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Warfarin treatment and risk of myocardial infarction – a cohort study of patients with atrial fibrillation treated in primary health care

Per Wändell[*,1,2], **Axel C Carlsson**[1,3], **Martin J Holzmann**[4,5], **Johan Ärnlöv**[3,6], **Sven-Erik Johansson**[7], **Jan Sundquist**[7], and **Kristina Sundquist**[7]

[1]Division of Family Medicine, Department of Neurobiology, Care Science and Society, Karolinska Institutet, Huddinge, Sweden

[2]Academic Primary Healthcare Centre, Stockholm County Council, Huddinge, Sweden

[3]Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden

[4]Department of Emergency Medicine, Karolinska University Hospital, Stockholm, Sweden

[5]Department of Internal Medicine, Karolinska Institutet, Stockholm, Sweden

[6]School of Health and Social Studies, Dalarna University, Falun, Sweden

[7]Centre for Primary Health Care Research, Lund University, Malmö, Sweden

Abstract

Objective—To study the risk of myocardial infarction (MI) in patients with atrial fibrillation (AF) treated in primary health care with warfarin or acetylsalicylic acid (ASA, aspirin).

Methods—The study population included subjects (n=11,699) 45 years or older diagnosed with AF who were treated in 75 primary care centres in Sweden between 2001 and 2007. MI was defined as a hospital stay for MI during 2001 through 2010 registered in the Swedish Patient Register. Associations between warfarin or ASA treatment and incident MI were explored using Cox regression analysis, by estimating hazard ratios (HRs) and 95% confidence intervals (95% CIs). Adjustment was made for age, socio-economic factors and cardio-vascular co-morbidity.

Results—Persistent treatment ("per protocol" treatment) with warfarin alone was present among 28.9% of women and 32.6% of men, and with ASA alone among 26.2% of women and 23.2% of men. The fully adjusted HRs for MI, compared to those with no antithrombotic treatment, with warfarin treatment for women were 0.24 (95% CI 0.16–0.40), and for men 0.27 (95% CI 0.19–0.38); and the corresponding HRs for those treated with ASA were for women 0.60 (95% CI 0.39–0.92), and for men 0.44 95% CI (0.31–0.63). The fully adjusted HR for MI, when comparing

[*]Corresponding author: Per Wändell, Division of Family Medicine, NVS Department, Karolinska Institutet, Alfred Nobels Allé 12, 141 83 Huddinge, Sweden., Phone: + 46-8-52488727, Fax: + 46-8-52488706, per.wandell@ki.se.

Disclosures

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patients with warfarin treatment to those with ASA treatment, was for women 0.45 (95% CI 0.26–0.77), and for men 0.58 (95% CI 0.38–0.88).

Conclusions—Warfarin seems to prevent MI among AF patients in a primary healthcare setting, which emphasizes the importance of persistent anticoagulant treatment in those patients.

Keywords

anticoagulant; atrial fibrillation; co-morbidity; follow-up; gender; myocardial infarction; antiplatelets

1. Introduction

Atrial fibrillation (AF) is considered as a major health problem [1], with an increasing trend of incidence and prevalence globally [2–4]. In Sweden, around 2% of the population are diagnosed with AF [5]. The most important complication of AF is ischemic stroke [6, 7], estimated to be 5 times as common as in individuals without AF [8].

Myocardial infarction (MI) is a risk factor for AF, and incident AF is present in 6–21% among patients with an acute MI [9]. Considering the reverse causation, AF could be associated with an increased risk of MI, and a higher risk of MI among women with AF has indeed been reported [10]. Interestingly, the mortality risk estimates were higher although not statistically significant in an American study comparing patients with AF and MI with patients with AF alone [10].

Among prescribed pharmacotherapies to AF patients, anticoagulant (predominantly warfarin) therapy has benefits over antiplatelet (mostly acetylsalicylic acid, i.e. ASA, aspirin) therapy [11]. This is because anticoagulant treatment is superior in preventing strokes [12]. Before the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), warfarin was the most commonly prescribed oral anticoagulant used to prevent stroke in patients with AF [13]. With regard to the risk of MI in patients with AF, a Cochrane report found a reduced, although not significantly reduced risk in patients with oral anticoagulant compared to antiplatelet therapy; the OR was 0.69, 95% CI 0.47 to 1.01, while the mortality risk was similar for oral anticoagulants and antiplatelets [14]. A review of stroke-preventive studies regarding the effect of warfarin compared to non-warfarin anticoagulants found a significant reduction in MI [15].

