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ORIGINAL PAPER

Sex differences in stroke prevention in atrial fibrillation in French primary care. Results of the AFIGP (Atrial Fibrillation In General Practice) Database

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Abstract
Background and objectives Most of the French patients diagnosed with atrial fibrillation (AF) are managed by general practitioners (GPs). The objective was to evaluate stroke prevention in AF patients ahead of the arrival of the non vitamin K oral anticoagulant in France.
Methods A cross-sectional study using a French GPs database of all patients with a diagnosis of AF consulting their GP between July-2010 and June-2011. Multivariate analyses were used to identify determinants of prevention prescription.
Results Among 15,623 AF patients, 42.5 % were ≥75 -years and 40.5 % women, 59.2 % had hypertension, 17.2 % diabetes, 11.4 % heart failure, 4.9 % stroke history. $CHADS_2$ score was ≥1 for 83.1 % and ≥2 for 50.9 % of patients (CHA2DS2-VASc score ≥1 for 93.7 % and ≥2 for 82.3 %). Antithrombotic therapies were vitamin K antagonists (VKA) for 50.7 % of patients, followed by aspirin for 19.9 %, clopidogrel ± aspirin for 4.3 % and none for 25.1 %. For patients with $CHADS_2$ scores ≥1, 73.3 % received an antithrombotic and for those with $CHADS_2$ scores ≥2, 54.9 % were treated by a VKA. An age-stratified multivariate analysis showed that women had an odds ratio to be treated with VKA compared to 0.83 (95 % CI: 0.72–0.95) and 0.66 (95 % CI: 0.59–0.74) when aged <75 years and ≥75 years, respectively.
Conclusions Most AF patients followed by French GPs required stroke prevention according to European guidelines, but many of them did not receive the recommended antithrombotic treatment. Women over 75 were a third less likely to be treated with recommended anticoagulants than men of similar age.

Keywords Atrial fibrillation · Primary care · Arrhythmia · Epidemiology · France

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in elderly persons [1] and a major preventable cause of stroke [2]. In France, it has been estimated that there are currently between 600,000 and 1 million people with AF, with two-thirds of these subjects aged ≥75 years [3]. Among them, the French health authorities recently estimated that between 500,000 and 800,000 patients should be eligible for stroke prevention with an anticoagulant treatment [4]. In 2010, the European society of cardiology (ESC) issued guidelines for the management of AF [5] (see also 2012-update in Ref. [6]). The $CHADS_2$ (a risk scoring system which awards one point each for history of cardiac failure, hypertension, age, and diabetes, and two points for prior stroke) stroke risk stratification scheme was

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recommended as an initial, rapid, and easy-to-remember means of assessing stroke risk in AF, particularly suited to primary care doctors and non-specialists [5].

Women with AF are at higher risk of stroke than men and are more likely to live with stroke-related disability and a significantly lower quality of life [7]. In the Canadian registry of atrial fibrillation (CARAF) study, women aged >75 years were 54 % less likely to receive warfarin than men [8] (see also Ref. [9, 10]). Reluctance among physicians and patients to use warfarin may be especially problematic in elderly women, who benefit most from it [7]. In line with this view, the ESC issued a guideline update, incorporating female sex as a risk factor in the CHA2DS2-VASc score [6].

In France, cardiologists are mostly in charge of the diagnosis and initial treatment of AF, whereas follow-up and stroke prevention are mostly managed by general practitioners (GPs) [11]. The observational French EPHA study on only 1,331 patients, included between February 2009 and May 2009, showed that cardiologists treated most patients with AF with a vitamin K antagonist (83 %) [11]. Conversely, no data are available in the literature concerning stroke prevention by French GPs and gender differences in antithrombotic therapy. Therefore, we decided to evaluate the risk of stroke in a large sample of AF patients followed by French GPs and the modalities of antithrombotic stroke prevention therapy, and in particular, potential discrepancies between the treatment of male and female patients, ahead of the arrival of the new oral anticoagulants (NOACs) in this indication.

