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Warfarin treatment and risk of stroke among primary care patients with atrial fibrillation

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Abstract

Objective—Our aim was to study the risk of a first ischemic stroke in patients with atrial fibrillation (AF) treated in primary health care.

Design—The study population included all adults (n=11,517), 45 years and older diagnosed with AF, from 75 primary care centres in Sweden between 2001 and 2007. Ischemic stroke was defined as a hospital care event of stroke between 2001 and 2010. Association between incident stroke and warfarin treatment was explored using Cox regression analysis, with hazard ratios (HRs), and 95% confidence intervals (95% CIs). Adjustment was made for age, socioeconomic factors and co-morbidity.

Results—Persistent treatment with warfarin was present among 34.7% of women and 40.9% among men. Persistent warfarin treatment, compared to no persistent treatment, was associated with a stroke preventing effect with fully adjusted HRs of 0.25 (95% CI 0. 0.26–0.45) in women, and 0.25 (95% CI 0.28–0.43) in men. A CHA_2DS_2-VASc score of at least two among women, and three among men, was associated with a stroke risk exceeding 18% during a mean follow-up of 5.4 years. Risk of haemorrhagic stroke was not increased.

Conclusions—Warfarin is effective in preventing stroke in AF patients in primary health care.

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Disclosures

The authors have no conflict of interest to disclose.

Keywords

atrial fibrillation; ischemic stroke; gender; follow-up; co-morbidity; anticoagulant

Introduction

Atrial fibrillation (AF) is the most common form of heart arrhythmia, with approximately 2% of the Swedish population being recorded with an AF diagnosis (1). Many patients in Sweden with AF receive medical care at their local primary health care center, and in Stockholm County 64% of the AF patients were registered in primary health care (1).

Ischemic stroke is the most important complication among patients with AF (2), being five times as common as in individuals without AF (3), with women experiencing a higher risk than men (4). Anticoagulant therapy (predominantly warfarin) plays a significant role in preventing stroke (5), and has benefits over antiplatelet (mostly aspirin) therapy (6).

Given the good effect of anticoagulant treatment in preventing stroke among patients with AF, and thus avoiding the debilitating consequences of stroke, it is important to identify individuals with increased risk of stroke (7). The most commonly used instruments to estimate the stroke risk in patients with AF are $CHADS_2$ (8), and the nowadays more commonly used CHA_2DS_2-VASc score (9). Yet, it is also of importance to assess the reliability of the CHA_2DS_2-VASc score in primary health care, and also in larger populations. There is also an uncertainty whether patients with a CHA_2DS_2-VASc score of 1 should be treated or not (10), why more studies on this topic are needed.

However, despite clear guidelines and stroke preventative evidence, the likelihood of having warfarin prescribed in accordance with $CHADS_2$ and CHA_2DS_2-VASc has been shown to be low in Sweden (5, 11), as well as in other European countries (12), and in the USA (13).

The objective of the present study was to explore the risk of first ischemic stroke in men and women diagnosed with AF in relation to warfarin treatment in a large cohort of AF patients treated in primary health care. As secondary aims we also wanted to study the mortality risk in patients experiencing a first stroke in comparison to those without stroke. We also aimed at explore the risk of haemorrhagic stroke in relation to warfarin treatment.

Methods

Design

This study was performed using individual-level patient data from 75 Swedish primary health care centers (PHCC), mostly located in Stockholm County (n=48). Men and women visiting any of the participating PHCCs between 2001 and 2007 were included in the study. We used *Extractor* software (http://www.slso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx; accessed September 19, 2010) to collect individual files from the electronic patient records (EPR) at the PHCCs. The EPR files were linked to a database constructed using national registers with individual-level population data for all residents registered in Sweden: The Total Population register (which contains data on, e.g., age and

education for the entire population of Sweden); The Inpatient Register (hospital admissions); and The Cause of Death Register (14). Thus, a new research database was created, containing individual clinical patient data from a total of 1,098,420 subjects registered at these 75 PHCCs, further linked to national demographic and socioeconomic data. A follow-up was performed using the Swedish Cause of Death Register, which has been shown to be almost complete (99.8%), and lacking data only for a few emigrants from Sweden to other countries and thus lost to follow-up (15). Individual identification numbers were replaced by serial numbers to ensure anonymity.