Many studies on AF patients are based on samples from hospitals although many patients with AF are cared for at their primary health care centres. Out of all patients recorded with an AF diagnosis in Stockholm County in Sweden, 64% had their AF diagnosis reported in the primary healthcare records [5]. Thus, it is important to study the risks and benefits of different therapies prescribed to patients with AF within this setting.

The objective of the present study was to explore the risk of MI associated with warfarin and ASA treatment compared with no antithrombotic treatment in women and men with AF in a large cohort treated in primary health care. Secondary aims were to explore the mortality risk in women and men with AF who experienced a MI with women and men who did not

experience a MI, and to explore mortality among patients with MI in relation to treatment with warfarin or ASA.

2. Methods

2.1 Design

This study was performed using individual-level patient data from 75 Swedish primary health care centres (PHCC). The majority of the centres were 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 19 September 2010) to collect individual files from the electronic patient records (EPR) at the PHCCs. Individual identification numbers were replaced by serial numbers to ensure anonymity. The EPR files from the PHCCs were linked to Swedish national registers [16]. The registers used were: The Total Population register (which contains data on, e.g., age and education); The Inpatient Register (hospital admissions); and the Cause of Death Register. These registers contain individual-level population data for all residents registered in Sweden. 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, linked to national demographic and socio-economic 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 [17].

2.2 Study population and co-morbidities

The study included all patients with diagnosed AF, identified by the presence of the ICD-10 code (10th version of the WHO International Classification of Diseases) for atrial fibrillation (I48) in patients' medical records. The following related cardiovascular disorders/co-morbidities were used as covariates: hypertension (I10–15), heart failure (CHF; I50 and I110), cerebrovascular diseases (CVD; I60–69), and diabetes mellitus (E10–14). Presence of coronary heart disease (CHD; I20–25) was noted, but we did not have access to reliable data as regards earlier MI before first AF diagnosis. Patients with a first myocardial infarction (MI) during the time period were identified, and patients with their first MI before the first registered AF diagnosis were excluded. In total, 6,301 men and 5,398 women who were aged 45 years or older at the time of AF diagnosis and who visited any of the 75 participating PHCCs from 1 January 2001 until 31 December 2007, and had data on neighbourhood socio-economic status, were included in the study [18].

2.3 Outcome variable

Time to first MI after registration of AF diagnosis during the assessment period until 31 December 2010, was defined as having an ICD-10 code indicating an acute myocardial infarction (I21) in the Patient Register (hospital admissions) or The Cause of Death Register [19].

In addition, time to mortality from first AF diagnosis to death was registered as a secondary outcome.

2.4 Demographic and socio-economic 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, who are not representative of AF patients in general).

The neighbourhood socio-economic 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). [20] 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 socio-economically 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. We also registered change of neighbourhood SES during the study period, i.e. until 31 December 2007.

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.

2.6 Antithrombotic treatment

Treatment with an antithrombotic drug was defined as a prescription noted in the electronic patient record in primary health care 2001 to 2007. The prescribed antithrombotic drugs were classified as “intention-to-treat” (“ITT”) if ever present before the years of the first MI, or if present at any time among subjects not experiencing a MI. The prescribed warfarin was classified as “per-protocol” (“PP”) if present the year before and the year of first MI, or present among subjects not experiencing a MI if present at least 50% of actual years after first recorded year of AF. Prescriptions of antithrombotic treatment were classified into anticoagulant treatment, i.e. of warfarin (B01AA03), and of antiplatelet agents (B01AC). Antiplatelet agents were classified into ASA (B01AC06, and ASA combined with dipyridamol, B01AC30), or clopidogrel (B01AC04), also including related drugs (ticlopidine, B01AC05), with only marginal prescription.

2.7 Statistical analysis

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

We also made stratified analyses in subjects classified as not having a “per-protocol” prescription of antithrombotic drugs. Thus, we were able to estimate the risk of MI when not being on antithrombotic treatment.