Methods

Design and setting

It was a cross-sectional analysis of the longitudinal patient data (LPD) database [12–14], a French medical and prescriptions files database owned by cegedim strategic data (CSD), a private company,. This database is supplied with anonymous information collected during daily practice of office-based physicians via their practice management software (Doc'Ware®). LPD provide information since 1994 from more than 1.6 million active patients followed by a sample of 1,200 active GPs in France. The panel is representative of French GPs in terms of age, sex and area of coverage. The tool reflects real-life settings; no intervention is made to recollect or to impute missing data. GPs regularly report their practice activity, without receiving any direct fee for their participation.

Study population and data extracted

The study population was all adult (≥18 years) patients with a diagnosis of atrial fibrillation and at least one GP consultation between July 1st 2010 and June 30th 2011. During this period, patient demographic data, stroke medical risks factor information (congestive heart failure or left ventricular dysfunction, hypertension, diabetes, stroke transient ischemic attack or systemic embolism, vascular pathology), as well as Vitamin K antagonists (VKAs) and antiplatelet agents prescriptions including aspirin were extracted.

Stroke risk evaluation and FA treatment recommendation

Risk of stroke was evaluated using the $CHADS_2$. A $CHADS_2$ score of 0 was taken as low risk, 1 as moderate risk, and ≥2 as high risk [5]. In addition, the CHA2DS2-VASc was also used to evaluate stroke risk, although this is out of the scope of primary care in "real-life" conditions [5] and the 2012-update was issued after our study was initiated [6]. Treatment status was defined according to European guidelines' recommendations (ESC) for stroke prevention in AF patients [5, 6].

Statistical analysis

The statistical analysis compared patient, disease and recommended treatment characteristics between men and women using univariate test (Chi square or Fischer's exact test in cases of insufficient observations for qualitative variables and analysis of variance or rank test in case of the normality assumption was questionable for quantitative variables) and two-sided 5 % p value threshold.

The risk (or chance) to be treated by a VKA was assessed using the procedure GLIMMIX (SAS 9.2) [15] for a multivariate analysis. This procedure allows the analysis of non-normal data and GP as a random effect. Potential covariates [patients' characteristics, $CHADS_2$ or CHA2DS2-VASc scores, athero-thrombotic disease, concomitant treatments of Anti-arrhythmic drugs (AA) and Non-steroidal anti-inflammatory drugs (NSAIDs)] concerning at least 5 % of the population significant at a 20 % threshold were introduced in the model and excluded with a backward procedure at a 0.001 threshold. Then all pairwise interactions were tested and due to complex interactions, two models were performed: one for patient <75 years and one for patients ≥75 years. Results are presented with odds ratios and their 95 % confidence intervals.

Table 1 Demographic and clinical aspects of AF patients participating in the study

	All patients $N = 15,623$ (100 %)	Males $N = 9,291$ (59.5 %)	Females $N = 6,332$ (40.5 %)	P
Age (years)	74.6 ± 11.1	72.8 ± 11.4	77.3 ± 10.2	<0.0001
BMI (kg/m^2)	27.9 ± 5.3	28.1 ± 4.8	27.4 ± 6.0	<0.0001
Blood pressure (mmHg)				
Systolic	132.7 ± 15.3	132.0 ± 15.0	133.8 ± 15.7	<0.0001
Diastolic	75.8 ± 9.1	75.9 ± 9.1	75.8 ± 9.1	<0.0001
Comorbidities (% of patients)				
Hypertension	59.2	56.3	63.4	<0.0001
Diabetes	17.2	18.9	14.6	<0.0001
Heart failure	11.4	11.2	11.5	0.55
Stroke	4.9	4.7	5.2	0.12
TIA	3.2	3.1	3.4	0.21
Concomitant drugs (% of patients)				
Anti-arrhythmic (AA)	47.5	47.6	47.4	0.8104
Non-steroidal anti-inflammatory drug (NSAID)	9.5	9.7	9.3	0.6150
$CHADS_2$ score	1.5 ± 1.1	1.5 ± 1.1	1.7 ± 1.0	<0.0001
Score = 0 (% of population)[a]	16.9	20.0	12.2	
Score = 1 (% of population)[a]	32.2	33.2	30.7	
Score ≥ 2 (% of population)[a]	50.9	46.8	57.1	
$CHA2DS_2$-VASc score	2.9 ± 1.5	2.4 ± 1.4	3.7 ± 1.3	<0.0001
Score = 0 (% of population)[a]	6.4	10.7	0.0	
Score = 1 (% of population)[a]	11.4	15.2	5.6	
Score ≥ 2 (% of population)[a]	82.3	74.0	94.4	

