2009.07.022
5. Friberg J, Scharling H, Gadsboll N, Truelsen T, Jensen GB (2004) Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). Am J Cardiol 94(7):889–894. doi:10.1016/j.amjcard.2004.06.023
6. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, Koudstaal PJ, Petersen P, Perez-Gomez F, Knottnerus JA, Boode B, Ezekowitz MD, Singer DE (2009) Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke 40(4):1410–1416. doi:10.1161/STROKEAHA.108.526988
7. van Walraven C, Hart RG, Singer DE, Koudstaal PJ, Connolly S (2003) Oral anticoagulants vs. aspirin for stroke prevention in patients with non-valvular atrial fibrillation: the verdict is in. Card Electrophysiol Rev 7(4):374–378. doi:10.1023/B:CEPR.0000023143.98705.ee
8. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B (2002) Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 288(19):2441–2448
9. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE (2008) Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol 51(8):810–815. doi:10.1016/j.jacc.2007.09.065
10. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE (1999) Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med 131(12):927–934
11. Go AS, Hylek EM, Phillips KA, Borowsky LH, Henault LE, Chang Y, Selby JV, Singer DE (2000) Implications of stroke risk criteria on the anticoagulation decision in nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. Circulation 102(1):11–13
12. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS (2009) The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 151(5):297–305
13. Henriksson KM, Farahmand B, Johansson S, Asberg S, Terent A, Edvardsson N (2010) Survival after stroke–the impact of CHADS2 score and atrial fibrillation. Int J Cardiol 141(1):18–23. doi:10.1016/j.ijcard.2008.11.122
14. Wandell PE (1999) Drug use in patients with atrial fibrillation in Swedish primary health care: a comparison 5 years apart. Eur J Clin Pharmacol 55(4):333–337
15. Hemminki K, Li X, Sundquist K (2007) Familial risks for nerve, nerve root and plexus disorders in siblings based on hospitalisations in Sweden. J Epidemiol Community Health 61(1):80–84. doi:10.1136/jech.2006.046615
16. Li X, Sundquist J, Sundquist K (2008) Socioeconomic and occupational risk factors for rheumatoid arthritis: a nationwide study based on hospitalizations in Sweden. J Rheumatol 35(6):986–991
17. Sundquist K, Li X (2006) Coronary heart disease risks in first- and second-generation immigrants in Sweden: a follow-up study. J Intern Med 259(4):418–427. doi:10.1111/j.1365-2796.2006.01630.x
18. Wandell PE, Carlsson AC, Sundquist K, Johansson SE, Sundquist J (2011) Total mortality among levothyroxine-treated women with atrial fibrillation in Swedish primary health care. Int J Cardiol 152(1):147–148. doi:10.1016/j.ijcard.2011.07.066
19. Carlsson AC, Wandell PE, Journath G, de Faire U, Hellenius ML (2009) Factors associated with uncontrolled hypertension and cardiovascular risk in hypertensive 60-year-old men and women–a population-based study. Hypertens Res 32(9):780–785. doi:10.1038/hr.2009.94
20. Journath G, Hellenius ML, Carlsson AC, Wandell PE, Nilsson PM (2010) Physicians' gender is associated with risk factor control in patients on antihypertensive and lipid lowering treatment. Blood Press 19(4):240–248. doi:10.3109/08037051003768247
21. Pimenta E, Stowasser M (2009) Uncontrolled hypertension: beyond pharmacological treatment. Hypertens Res 32(9):729–731. doi:10.1038/hr.2009.108
22. Glader EL, Sjolander M, Eriksson M, Lundberg M (2010) Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke 41(2):397–401. doi:10.1161/STROKEAHA.109.566950
23. Humphries KH, Kerr CR, Connolly SJ, Klein G, Boone JA, Green M, Sheldon R, Talajic M, Dorian P, Newman D (2001) New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation 103(19):2365–2370
24. Bajpai A, Savelieva I, Camm AJ (2008) Treatment of atrial fibrillation. Br Med Bull 88(1):75–94. doi:10.1093/bmb/ldn046
25. Chan JD, Rea TD, Smith NL, Siscovick D, Heckbert SR, Lumley T, Chaves P, Furberg CD, Kuller L, Psaty BM (2005) Association of beta-blocker use with mortality among patients with congestive

heart failure in the Cardiovascular Health Study (CHS). Am Heart J 150(3):464–470. doi:10.1016/j.ahj.2004.12.022
26. Glazer NL, Dublin S, Smith NL, French B, Jackson LA, Hrachovec JB, Siscovick DS, Psaty BM, Heckbert SR (2007) Newly detected atrial fibrillation and compliance with antithrombotic guidelines. Arch Intern Med 167(3):246–252. doi:10.1001/archinte.167.3.246
27. Wandell PE (2001) Anticoagulant treatment of patients in Swedish primary health care. Safety aspects. Eur J Clin Pharmacol 57 (1):61–64
28. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS (2005) Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. Circulation 112 (12):1687–1691. doi:10.1161/CIRCULATIONAHA.105.553438
29. Lip GY, Frison L, Halperin JL, Lane DA (2010) Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke 41(12):2731–2738. doi:10.1161/STROKEAHA.110.590257
30. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 137 (2):263–272. doi:10.1378/chest.09-1584
31. Sundquist K, Chaikiat A, Leon VR, Johansson SE, Sundquist J (2011) Country of birth, socioeconomic factors, and risk factor control in patients with type 2 diabetes: a Swedish study from 25 primary health-care centres. Diabetes Metab Res Rev 27(3):244–254. doi:10.1002/dmrr.1161