We also estimated the incidence rates of MI per 100 person-years at risk for men and women. As a sensitivity analysis we assessed the incidence rate for MI for subjects with no antithrombotic treatment. The age-adjusted relative risk of MI for patients on “ITT” and “PP” warfarin or ASA treatment was analysed using Cox proportional hazard regression analysis, and presented as hazard ratios (HR) with 95% confidence intervals (CI). Adjustments were also made for socio-economic factors (educational level, marital status and neighbourhood SES), and also for co-morbidity (hypertension, CHF, CVS and diabetes). Models were checked for interactions by the Breslow method for ties. When interaction was present, interaction terms were used. Model specification was also tested.

In secondary analysis, Cox regression was used for estimating mortality risk in patients with MI, with patients without a MI as referents, with HRs and 95% CI, for men and women separately, with adjustments for age and sex, for socio-economic factors and for co-morbidity. Furthermore, Cox regression was used for estimating mortality risk in patients with MI in relation to antithrombotic treatment, with adjustment as stated above.

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

3. Results

The characteristics of the men and women with AF treated in primary care without (n=10,699) or with a MI during follow-up (n=1,000) are shown in Table 1. The mean follow-up time was 5.59 years (SD 2.54), and median follow-up time 5.50 years, and in total the analyses included 65,404 patient years.

Antithrombotic treatment by different combinations of drugs according to per-protocol analysis is shown in Table 2. Only a few patients had treatment with two drugs, the most common being warfarin and ASA (3.4% among women, and 4.2% among men).

Incidence rates of first MI by sex are shown in Table 3. Women showed a non-significantly lower risk of a MI than men, fully adjusted HR 0.88 (95% CI 0.71–1.10). The fully adjusted HRs for MI, compared to those with no antithrombotic treatment, was with PP warfarin treatment for women 0.24 (95% CI 0.16–0.40), and for men 0.27 (95% CI 0.19–0.38); and the corresponding HRs was for those treated with PP ASA for women 0.60 (95% CI 0.39–0.92), and for men 0.44 95% CI (0.31–0.63). In the comparison between PP warfarin and PP ASA treatment, the fully adjusted HR was for women 0.45 (95% CI 0.26–0.77), and for men 0.58 (95% CI 0.38–0.88). The number needed to treat (NNT) for PP warfarin treatment to prevent one MI was 59.8 per year in women and 67.1 per year in men. The NNT for treatment with PP ASA to prevent one MI was 113.4 per year in women and 124.1 per year in men.

Mortality risks for women and men with MI or without MI were estimated (Supplementary Table 1), with incidence rates per 100 person-years at risk for women with MI 9.584 (95% CI 8.481–10.830), and women without MI 5.596 (95% CI 5.328–5.876); and for men with MI 9.198 (95% CI 8.176–10.347), and men without MI 4.559 (95% CI 4.339–4.790). In fully adjusted Cox regression models, women with MI vs. those without MI had a higher

risk, HR 1.42 (95% CI 1.21–1.65), as do men with MI vs. those without MI, HR 1.56 (95% CI 1.36–1.78). Women had a lower mortality risk than men after MI, fully adjusted HR 0.79 (95% CI 0.64–0.98).

When estimating the mortality risk among patients with PP warfarin, PP ASA or PP any antithrombotic treatment was non-significant in fully adjusted models (Supplementary Table 2), HRs 1.00 (95% CI 0.93–1.07), 0.91 (95% CI 0.71–1.17) and 0.91 (95% CI 0.75–1.11), respectively.

Risk of MI was also assessed in relation to scores on $CHADS_2$ and CHA_2DS_2-VASc, with values for all patients and for those with no antithrombotic treatment according to “per protocol” analysis (supplementary Table 3). Incidence rates per 100 person-years at risk exceeded 2 for patients with no antithrombotic treatment according to “per protocol” analysis, at $CHADS_2$ scores ≥2 for women and men, and at CHA_2DS_2-VASc scores ≥4 for women, and ≥2 for men.

Discussion

The main finding was that warfarin treatment in patients with AF was associated with a lower risk of incident MI in comparison to patients with no antithrombotic treatment, as well as to patients with ASA treatment. The results remained significant after adjustments for socio-economic factors and relevant cardiovascular co-morbidities. The magnitude of the effect of warfarin treatment in preventing MI was remarkably high.