Values are given as % of patients or mean ± SD

BMI, body mass index, *TIA* transient ischemic attack

[a] CHADS2 scores are given as % of total, male or female population for all patients, male patients and female patients, respectively

Results

Participating patients

A total of 15,623 AF patients were included in the study. Almost half of the patients were older than 75 years and 40.5 % of them were women (Table 1). Hypertension was the most common stroke risk factor (59.2 % of patients), while diabetes, heart failure and stroke were prevalent in 17.2, 11.4 and 4.9 % of patients, respectively. More than four patients out of five (83.1 %) had a $CHADS_2$ score ≥1 and half had a $CHADS_2$ score ≥2 while close to 100 % had a CHA2DS2-VASc score ≥1 and 82.3 % a CHA2DS2-VASc score ≥2. Women were older than men with more hypertension, less diabetes, and higher CHADS2 and CHA2DS2-VASc score (Table 1; Fig. 1). Regarding concomitant medications, non-steroidal anti-inflammatory drugs (NSAIDs) and antiarrhythmics (AA) were often prescribed (9.5 and 47.5 % of patients, respectively). Injectable anticoagulants were prescribed only in 3.1 % of patients, high-dose aspirin in 0.3 % of them and anti-platelet agents (excluding clopidogrel and low-dose aspirin) in 0.2 % of our sample.

Stroke prevention

In total, 25.1 % of patients received no antithrombotic therapy, 50.7, 19.9 and 4.3 % were treated with VKA, aspirin and clopidogrel (±aspirin), respectively. Due to the relatively small number of patients receiving clopidogrel, they were grouped with patients with aspirin in all subsequent analyses. Figure 2 shows stroke prevention treatments as a function of $CHADS_2$ scores and gender. Among patients eligible for stroke prevention (i.e., $CHADS_2$ scores ≥ 1), 62.0 % received a recommended antithrombotic therapy i.e., 73.3 % of patients with $CHADS_2$ scores = 1 treated with VKAs or aspirin and 54.9 % of patients with $CHADS_2$ scores ≥ 2 treated with VKAs.

VKA treatment was less frequent for women than for men irrespective of the $CHADS_2$ score (Fig. 2). An age-stratified multivariate analysis (Table 2) showed that, as compared with men, women were 17 and 34 % less likely to be treated with VKA when aged <75 years [OR: 0.83, 95 % CI (0.72–0.95)] and ≥75 years [OR = 0.66, 95 % CI (0.59–0.74)], respectively. A higher $CHADS_2$ score and a diagnosis of athero-thrombotic disease were also associated with VKA prescription. Interaction was found between the

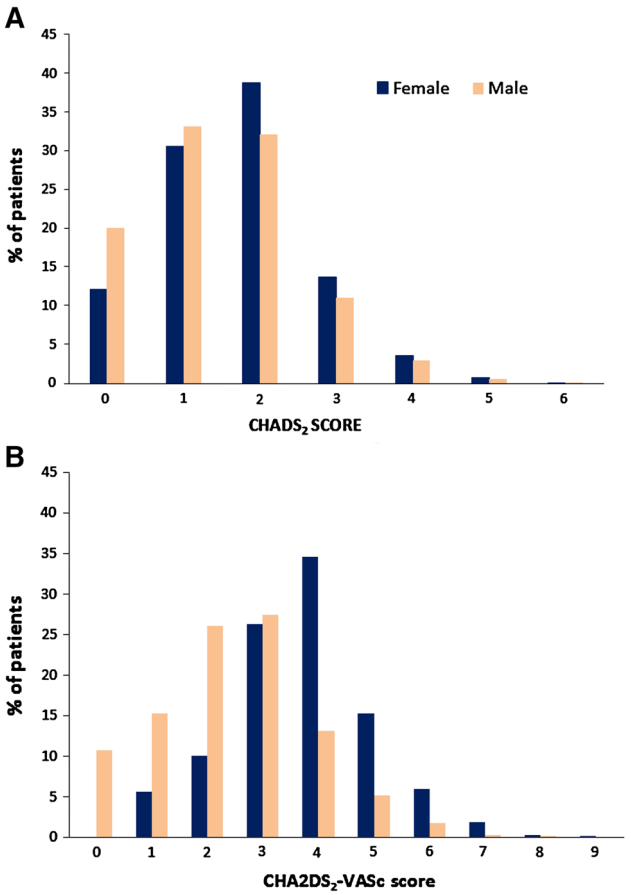

Fig. 1 Distribution of $CHADS_2$ (**a**) and $CHA2DS_2$-VASc (**b**) scores according to gender ($N = 15{,}623$)