Study population and co-morbidities

The study included all patients aged 45 years or older at the time of AF diagnosis, and who had visited any of the 75 participating PHCCs from 1 January 2001 until 31 December 2007. Atrial fibrillation was 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. The following related cardiovascular disorders were used as covariates: hypertension (I10-15), coronary heart disease (CHD; I20-25), congestive heart failure (CHF; I50 and I110), cerebrovascular diseases (CVD; I60-69), and diabetes mellitus (E10-14). First hospital-admitted ischemic stroke (I63) between 1998 and 2010 were registered, and patients with an earlier registered ischemic stroke before first diagnosis of AF were excluded, in total 766 patients, 389 women and 377 men. A total of 6,269 men and 5,248 women were included in the study.

Outcome variable

Time was registered to first ischemic stroke, defined as having an ICD-10 code indicating an ischemic stroke (I63) in the Inpatient Register (hospital admissions) or in The Cause of Death Register (16). The follow-up period ran from registration of first AF diagnosis during the assessment period until hospitalisation of first ischemic stroke, death, emigration or the end of the study period on December 31, 2010, whichever came first. Time to mortality was registered from first AF diagnosis in the similar way.

Demographic and socioeconomic variables

Sex: Men and women.

Age was categorized as follows: 45–54, 55–64, 65–74, 75–84 and >85 years. Individuals younger than 45 years were excluded (AF was rare in individuals below 45 years of age and non-representative of AF patients in general).

The neighbourhood socioeconomic status (SES) areas were categorized into three groups according to the neighbourhood index: more than one standard deviation (SD) below the mean (high SES or low deprivation level), more than one SD above the mean (low SES or high deprivation level), and within one SD of the mean (middle SES or deprivation level) (17). The neighbourhood summary index was based on information about female and male residents, aged 20 to 64 years, because this age group represents those who are among the most socioeconomically active in the population. The index was based on the following four variables: low educational status (<10 years of formal education); income from all sources,

including interest and dividends, that is <50% of the median individual income); unemployment (excluding full-time students, those completing military service and early retirees); and receipt of social welfare.

Educational attainment was categorized as ≤9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling) and >12 years (attendance at college and/or university).

Marital status was characterized as married, unmarried, divorced or widowed.

Risk classification of stroke

Evaluation of the stroke risk by $CHADS_2$ is based on the following risk factors (each factor yielding one point, except previous stroke yielding two points): congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus and a history of stroke or previous transient ischemic attacks and thromboembolism (18, 19). The CHA_2DS_2-VASc score differs from $CHADS_2$ in the following ways: being a woman yields one point; age between 65 and 74 years yields one point, and 75 years and above two points) the presence of any cardiovascular disease is credited with one point (recorded as myocardial infarction, peripheral artery disease or plaque in the aorta) (9).

Anticoagulant treatment

Prescriptions of anticoagulant treatment, i.e. of warfarin, from 2001 to 2007 were obtained from patient records in primary health care. The prescribed warfarin was classified as “intention-to-treat” (“ITT”) if ever-present before the years of first stroke, or if present at any time among subjects not experiencing a stroke. The prescribed warfarin was classified as “per-protocol” (“PP”) if present the year before and the year of first stroke. Besides, it was also classified as “PP” if present among subjects not experiencing a stroke if present at least during three years, of at least 50% of actual years after first recorded year of AF, or during both 2006 and 2007.

Statistical analysis

Baseline characteristics for all included men and women, as well as for those with a recorded first ischemic stroke, were presented as mean (SD) if continuous and as frequencies if categorical.

We classified subjects, without and with a first ischemic stroke, according to their CHA_2DS_2-VASc scores and also according their $CHADS_2$ scores. We also made stratified analyses in subjects classified as not having a “per-protocol” prescription of warfarin. Thus, we were able to estimate the risk of stroke when not on warfarin treatment.

We also estimated the incidence rates of a first ischemic stroke per 100 person-years at risk for men and women, and also in relation to CHA_2DS_2-VASc and $CHADS_2$ scores. We also assessed the incidence rate for subjects with no warfarin treatment. The age-adjusted relative risk of stroke for women versus men, as well as for patients on “ITT” and “PP”-warfarin treatment versus patients with no “ITT” or no “PP” warfarin treatment was analyzed using Cox proportional hazard regression analysis, and presented as hazard ratios (HR) with 95%

confidence intervals (CI). Adjustments were also made for socioeconomic factors (educational level, marital status and neighbourhood SES) and cardiovascular-related co-morbidity (hypertension, CHD, CHF and diabetes).