According to our findings it seems relevant to primarily use warfarin with regard to the risk of MI among AF patients, since the risk estimates compared to those without antiplatelet and antithrombotic treatment were higher than for warfarin. The use of warfarin is also in accord with current stroke prevention recommendations for patients with AF [11]. A similar suggestion was also proposed beyond the first year after an acute coronary syndrome in a recent systematic review [21].

Lower risk of MI was also found for patients treated with ASA, which has previously been shown to be effective in the prevention of MI [22, 23], even if the effect of seemed to lower among women than among men. Interestingly, some therapy recommendations suggest that both warfarin and ASA should be used simultaneously [24]. A large Danish study found no benefits of combining antiplatelet therapy with warfarin on recurrent coronary events or thromboembolism, but a significantly increased risk of bleeding complications [25]. It is also suggested that the risks associated with the combination of ASA with anticoagulation in patients with AF outweighs the benefit [26].

We have previously shown that warfarin is more often prescribed to women and men living in high socio-economic neighbourhoods [20]. Moreover, both individual-level and neighbourhood-level socio-economic status may affect the prescribing of warfarin as well as the mortality rate [27]. It is thus possible that the lower MI risk seen among those prescribed warfarin can be explained by factors associated with having warfarin prescribed, rather than the warfarin itself. Yet the association found between warfarin treatment and reduced risk of MI remained significant when we adjusted for several factors including education level,

marital status and neighbourhood socio-economic status; suggesting that the lower MI risk is explained by protective effects of warfarin itself. There may, however, be residual confounding that we could not adjust for which may explain differences between those prescribed warfarin and those not prescribed warfarin [20, 28].

As expected, the mortality was higher among AF patients with MI than AF patients without MI during follow-up, even if the increased mortality risk was not as high as could have been expected, i.e. the relative risk was around 1.4 for women and 1.5 for men. In general the MI mortality in Sweden is decreasing [29], as in other EU countries [30]. Surprisingly, we found no mortality-reducing effect from antithrombotic treatment in general after MI. The reason for the non-significant findings is puzzling, but we could speculate that they are explained by non-adherence, or treatment by specialists in open care, e.g. cardiologists (we only had prescription data from primary care).

The incidence rate overall was 1.6 events per 100 patient-years among women and 1.5 among men. In Sweden in 2013, the incidence rate of a first MI was 1.1% among women aged 80–84 years; and 1.3% among men aged 75–79, with the corresponding figure in Stockholm County being 1.1%, reflecting the mean ages in the cohort of women and men during the time period [31].

The risk of MI among AF patients was lower in women than in men, HR 0.88, but non-significant. The aforementioned US study found a significantly higher MI risk among women [10].

There are certain limitations of this study. This is an observational study, and prescription of warfarin may have been influenced by other factors than we recorded, i.e. confounding by indication may be one explanation for the high magnitude of the preventive effect of warfarin on first stroke [32]. An earlier Swedish study concluded that “warfarin-treated patients are highly selected and that decisions not to treat elderly, frail high-risk patients are at higher risk of having complicating co-morbidities and a poor prognosis” [12]. 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, and less than 2% of the total number of diagnoses was missing [33]. Besides, we used hospital data for the diagnosis of MI. We had no data available on the type of atrial fibrillation (paroxysmal, persistent, permanent). We had no data on electro-conversion of AF, nor had we information on procedures such as catheter ablation or Cox-Maze operations. Furthermore, data on the severity of the cardiovascular co-morbidities, e.g. NYHA classification of congestive heart failure, were not available. However, since the variables available in the present study were obtained from primary health care electronic patient records they are made by active clinicians. We had no data on time in therapeutic INR range (TIR). Our analyses of PP-treatment are attempts to try to reflect a regular treatment, while analyses of ITT or not reflect a more crude division. In the statistical analyses, it was not possible to find a balanced model when trying to use a propensity score analysis.

Despite the limitations, one of the key strengths of this study is the linkage of clinical data from individual patients to national demographic and socio-economic data with less than 1% missing data. The clinical data were also highly complete, and studies using only hospital patients may underestimate the burden of co-morbidities [5]. For example, most patients with hypertension (70%) and diabetes (55%) are exclusively diagnosed in primary healthcare [34]. The comprehensive nature of our data made it possible to analyse men and women from all educational backgrounds and marital statuses. Another strength is the sample size of the study, i.e. 6,301 men and 5,398 women, and 65,000 person-years at risk analysed.