NSAIDs and AA treatments. Patients treated by AA without any NSAIDs concomitant treatment were associated with VKA prescription. On the contrary, being treated by NSAIDs without any AA concomitant treatment was associated with the absence of VKA prescription.

Discussion

Most of the 15,623 AF patients followed by French GPs (83.1 %) were at high or moderate risk of stroke (CHADS2 scores ≥ 1), but only 62 % of them received antithrombotic treatment as recommended in European guidelines. An age-stratified multivariate analysis showed that women were less equally treated with VKA than men.

AF is a major preventable cause of stroke [2], but anticoagulants (AC) remain underused to prevent strokes due to AF, particularly in elderly patients [16–20]. Cowan et al. [17] recently investigated 231,833 patients with a history of AF among 1,857 general practices in England representing a practice population of 13.1 million registered patients. Over one-third of AF patients with known risk factors who were eligible for AC did not receive them. There was a high use of antiplatelet agents (AP) among patients not receiving AC. Uptake of AC was particularly poor among patients aged 80 years and over [17]. With an aging population, the AF prevalence is rapidly rising. Left atrial enlargement seems to explain the increased AF risk with age and obesity [21]. Approximately 60 % of people

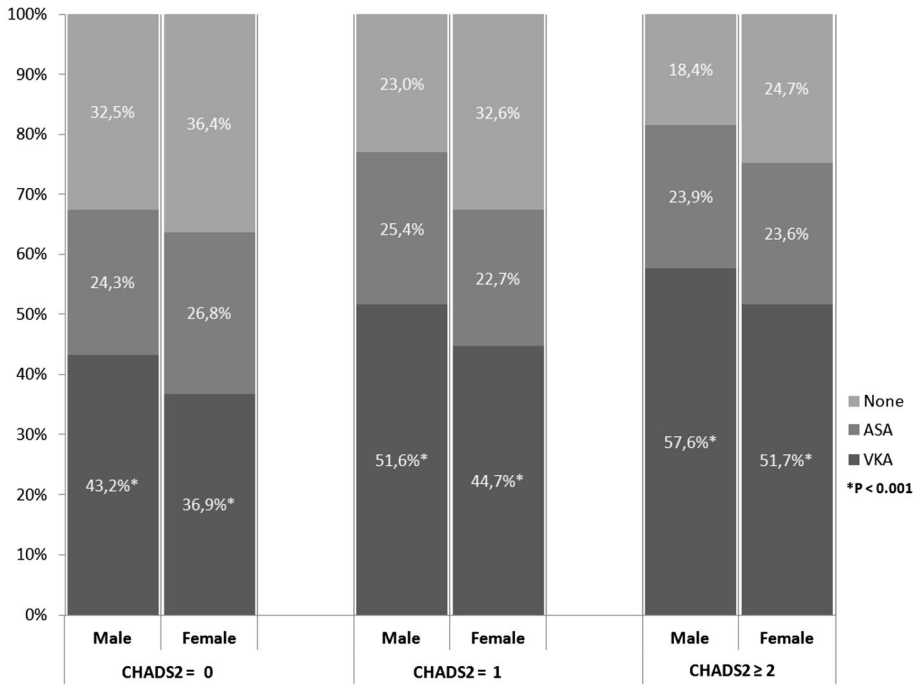

Fig. 2 Stroke prevention treatments as a function of $CHADS_2$ scores and gender. *VKA* vitamin K antagonist, *ASA* aspirin and/or clopidogrel. *Asterisk* denote statistical comparison between males and females

Table 2 Age-stratified multivariate analysis of VKA prescription in males and females with AF