Cox regression (with HRs and 95% CI) was used for estimating mortality risk in men and women separately with a first ischemic stroke vs. patients without a stroke in three models: Model 1 age-adjusted, Model 2 also including socioeconomic factors and Model 3 also including cardiovascular-related co-morbidity as stated above. The risk of haemorrhagic stroke with PP warfarin treatment was explored by Cox regression. Model specification was tested, and interaction terms were used when appropriate.

Numbers needed to treat (NNT) were estimated for using PP warfarin treatment in preventing one ischemic stroke during the mean follow-up time of 5.4 years.

The study was approved by the regional ethics boards at Karolinska Institutet and Lund University, Sweden.

Results

The characteristics of the men and women with AF (all, n=11,517) treated in primary care, and in those with AF and at least one stroke (n=1,465) are shown in Table 1 (and in patients with no PP warfarin treatment or no warfarin treatment at all in Supplementary Table 1). Women had a higher proportion of first ischemic stroke than men, 14.6% vs 11.1%, with an age-adjusted relative risk of in women versus men: HR 1.15 (95% CI 1.03–1.28). Results were based on 62,147 patient-years, with a mean follow-up of 5.40 years (sd 2.63), median 5.50 years.

First ischemic stroke during 2001–2010 by CHA_2DS_2-VASc scores are shown in Table 2, where data are also presented separately for those without PP treatment with warfarin. Strokes were more common in those without warfarin than in those with warfarin, regardless of CHA_2DS_2-VASc. A similar pattern was found for $CHADS_2$ scores (Supplementary Table 2).

In total, the percentages with incident first stroke was: in women 19.3% without warfarin PP treatment vs. 14.6% with warfarin PP treatment, and in men 15.5% without warfarin PP treatment vs. 11.1% with warfarin PP treatment. Incidence rates (IR) per 100 person-years at risk were calculated in relation to CHA_2DS_2-VASc and $CHADS_2$ scores, with increased risk in IR of first IS for CHA_2DS_2-VASc score of two and above (Table 2), and an increased risk in IR in $CHADS_2$ score of one and above (Supplementary Table 2), for both men and women. In subjects with no warfarin treatment the same pattern was seen (Supplementary Table 3). Numbers needed to treat (NNT) were calculated using PP warfarin treatment, with overall NNT based on a mean follow-up of 5.40 years, with an NNT for women of 7.3 and 9.1 for men (Table 2). NNT (when possible to assess) was below 10 for women at a CHA_2DS_2-VASc score of two and above (except for a score of seven), and for men at a CHA_2DS_2-VASc score of three and above.

Incidence rates, per 100 person-years at risk, were also calculated in subjects without PP warfarin treatment. The incidence rate for a first ischemic stroke for women was 3.89 (95% CI 3.61–4.20), and for men 2.98 (95% CI 2.75–3.23).

The risk of a first stroke with ITT- and PP-treatment, with warfarin, are shown in men and women in Table 3, with fully adjusted HRs of ITT-warfarin among women of 0.34 (95% CI 0.26–0.45) and among men of 0.34 (95% CI 0.28–0.43), and with fully adjusted HRs of PP-treatment among women of 0.25 (95% CI 0.18–0.36) and among men of 0.25 (95% CI 0.19–0.32). The results were only marginally attenuated but remained when adjusted for socioeconomic factors and co-morbidity. The estimated risk of first bleeding episode on PP-warfarin treatment (n= 162) versus no PP-warfarin treatment was not significantly increased, age- and sex-adjusted HR 1.21 (95% CI 0.88–1.66). When also adjusting for socio-economic factors and co-morbidity (with interaction terms between age and sex, age and CHD, age and hypertension and age and diabetes included), HR was 1.08 (95% CI 0.69–1.67).

Mortality risk for men and women with a first stroke compared to their counterparts without a stroke was estimated (Supplementary Table 4). Women showed higher incidence rates per 100 patient-years than men, 8.67 (95% CI 7.85–9.56) vs 6.87 (95% CI 6.13–7.70). Women experiencing a first stroke vs. women without this showed a fully adjusted HR of mortality of 1.43 (95% CI 1.26–1.63), with the corresponding HR of men of 1.23 (95% CI 1.08–1.41).