In conclusion, our results show that warfarin prevents MI when used to treat AF patients in a primary healthcare setting, and emphasize the importance of persistent anticoagulant treatment in those patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Messages

What is already known about this subject?

In patients with atrial fibrillation there is an uncertainty whether anticoagulants are superior to antiplatelets in preventing myocardial infarction.

What does this study add?

We found anticoagulants to be superior to antiplatelets among both men and women with atrial fibrillation in preventing myocardial infarction.

How might this impact on clinical practice?

Persistent anticoagulant treatment is important among patients with atrial fibrillation not only in preventing stroke but also in preventing myocardial infarction.

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Table 1

Data on subjects aged 45+ years (n=11,699) with a diagnosis of atrial fibrillation and without (n=10,699) or with (n=1000) myocardial infarction (MI) after AF diagnosis in primary care from 1 January 2001 to 31 December 2007

	Women			**Men**		
	Without MI	**With MI**		**Without MI**	**With MI**	
	***n*=4,926**	***n*=472**	**p-value**	***n*=5,773**	***n*=528**	**p-value**
Age (years), mean (SD)	**76.8 (9.4)**	**79.8 (8.0)**	**<0.001**	**71.7 (10.3)**	**75.6 (8.8)**	**<0.001**
Age group (years)			**<0.001**			<0.001
45–54	**101 (2.1)**	**1 (0.2)**		**352 (6.1)**	**14 (2.7)**	
55–64	**484 (9.8)**	**23 (4.9)**		**1,119 (19.4)**	**55 (10.4)**	
65–74	**1,144 (23.2)**	**75 (15.9)**		**1,795 (31.1)**	**132 (25.0)**	
75–84	**2,176 (44.2)**	**246 (52.2)**		**1,943 (33.7)**	**261 (49.4)**	
85+	**1,021 (20.7)**	**127 (26.9)**		**564 (9.8)**	**66 (12.5)**	
Neighborhood SES			0.043			0.016
High	1,729 (35.1)	146 (30.9)		2,330 (40.4)	200 (37.9)	
Middle	2,420 (49.1)	233 (49.4)		2,646 (45.8)	231 (43.8)	
Low	777 (15.8)	93 (19.7)		797 (13.8)	97 (18.4)	
Marital status			**0.002**			**<0.001**
Married	**1,485 (30.3)**	**115 (24.5)**		**3,443 (59.9)**	**298 (56.7)**	
Unmarried	**361 (7.4)**	**26 (5.5)**		**561 (9.8)**	**40 (7.6)**	
Divorced	**695 (14.2)**	**60 (12.8)**		**903 (15.7)**	**74 (14.1)**	
Widowed	**2,362 (48.2)**	**268 (57.1)**		**844 (14.7)**	**114 (21.7)**	
Educational level			**<0.001**			**<0.001**
Compulsory school	**2,240 (51.5)**	**236 (59.8)**		**2,114 (38.6)**	**238 (48.2)**	
Secondary school	**1,442 (33.2)**	**126 (31.9)**		**2,068 (37.8)**	**173 (35.0)**	
College/university	**665 (15.3)**	**33 (8.3)**		**1,292 (23.6)**	**83 (16.8)**	
AF-related disease						
Hypertension	2,394 (48.6)	239 (50.6)	0.40	2,377 (41.2)	236 (44.7)	0.12
CHD	**801 (16.3)**	**210 (44.5)**	**<0.001**	**849 (14.7)**	**255 (48.3)**	**<0.001**
Heart failure	974 (19.8)	116 (24.6)	0.013	**933 (16.2)**	**133 (25.2)**	**<0.001**
Valvular disease	232 (4.7)	33 (7.0)	0.028	254 (4.4)	25 (4.7)	0.72

