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Effectiveness, Safety and Costs of Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation: Phase I ESC-FA Protocol Study and Baseline Characteristics of a Cohort from a Primary Care Electronic Database.

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ABSTRACT

Purpose

Atrial fibrillation is the most common arrhythmia. Its management aims to reduce symptoms and to prevent complications through rate and rhythm control, management of concomitant cardiac diseases and prevention of related complications, mainly stroke.

The main objective of ESC-FA study is to analyse the drugs used for the management of the disease in real-use conditions, in particular antithrombotic agents for stroke prevention. The aim of this work is to present the study protocol of Phase I of the ESC-FA study and the baseline characteristics of newly diagnosed patients with atrial fibrillation in Catalonia, Spain.

Participants

The data source is SIDIAP database. The population included are all patients with non-valvular atrial fibrillation diagnosis registered in the electronic health records during 2007-2012.

Findings to date

A total of 22,585 patients with non-valvular atrial fibrillation were included in the baseline description. Their mean age was 72.8 years and 51.6% were men. The most commonly prescribed antithrombotics were vitamin K antagonists (40.1% of patients) and platelet aggregation inhibitors (32.9%); 25.3% had not been prescribed antithrombotic treatment. Age, gender, comorbidities and comedication at baseline were similar to those reported for previous studies.

Future plans

The next steps in the ESC-FA study will be assessing effectiveness and safety of antithrombotic treatments, analysing stroke events and bleeding episodes' rates in our patients (rest of phase I), describing the current management of the disease and its costs in our setting, and assessing how the introduction of new oral anticoagulants changes the stroke prevention in non-valvular atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is the most common chronic arrhythmia, with increasing health-care burden because of an ageing population and improved survival from cardiovascular events.[1] Its estimated prevalence is approximately 1-2% of general population.[1,2] AF increases with age, from 0.5% in people under 50 [2] to 10-15% in people over 80 years of age.[3]

AF is associated with various cardiovascular conditions such as hypertension, symptomatic heart failure or heart valve disease. It increases the risk of stroke by 5-fold, and one in five strokes is attributed to this arrhythmia.[4]

Management of patients with AF aims to reduce symptoms by means of rate and rhythm control and management of concomitant cardiac diseases, and to prevent AF complications such as stroke and thromboembolism.[4] Antithrombotic drugs used for stroke prevention in non-valvular AF are oral anticoagulants (OAC), specifically vitamin K antagonists (VKA), and antiplatelet agents.[4] Recently, new OAC have received marketing authorisation in the European Union for this indication: dabigatran received authorisation in Spain in October 2011; rivaroxaban in June 2012 and apixaban in August 2013.

The use of OAC and/or antiplatelet therapy depends on patient's risk of developing thromboembolic and bleeding events,[5,6] taking into account that some risk factors for bleeding are also risk factors for stroke.[1] It is generally recommended to assess stroke risk with the $CHADS_2$ [7,8] and CHA_2DS_2-VASc [1,9] scores, and bleeding risk with the HAS-BLED score.[2,10,11]

Net clinical benefit of antithrombotic prophylaxis in AF patients has been demonstrated in some studies.[12,13] However, studies on OAC conducted in our setting indicate underuse,[3,5,14–17] possibly because of the VKA risk for bleeding; significant interactions with other drugs, food and alcohol; need of frequent INR monitoring and high inter- and intra-individual variability in INR.[1,4] In fact, the current number of AF patients under antithrombotic treatment in our setting is unknown. Also, no data on adequacy of prescription based on stroke and bleeding risk exist. Similarly, no studies on antithrombotic effectiveness in stroke prevention in our setting have been published.

Therefore, the ageing population, which increases AF and stroke incidences;[2,3] the recent approval of new OAC for stroke prevention in non-valvular AF; and the need to assess use of OAC and their clinical results through population studies of the VKA most used in our setting (acenocoumarol instead of warfarin, which has been evaluated in most clinical trials); underscore the need for the ESC-FA study.