Discussion

The main findings of this study were that warfarin showed a strong preventive effect of ischemic stroke in clinical primary health care settings, which remained significant after adjustments for socioeconomic factors and co-morbidity. Our results confirm earlier studies that found an under-treatment with warfarin, as the rates of persistent treatment with warfarin were low in the current study. Besides, we found that a CHA_2DS_2-VASc score of two exerted a high risk of stroke in women and of one in men, indicating that warfarin should be already considered at this score level. When considering the crude risk of an ischemic stroke exceeding 1% as the clinical threshold for a net clinical benefit, our results would rather indicate a benefit of anticoagulant treatment at a CHA_2DS_2-VASc score of one (10).

As this is an observational study, it is quite possible that patients that exerted a high risk of both ischemic stroke and bleeding complications may have been declined warfarin treatment. The fact that there was no significantly higher risk of bleedings in the individuals with warfarin also supports the fact that there was a strict selection of patients that received warfarin based on clinical considerations (counter-indication), apart from other potential confounding not measured in this study (such may be morbidity associated to bleedings, dementia, alcohol abuse etc.).

We have previously shown that warfarin is more often prescribed to married men than unmarried men (17), and that the mortality rate is higher in unmarried men with AF (20). Moreover, both individual and neighbourhood level socioeconomic status may affect both

the prescribing of warfarin and the mortality rate (17). Yet, the present results regarding PP treatment with warfarin remained significant in models adjusted for education, marital status and neighbourhood SES, indicating that these factors do not explain the effects of PP treatment of warfarin.

We a slightly higher stroke risk associated in women, with incidence rates per 100 person-years at risk of 2.77 vs. 2.02 (absolute crude risk), and an age-adjusted HR of 1.15 (relative risk), confirming results in earlier studies (4). Besides, women also exerted a higher mortality risk than men in AF, both with and without a stroke.

There are certain limitations of this study. This is an observational study and it was not possible to follow prescriptions in detail for patients experiencing an IS versus patients without stroke, why we used a pragmatic approach to PP-warfarin. Thus, we also used another approach, i.e. ITT-warfarin without the persistent use of warfarin as in the PP-warfarin definition. Furthermore, prescription of warfarin may have been influenced by other factors than we recorded, i.e. confounding by indication may be one explanation (21). We cannot exclude that this could have affected the results. An earlier Swedish study concluded that “warfarin-treated patients are highly selected and that decisions not to treat elderly, frail, high-risk patients often may be related to complicating co-morbidities and a poor prognosis” (5). We did not estimate the probable effect of aspirin on stroke prevention, and an earlier Swedish study actually found no preventive effect of aspirin (22), thus supporting our decision. Nowadays NOACs are becoming more common as anticoagulants, but still we think results from warfarin-treatment to be of value to show possible gains with anticoagulant treatment in general, also possible to generalize to all anticoagulants. Our data were extracted from electronic patient records in primary health care, and data may have been incomplete, e.g. for listings of diagnoses. However, we could expect the diagnoses of cardiovascular diseases and diabetes to be more accurate and complete than many other diagnoses; less than 2% of the total number of diagnoses was missing. Besides, we used hospital data for the diagnosis of ischemic stroke, why we could expect that the results on first ischemic stroke are accurate (23). In Sweden all stroke patients are encouraged to seek hospital care, to enable early active treatment interventions. We had no data available on the type of atrial fibrillation (paroxysmal, persistent, permanent) and rhythm (sinus rhythm, fibrillation). HAS-BLED score was not possible to calculate as we had no data on abnormal renal/liver function, bleeding history or predisposition, labile international normalized ratio, or drugs/alcohol intake (24). However, since the variables available in the present study were obtained from primary health care electronic patient records they may be assumed to mirror the information available for the clinician in general practice.

Despite the limitations, one of the key strengths of this study is the linkage of clinical data from individual patients to national demographic and socioeconomic data with less than 1% missing data. The clinical data were also highly complete, and studies using hospital patients only may underestimate the co-morbidity (1). For example, most patients with hypertension (70%) and diabetes (55%) are exclusively diagnosed in primary health care (25). The comprehensive nature of our data made it possible to analyze men and women from all educational backgrounds and marital statuses. Another strength is the sample size of the

study, i.e. 6,646 men and 5,637 women, and 66,000 person-years at risk analyzed, and the large number of events, i.e. first ischemic stroke (n=1,465).