		Age <75 years		Age ≥75 years	
		Univariate	Multivariate	Univariate	Multivariate
Variables	Modalities	OR (CI 95 %)	OR (CI 95 %)	OR (CI 95 %)	OR (CI 95 %)
Gender	Male	1	1	1	1
	Female	0.86 (0.76; 0.98)	0.83 (0.72; 0.95)	0.69 (0.62; 0.77)	0.66 (0.59; 0.74)
Artero-thrombotic disease	No	1	1	1	1
	Yes	1.78 (1.39; 2.27)	1.41 (1.11; 1.80)	1.19 (1.008; 1.40)	1.13 (0.97; 1.31)
NSAID *AA (interaction factor)	No*No	1	1	1	1
	Yes*Yes	1.279 (0.970; 1.688)	1.36 (1.02; 1.80)	1.138 (0.827; 1.566)	1.18 (0.86; 1.63)
	Yes*No	0.427 (0.329; 0.555)	0.44 (0.34; 0.58)	0.804 (0.590; 1.095)	0.81 (0.59; 1.11)
	No*Yes	4.335 (3.740; 5.026)	4.34 (3.73; 5.04)	4.829 (4.233; 5.509)	4.92 (4.31; 5.62)
$CHADS_2$ score	0	1	1	NE	NE
	1	2.00 (1.74; 2.29)	1.97 (1.71; 2.26)	1	1
	>=2	3.14 (2.61; 3.77)	2.77 (2.27; 3.38)	1.70 (1.51; 1.91)	1.73 (1.53; 1.95)

NSAID non-steroidal anti-inflammatory drug, *AA* anti-arrhythmic, *NA* not applicable, *NE* not estimable (age of ≥ 75 years accounts for one point in $CHADS_2$ score)

over the age of 75 with AF are women [7, 22]. However, despite this difference in life expectancy, males are more often affected by AF [7, 21, 23] and also represented the majority of the patients in our study. Furthermore, women with AF are at higher risk of stroke compared with men. Reasons for this higher stroke risk in women remain unclear, although some studies suggest that under treatment with warfarin may be a cause [24].

Warfarin therapy substantially reduces the risk of atrial fibrillation-related thromboembolism but also increases the risk for hemorrhage [25, 26]. As pointed out by Volgman et al. [7], the reluctance of (American) physicians and patients to use warfarin anticoagulation in women may be due to an increased risk of bleeding. In the CARAF and stroke prevention using an oral thrombin inhibitor (SPORTIF) studies [8, 27], women were more susceptible to anticoagulant-related bleeding [7]. Moreover, anticoagulation therapy in women is frequently interrupted for various reasons (e.g., breast biopsy, minor and major surgery) [7]. Our study showed that NSAIDs concomitant treatment also influenced VKA prescription. Indeed, all types and formulations of NSAIDs may increase the risk of upper gastrointestinal bleeding [28], and GPs are perhaps sometime prioritizing other comorbidities rather than stroke prevention.

Oral VKA are associated with a number of limitations, including excessive bleeding risk when not adequately controlled [29]. Antiplatelet agents do not match VKAs in terms of their preventive efficacy. As pointed out by Bassand [29], NOACs, including the direct thrombin inhibitor dabigatran and direct Factor Xa inhibitors such as rivaroxaban, and apixaban, have now been approved or are currently in late-stage clinical development in AF. These newer agents are of a particular importance due to a rapid growth of their prescription in AF in Europe.

As pointed out by Sandhu and McAlister [2], a better understanding of the stroke prevention practices in real-world settings is critically important to implement preventive strategies that will improve the outcomes and reduce healthcare costs. We therefore evaluated antithrombotic management in AF by GPs in France. Similarly to other European studies using primary care registries [30–32], the most common concomitant conditions observed in our study were hypertension, diabetes and heart failure. In our study, a quarter of patients eligible for stroke prevention were not treated at all. On the contrary, 36.9 % of females and 43.2 % of males received VKA treatment despite an absence of additional risk factor. Similar findings were also observed in the ongoing world wide GARFIELD registry, where the overall use of anticoagulant therapy was relatively low. A total of 40.7 % of the patients with a CHA2DS2-VASc score <2 did not receive guideline-recommended anticoagulant prophylaxis. Conversely, 38.7 % of patients with a CHA2DS2-VASc score of 0 received anticoagulant therapy. This indicates that, in real-world practice, the identification of patients perceived to be at risk of stroke is often not based on evidence-based risk schemes and guidelines [33].