The main objective of ESC-FA study is to analyse the drugs used for the management of non-valvular AF, in particular antithrombotic agents for stroke prevention.

The study is divided in four different phases. The specific objectives of phase I are: 1) to describe the antithrombotic management in AF in our setting, 2) to assess the effectiveness of antithrombotics in real-use conditions according to stroke rates and 3) to assess the safety of antithrombotic according to bleeding events rates.

The specific objective of phase II is to describe the management of rhythm and rate control. The specific objective of phase III is to estimate the cost of managing non-

valvular AF in our setting. The specific objective of phase IV is to assess changes of effectiveness, safety and costs associated with the introduction of new OAC.

In this paper we present the protocol of phase I of the ESC-FA study, with the description of baseline characteristics of patients with non-valvular AF and the drugs currently used for stroke and thromboembolism prevention in our setting.

METHODS

Study design

The ESC-FA study is a retrospective observational cohort study in ≥ 18 years-old individuals with a diagnosis of non-valvular AF registered in the electronic health records throughout 2007 and 2012 in all Primary Care Centres of the Catalan Health Institute (ICS), with a follow-up period up to the end of 2013. The ICS is the main provider of health services in Catalonia and it manages 274 Primary Care practices with a catchment population of 5,835,000 patients (80% of the Catalan population, or more than 10% of the Spanish population).

Data source

The data source is SIDIAP database (Information System for the Development of Research in Primary Care). SIDIAP contains anonymized clinical information that originates from different data sources:[18–22] 1) eCAP™ (electronic health records in Primary Care of the ICS); which includes information since 2006 on socio-demographic characteristics, health conditions registered as ICD10 codes, General Practitioners' (GP)

prescriptions, clinical parameters and toxic habits. 2) Laboratory data. 3) Prescriptions and their corresponding pharmacy invoice data; available since 2005: information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions, by ATC codes. 4) The CMBD-AH database, which includes diagnoses at hospital discharge registered as ICD9 codes.

Study population

Inclusion criteria: all patients older than 18 years with a new diagnosis of non-valvular AF registered in SIDIAP from 2007 to 2012.

Exclusion criteria: valvular AF and antithrombotic treatment registered more than 6 months before the AF diagnosis, to avoid prescriptions for indications other than AF.

The cohorts were defined according to the antithrombotic treatment registered in the pharmacy invoice database at the time of diagnosis, considering an overall 6 month-period for the definition of baseline date (± 3 months between diagnosis date and antithrombotic treatment date). All patients with more than one dispensed package of antithrombotic registered in this period of time were included in the study.

To define dual therapy at baseline (VKA + antiplatelet, or aspirin + another antiplatelet), we considered at least two following entries in the pharmacy invoice database for both drugs during the baseline period.

Study variables

At baseline the following variables were collected: gender, age at diagnosis, MEDEA Index (deprivation index which shows the social or material disadvantage of a person or group respect their city/region/country, according to census data in Catalonia. The higher it is, the worse the deprivation [23]), smoking status (last register before diagnosis), alcohol intake (last register before diagnosis), body mass index (BMI, nearest value to diagnosis date, within an interval of ± 2 years of diagnosis date), stroke and bleeding risk ($CHADS_2$ and HAS-BLED were calculated at baseline with the information registered in SIDIAP. For bleeding risk, HAS-BLED was calculated without "L: labile INR" item, since INR values were missing in most patients); comorbidities of interest and cardiovascular risk factors registered before AF diagnosis (cardiovascular comorbidities, previous bleedings, and kidney and liver function; as ICD10 codes specified in the ICD10 codes list), laboratory data (the nearest value to diagnosis date, within an interval of ± 1 year of diagnostic date), blood pressure (BP, the nearest values of systolic and diastolic BP to diagnosis date, within an interval of ± 1 year of diagnosis date), antithrombotic drugs registered in the pharmacy invoicing database within ± 3 months from diagnosis date (registered as ATC codes specified in the ATC codes list), concomitant drug therapy of interest registered in the pharmacy invoicing database within ± 3 months from diagnosis date (rate and rhythm control drugs, other cardiovascular medication, diabetes treatments, proton pump inhibitors, and non-steroidal anti-inflammatory drugs [NSAID]; as ATC codes specified in the ATC codes list), stroke and other thromboembolic events rates and bleeding episodes (cerebral, gastrointestinal, eye and other haemorrhages) rates registered at CMBD-AH before AF