In conclusion, our results confirm the strong effectiveness of warfarin in preventing stroke when used to treat AF patients in a primary health care setting and emphasize the importance of persistent anticoagulant treatment. Moreover, despite the fact that women have a higher risk of stroke, they are at the same time being undertreated, so the take home message to clinicians is that women need to be considered for anticoagulant treatment at a higher rate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Data on subjects aged 45+ years with a diagnosis of atrial fibrillation in primary care from 1 January 2001 to 31 December 2007, and patients with an ischemic stroke (IS)

	All (*n*=11,517)		With IS (*n*=1,465)	
	Women *n*=5,248	**Men *n*=6,269**	**Women *n*=768**	**Men *n*=697**
Age (years), mean (SD)	76.9 (9.3)	71.8 (10.2)	79.0 (8.0)	74.7 (8.8)
Age group (years)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
45–54	105 (2.0)	363 (5.8)	6 (0.8)	17 (2.4)
55–64	499 (9.5)	1,184 (18.9)	43 (5.6)	79 (11.3)
65–74	1,199 (22.9)	1,951 (31.1)	137 (17.8)	213 (30.6)
75–84	2,343 (44.7)	2,162 (34.5)	381 (49.6)	298 (42.8)
85+	1,102 (21.0)	609 (9.7)	201 (26.2)	90 (12.9)
Neighbourhood SES				
High	1,810 (34.5)	2,508 (40.0)	396 (51.6)	318 (45.6)
Middle	2,508 (49.2)	2,866 (45.7)	265 (34.5)	281 (40.3)
Low	858 (16.4)	895 (14.3)	107 (13.9)	98 (14.1)
Marital status				
Married	1,552 (29.7)	3,705 (60.1)	188 (24.6)	405 (58.3)
Unmarried	374 (7.2)	606 (9.7)	50 (6.5)	53 (7.6)
Divorced	739 (14.2)	942 (15.1)	91 (11.9)	96 (13.8)
Widowed	2,558 (49.0)	956 (15.2)	435 (56.9)	141 (20.3)
Educational level				
Compulsory school	2,407 (52.2)	2,340 (39.4)	372 (57.2)	251 (38.1)
Secondary school	1,527 (33.1)	2,234 (37.6)	200 (30.8)	266 (40.4)
College/university	680 (14.7)	1,369 (23.0)	78 (12.0)	142 (21.6)
AF-related disease				
Hypertension	2,553 (48.7)	2,591 (41.3)	387 (50.4)	324 (46.5)
Coronary heart disease	1,098 (20.9)	1,260 (20.1)	155 (20.2)	157 (22.5)
Congestive heart failure	1,084 (20.7)	1,082 (17.3)	157 (20.4)	121 (17.4)
Diabetes mellitus	1,021 (19.5)	1,231 (19.6)	134 (17.5)	181 (26.0)
Drugs				

	All (*n*=11,517)		With IS (*n*=1,465)	
	Women *n*=5,248	**Men *n*=6,269**	**Women *n*=768**	**Men *n*=697**
Ever-present warfarin	2461 (46.9)	3485 (55.6)	354 (46.1)	397 (57.0)
Warfarin ITT	2310 (44.0)	3306 (52.7)	236 (30.7)	251 (36.0)
Warfarin PP	1768 (33.7)	2508 (40.0)	160 (20.8)	148 (21.2)

SES denotes “socio-economic status”.

ITT denotes “intention-to-treat”: prescription before the years of first stroke, or present among subjects not experiencing a stroke.

PP denotes “per-protocol” (“PP”): prescription the year before and the year of first stroke, or present among subjects not experiencing a stroke if present at least during three years, of at least 50% of actual years after first recorded year of AF, or during both 2006 and 2007.