Since recently in Europe, individual stroke risk is estimated using the CHA2DS2-VASc schema, a score ranging from 0 (lower risk) to 9 (higher risk) [6, 34]. This new schema notably adds female sex as a specific risk factor, thus favouring a better stroke prevention in women would in the near future. The period assessed in our study corresponds to the time before these recent updates of International guidelines and particularly, before the arrival

of NOACs. In France, drug reimbursement in AF indication occurred in July 2012 for dabigatran and rivaroxaban and in December 2013 for apixaban. In the next years, a new analysis using a similar methodology would be relevant to evaluate stroke prevention in French primary care before and after the CHA2DS2-VASc and the NOACs .

This study has several limitations. Some of these are linked to the use of a primary care database as source. The use of such databases for observational studies has become popular since it allows access to information on a large number of patients gathered in real-world conditions. The database is offered as a good source because the GPs included are representatives in many desirable ways (i.e., age, sex and area of coverage) [35, 36]. However, GPs were recruited on a voluntary basis, and thus, the sample may be subject to some response biases with respect to the GPs. Nevertheless, as data are routinely collected, all their AF patients were included in the study without any selection bias from the GPs.

It is not possible to ascertain ascribed diagnoses and to ensure that these are exhaustive. Given that perfect tools to gather data are very uncommon, we should assume a certain degree of misclassification bias, similarly to other studies [37]. Data were collected during GPs consultation and it is unlikely that they have been able to collect all determinants for prescription choice. Also, data on variables that may influence the anticoagulant prescription could be not available or miscoded. Particularly, cardiologists represent around a third of the AF-related consultations in France [11] and, their influence on GPs prescription could not been assessed. However, such a bias is in principle non-differential between the male and female patients.

In conclusion, most AF patients followed by French GPs were at high or moderate risk of stroke according to European guidelines (CHADS2 scores $\geq$1), but only two-third of them received the recommended antithrombotic treatment. Under treatment was more pronounced in women, particularly in those aged $\geq$75 years. This finding supports the use of the CHA2DS2-VASc score which includes female gender. An educational effort should be undertaken to inform French MGs about the therapeutic benefit to use European guidelines to reduce the risk of stroke in AF patients.

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References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE (2001) Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 285:2370–2375
2. Sandhu RK, McAlister FA (2013) Stroke prevention for patients with atrial fibrillation: improving but not perfect yet. Heart 99:1141
3. Charlemagne A, Blacher J, Cohen A, Collet J-P et al (2011) Epidemiology of atrial fibrillation in France: extrapolation of international epidemiological data to France and analysis of French hospitalization data. Arch Cardiovasc Dis 104:115–124
4. HAS (2013) Haute Autorité de Santé. Eliquis. Commission de la Transparence Avis, 12 juin 2013
5. Camm AJ, Kirchhof P, Lip GYH, Schotten U et al (2010) Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European society of cardiology (ESC). Europace 12:1360–1420
6. Camm AJ, Lip GYH, De Caterina R, Savelieva I et al (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation developed with the special contribution of the European heart rhythm association. Eur Heart J 33:2719–2747
7. Volgman AS, Manankil MF, Mookherjee D, Trohman RG (2009) Women with atrial fibrillation: greater risk, less attention. Gend Med 6:419–432
8. Humphries KH, Kerr CR, Connolly SJ, Klein G et al (2001) New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation 103:2365–2370
9. Carlsson A, Wändell P, Sundquist K, Johansson S-E et al (2013) Differences and time trends in drug treatment of atrial fibrillation in men and women and doctors' adherence to warfarin therapy recommendations. Eur J Clin Pharmacol 69:245–253
10. Gage BF, Boechler M, Doggette AL, Fortune G et al (2000) Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. Stroke 31:822–827
11. Cohen A, Dallongeville J, Durand-Zaleski I, Bouée S et al (2010) Characteristics and management of outpatients with history of or current atrial fibrillation: the observational French EPHA study. Arch Cardiovasc Dis 103:376–387
12. Mease PJ, Zimetbaum PJ, Duh MS, Vekeman F et al (2011) Epidemiologic evaluation of cardiovascular risk in patients receiving milnacipran, venlafaxine, or amitriptyline: evidence from French health data. Ann Pharmacother 45:179–188
13. Cotté FE, Fardellone P, Mercier F, Gaudin AF et al (2010) Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. Osteoporos Int 21:145–155
14. Fourcade R-O, Lacoin F, Rouprêt M, Slama A et al (2012) Outcomes and general health-related quality of life among patients medically treated in general daily practice for lower urinary tract symptoms due to benign prostatic hyperplasia. World J Urol 30:419–426
15. Brown H, Prescott R (1999) Applied mixed models in medicine. Wiley, Chichester
16. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB et al (2005) Atrial fibrillation management: a prospective survey in ESC member countries: the euro heart survey on atrial fibrillation. Eur Heart J 26:2422–2434
17. Cowan C, Healicon R, Robson I, Long WR et al (2013) The use of anticoagulants in the management of atrial fibrillation among general practices in England. Heart 99(16):1166–1172