diagnosis in order to confirm the stroke and bleeding rates registered at SIDIAP (as ICD9 codes specified in the ICD9 codes list).

During follow-up the following variables will be assessed for objectives 2 and 3: stroke and bleeding risk calculated during follow-up; stroke and other thromboembolic events and haemorrhages rates; antithrombotic drugs during follow-up to assess treatment changes, new treatments or end of treatment and analysis of effectiveness and safety of the main treatment options – VKA, antiplatelet drugs and no antithrombotic treatment –; through the variable "net clinical benefit".

"Net clinical benefit" has been defined in a previous publication [24] as the annualized rate of thromboembolic events prevented minus the annualized rate of intracranial haemorrhages (ICH) induced multiplied by a weighting factor of 1.5; which reflects the relative impact, in terms of disability, of an ICH while receiving VKA (studied with warfarin) versus experiencing an ischemic stroke while not receiving VKA:

Net clinical benefit =

(Stroke rate off-VKA – Stroke rate on-VKA) – 1.5 x (ICH rate on-VKA – ICH rate off-VKA)

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical variables were expressed as frequencies (percentage) and quantitative variables as mean (Standard deviation, SD) or median (interquartile range, IQR) for non-normally distributed

variables. The differences between cohorts were tested using Analysis of variance (ANOVA) or Kruskal-Wallis test, Chi square or Fisher exact test for unadjusted comparison, as appropriate.

Incidence rates and incidence rate ratios of stroke and bleeding events during the follow-up will be estimated using Poisson regression. The resulting person-time value will be used as an offset variable. Time-to-event analysis will be performed using non-parametric methods like Kaplan-Meier and log-rank test. Multivariate Cox proportional-hazards regression models will be fitted, adjusting for baseline socio-demographical characteristics and confounding and predictive factors of each event. Extended Cox models will be used when the model's proportional hazards assumption does not hold.

Sensitivity analysis will be carried out excluding patients that change from one cohort to another during the follow-up and censoring by patient's change of cohort.

All statistical tests were two-tailed using a significance level of 5%. The analyses were performed using Stata ver. 11 (Stata Corp., Collage Station, TX) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical and legal issues

The present study follows national and international regulations: Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and Good Research Practice principles and guidelines.

The IDIAP Jordi Gol Clinical Research Ethics Committee, the reference institution for research in Primary Care of the ICS, approved the study protocol.

Regarding the data contained in the databases and according to Spanish legislation about confidentiality and data protection (Ley Orgánica 15/1999 de 13 de diciembre de Protección de Datos de Carácter Personal), data included in SIDIAP are always anonymized and identified by an internal code, which makes impossible to identify the individuals included. Thus, it is not necessary to ask for informed consent to the participants. Each individual is identified through an encrypted, anonymized code.

For the linkage with CMBD database (or other databases), SIDIAP uses a "trusted third party" in order to ensure confidentiality when linking both data sources. This third party has no access to clinical information, only to codes and IDs.

COHORT DESCRIPTION AND FINDINGS TO DATE

There were 41,468 patients with a new AF diagnosis registered in SIDIAP between 2007 and 2012. Of the newly diagnosed patients, 25,601 (61.7%) fulfilled the inclusion criteria and none of the exclusion criteria (Figure 1). Study cohorts were based on antithrombotic treatment registered at the time of AF diagnosis (± 3 months interval). Two treatment groups were excluded from the baseline description of the cohorts (11.8% of patients included): patients with only 1 dispensed package of antithrombotic registered during study period (n= 1,755) and patients with ≥ 3 different antithrombotic drugs registered (n= 1,261), as it is a group excessively heterogeneous.