Table 2

Patients with atrial fibrillation in primary care: all women and men, and women and men without persistent warfarin treatment ("per protocol" warfarin treatment), respectively, divided into patients without or with first hospital-admitted ischemic stroke (IS), during 2001–2010 by scores on CHA_2DS_2-VASc, with number of patients (percentage). Incidence rates (IR) for IS in patients without PP-warfarin treatment. Numbers needed to treat (NNT) shown for prevention of first ischemic stroke by warfarin treatment during 5.4 years of follow-up

CHA_2DS_2- VASc:	Women						Men					
	All		Without PP-warfarin				All		Without PP-warfarin			
	No IS	IS	No IS	IS			No IS	IS	No IS	IS		
	n	n (%)	n	n (%)	IR	NNT	n	n (%)	n	n (%)	IR	NNT
0	–	–	–	–	–		720	39 (5.1)	482	34 (6.6)	1.09 (0.78–1.52)	22.1
1	258	21 (7.5)	184	19 (9.4)	1.55 (0.99–2.42)	14.9	1064	81 (7.1)	581	71 (10.9)	1.86 (1.48–2.36)	11.3
2	494	73 (12.9)	309	67 (18.3)	3.20 (2.51–4.06)	6.6	1557	159 (9.3)	888	133 (13.0)	2.52 (2.12–2.98)	10.8
3	1157	191 (14.2)	730	165 (18.4)	3.71 (3.18–4.32)	7.9	1287	194 (13.1)	696	161 (18.8)	3.81 (3.27–4.45)	7.4
4	1419	231 (14.0)	895	206 (18.7)	3.84 (3.35–4.40)	7.1	631	133 (17.4)	354	109 (23.5)	5.27 (4.37–6.36)	6.4
5	814	167 (17.0)	498	143 (22.3)	4.95 (4.20–5.84)	6.8	225	58 (20.5)	131	47 (26.4)	5.96 (4.48–7.94)	6.3
6	266	60 (18.4)	156	52 (25.0)	5.91 (4.51–7.76)	5.5	70	28 (28.6)	36	25 (41.0)	10.70 (7.23–15.84)	3.0
7	57	22 (27.9)	36	16 (30.8)	6.28 (3.85–10.26)	11.7	17	4 (19.1)	9	3 (25.0)	5.66 (1.83–17.65)	N/A
8	14	3 (17.7)	10	2 (16.7)	4.12 (1.03–16.48)	N/A	1	1 (50.0)	0	1 (100.0)	N/A	N/A
9	1	0 (0.0)	1	0 (0.0)	N/A	N/A	–	–	–	–	–	
All	4480	768 (14.6)	2810	670 (19.3)	3.89 (3.61–4.20)	7.3	5,572	697 (11.1)	3177	584 (15.5)	2.98 (2.75–3.23)	9.1

Values for all patients and for those with no warfarin treatment according to "per protocol"-analysis. Incidence Rate per 100 Person-Years at Risk (95% CI) shown for ischemic stroke without warfarin treatment.

NNT denotes "numbers needed to treat" during a mean follow-up of 5.4 years

Table 3

Incidence rates and Cox regression for risk of first ischemic stroke in women and men with atrial fibrillation treated with ITT- or PP-warfarin, versus patients without ITT- or PP-warfarin treatment as referents.

	Events/At Risk (n, %)	Incidence Rate (95% CI)	Warfarin ITT br1>HR (95% CI)	Warfarin PP HR (95% CI)		
				Model 1	Model 2	Model 3
First ischemic stroke						
Women	768/5,248 (14.6%)	2.77 (2.58–2.98)	0.66 (0.46–0.97)	0.27 (0.21–0.33)	0.24 (0.17–0.34)	0.25 (0.18–0.36)
Men	697/6,269 (11.1%)	2.02 (1.88–2.18)	0.73 (0.55–0.96)	0.27 (0.22–0.33)	0.26 (0.20–0.33)	0.25 (0.19–0.32)

ITT denotes “Intention-to-treat”: prescription before the years of first stroke, or present among subjects not experiencing a stroke.

PP denotes “Per-protocol”: prescription the year before and the year of first stroke, or present among subjects not experiencing a stroke if present at least during three years, of at least 50% of actual years after first recorded year of AF, or during both 2006 and 2007.

Incidence rate per 100 Person-Years at Risk.

Model for warfarin ITT (with patients on PP-warfarin treatment excluded): fully adjusted (age, neighbourhood socioeconomic status, educational level, marital status, hypertension, CHD, CHF and diabetes, with interaction term between age and marital status)

Models for warfarin PP: Model 1 age-adjusted, Model 2 also adjusted for socioeconomic factors (neighbourhood socioeconomic status, educational level and marital status), and Model 3 also for co-morbidity (hypertension, CHD, CHF and diabetes).