18. Friberg L, Hammar N, Ringh M, Pettersson H et al (2006) Stroke prophylaxis in atrial fibrillation: who gets it and who does not? report from the Stockholm cohort-study on atrial fibrillation (SCAF-study). Eur Heart J 27:1954–1964
19. Ogilvie IM, Newton N, Welner SA, Cowell W et al (2010) Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 123(638–645):e4
20. Arts DL, Visscher S, Opstelten W, Korevaar JC et al (2013) Frequency and risk factors for under- and over-treatment in stroke prevention for patients with non-valvular atrial fibrillation in general practice. PLoS One 8:e67806
21. Conen D, Glynn RJ, Sandhu RK, Tedrow UB et al (2013) Risk factors for incident atrial fibrillation with and without left atrial enlargement in women. Int J Cardiol 168(3):1894–1899
22. Fang MC, Singer DE, Chang Y, Hylek EM et al (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 112:1687–1691
23. Karasoy D, Bo Jensen T, Hansen ML, Schmiegelow M et al (2013) Obesity is a risk factor for atrial fibrillation among fertile young women: a nationwide cohort study. Europace 15:781–786
24. Tsadok AM, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L (2012) Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 307:1952–1958
25. Atrial fibrillation Investigators (AFI) (1994) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 154:1449–1457
26. Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C (2013) Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? a sex-based meta-analysis. Thrombosis Res 132:185–189
27. Gomberg-Maitland M, Wenger NK, Feyzi J, Lengyel M et al (2006) Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. Eur Heart J 27:1947–1953
28. Mellemkjær L, Blot WJ, Sørensen HT, Thomassen L et al (2002) Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br J Clin Pharmacol 53:173–181
29. Bassand J-P (2012) Review of atrial fibrillation outcome trials of oral anticoagulant and antiplatelet agents. Europace 14:312–324
30. Meinertz T, Kirch W, Rosin L, Pittrow D et al (2011) Management of atrial fibrillation by primary care physicians in Germany: baseline results of the ATRIUM registry. Clin Res Cardiol 100:897–905
31. de Lusignan S, van Vlymen J, Hague N, Thana L, Dzregah B, Chan T (2005) Preventing stroke in people with atrial fibrillation: a cross-sectional study. J Public Health (Oxf) 27:85–92
32. Barrios V, Calderón A, Escobar C, de la Figuera M, Primary care group in the clinical cardiology section of the Spanish society of cardiology (2012) Patients with atrial fibrillation in a primary care setting: val-FAAP study. Rev Esp Cardiol (Engl Ed) 65:47–53
33. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA et al (2013) Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One 8:e63479
34. 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 137:263–272
35. Ganse EV, Letrilliart L, Borne H, Morand F et al (2012) Health problems most commonly diagnosed among young female patients during visits to general practitioners and gynecologists in France before the initiation of the human papillomavirus vaccination program. Pharmacoepidemiol Drug Saf 21:261–268
36. Le Ray I, Barkun AN, Vauzelle-Kervroedan F, Bardou M (2013) Failure to renew prescriptions for gastroprotective agents to patients on continuous nonsteroidal anti-inflammatory drugs increases rate of upper gastrointestinal injury. Clin Gastroenterol Hepatol 11:499–504 e1
37. Delgado-Rodriguez M, Llorca J (2004) Bias. J Epidemiol Community Health 58:635–641