	Women			Men		
	Without MI	**With MI**		**Without MI**	**With MI**	
	***n*=4,926**	***n*=472**	**p-value**	***n*=5,773**	***n*=528**	**p-value**
Cardiomyopathy	27 (0.6)	1 (0.2)	0.51	53 (0.9)	5 (1.0)	0.95
CVS	582 (11.8)	48 (10.2)	0.29	638 (111)	49 (9.3)	0.22
Diabetes mellitus	**914 (18.6)**	**120 (25.4)**	**0.001**	**1,072 (18.6)**	**134 (25.4)**	**0.001**
Drugs						
Ever warfarin	**2,381 (48.3)**	**187 (39.6)**	**<0.001**	3,227 (55.9)	272 (51.5)	0.052
Warfarin ITT	**2,296 (46.6)**	**158 (33.5)**	**<0.001**	**3,118 (54.0)**	**241 (45.6)**	**<0.001**
Warfarin PP	**1,679 (34.1)**	**67 (14.2)**	**<0.001**	**2,229 (38.6)**	**97 (18.4)**	**<0.001**
Ever ASA	**2,786 (56.6)**	**330 (69.9)**	**<0.001**	**2,910 (50.4)**	**352 (66.7)**	**<0.001**
ASA ITT	**2,461 (50.0)**	**296 (62.7)**	**<0.001**	**2,584 (44.8)**	**299 (56.6)**	**<0.001**
ASA PP	1,479 (30.0)	125 (26.5)	0.11	1,614 (28.0)	124 (23.5)	0.028
Ever clopidogrel	**122 (2.5)**	**40 (8.5)**	**<0.001**	**111 (1.9)**	**59 (11.2)**	**<0.001**
Clopidogrel ITT	89 (1.8)	8 (1.7)	0.58	91 (1.6)	10 (1.9)	0.86
Clopidogrel PP	38 (0.8)	4 (0.9)	0.78	34 (0.6)	6 (1.1)	0.13

Prescription of warfarin was classified as “intention-to-treat” (“ITT”) if ever present before the years of MI, or present among subjects without MI. Prescription of warfarin was classified as “per-protocol” (“PP”) if present the year before and the year of first MI, or present among subjects without MI if present during at least three years, at least 50% of actual years after first recorded year of AF, or during both 2006 and 2007.

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Table 2

Data on antithrombotic treatment (according to “PP”) in subjects aged 45+ years (n=11,699) with a diagnosis of atrial fibrillation. Number of patients (percentage)

Treatment	Women n=5,398	Men n=6,301
No treatment	2,201 (40.8)	2,478 (39.3)
ASA	1,414 (26.2)	1,463 (23.2)
Clopidogrel	29 (0.5)	23 (0.4)
ASA + clopidogrel	8 (0.2)	11 (0.2)
Warfarin	1,560 (28.9)	2,056 (32.6)
Warfarin + ASA	181 (3.4)	264 (4.2)
Warfarin + clopidogrel	4 (0.1)	6 (0.1)
Warfarin + ASA + clopidogrel	1 (0.0)	0 (0.0)

Prescription was classified as “per-protocol” (“PP”) if present the year before and the year of MI, or present among subjects without MI if present during at least three years, at least 50% of actual years after first recorded year of AF, or during both 2006 and 2007.

Table 3

Cox regression for risk of first myocardial infarction (MI) in women and men with atrial fibrillation treated with antithrombotic drugs, using those without warfarin treatment as referents. Models shown by “per protocol” analysis (PP) for warfarin and for ASA treatment. Incidence rate per 100 Person-Years at Risk.

	Events/At Risk (n)	Incidence Rate (95% CI)	Warfarin			ASA		
			Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
MI								
Women	472/5,398	1.587 (1.450–1.737)	0.26 (0.20–0.35)	0.27 (0.17–0.42)	0.25 (0.16–0.40)	0.55 (0.44–0.69)	0.63 (0.41–0.95)	0.60 (0.39–0.92)
Men	528/6,301	1.481 (1.359–1.612)	0.30 (0.23–0.38)	0.30 (0.21–0.41)	0.27 (0.19–0.38)	0.48 (0.39–0.60)	0.47 (0.33–0.67)	0.44 (0.31–0.63)

Prescription of warfarin and ASA was classified as “per-protocol” (“PP”) if present the year before and the year of MI, or present among subjects without MI if present at least 50% of actual years after first recorded year of AF. For warfarin, patients on ASA or clopidogrel were excluded from analyses, and for ASA, patients on warfarin or clopidogrel were excluded.

Model 1 age-adjusted, and Model 2 as Model 1 but also adjusted for socio-economic factors (neighbourhood socio-economic status, educational level and marital status, also including interaction terms between age and marital status), and Model 3 as Model 2 but also adjusted for cardiovascular co-morbidity (hypertension, cerebrovascular disease, CHF and diabetes; also including interaction terms between age and marital status, and for women also between age and diabetes.