We present the baseline characteristics of 22,585 individuals with non-valvular AF, diagnosed from 2007 to 2012. Their mean age was 72.8 (SD 13.1) years and 51.6% were men. The number of patients diagnosed per year with AF in each cohort is shown in Figure 2.

There were 5,724 (25.3%) of patients with no antithrombotic treatment registered at baseline. The most prescribed treatment were VKA (9,057 patients, 40.1%), followed by platelet aggregation inhibitors (7,424, 32.9%). The remaining patients were initiated on VKA + antiplatelet (1.0%) or on dabigatran (0.7%).

The proportion of patients with no antithrombotic treatment decreased during the study period from 28.2% in 2007 to 26.1% in 2012, while the proportion of VKA-treated increased from 37.5% in 2007 to 41.8% in 2012. A decrease in the prescription of antiplatelet agents was observed, form 33.4% in 2007 to 27.9% in 2012.

The baseline characteristics of our patients, including percentages of patients with missing data, are described in Tables 1, 2, 3 and 4.

Table 1 shows higher proportions of men in all cohorts except in the antiplatelet group. Patients treated with any antithrombotic drug were older than non-treated patients. There were more patients over 75 years in the group of antiplatelets. There were more current smokers in the group of patients with no antithrombotic treatment, but this group had a higher percentage of missing values than the rest of the groups. There was also a high percentage of missing values in alcohol intake.

Table 1. Socio-demographic characteristics and cardiovascular, stroke and bleeding risk factors

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
Gender					
Female (%)	46.9	48.3	50.3	36.6	38.6
Male (%)	53.1	51.7	49.7	63.4	61.4
Age (years; mean, SD)	69.6 (16.4)	73.4 (10.3)	74.6 (12.9)	72.4 (9.9)	71.4 (11.0)
> 75 years (%)	45.5	51.1	53.6	43.6	39.2
MEDEA[23] (mean, SD)	0.44 (0.92)	0.52 (0.90)	0.50 (0.91)	0.51 (0.82)	0.29 (0.97)
≥ 4th quintile (%)	36.6	39.4	39.1	41.0	29.9
BMI (kg/m2; mean, SD)	28.6 (5.1)	30.2 (5.3)	29.2 (5.2)	30.1 (5.5)	29.5 (4.4)
BMI ≥30: obesity (%)	34.7	46.8	38.8	44.4	40.2
Missing values (%)	*46.4*	*25.3*	*33.9*	*25.6*	*39.9*
Smoking status (%)					
Non smoker	65.7	70.0	70.3	62.8	66.2
Current smoker	16.9	10.3	11.8	12.2	9.6
Ex-smoker	17.4	19.7	17.9	25.0	24.2
Missing values	*30.9*	*19.5*	*18.4*	*17.2*	*11.1*
Alcohol intake (%)					
Non consumer	71.8	70.3	70.4	67.5	63.3
Mild-moderate	25.7	27.3	27.2	31.3	32.7
Alcohol abuse	2.5	2.4	2.4	1.2	4.1
Missing values	*49.0*	*29.0*	*35.2*	*26.9*	*35.9*
$CHADS_2$ score[7] **(%)**					
0	31.7	15.4	19.9	11.9	18.3
1	29.8	32.2	32.7	31.3	39.2
2	24.9	35.0	30.8	27.8	26.1
≥3	13.5	17.5	16.5	29.1	16.3
HAS-BLED score[10,11] **(%)**					
0	16.5	6.8	0.0	0.0	4.1
1-2	64.9	70.2	43.1	37.3	83.7
≥3	18.5	23.0	56.9	62.7	12.2

Regarding the distribution of the $CHADS_2$ score, only 31.7% of patients not receiving antithrombotic therapy had a $CHADS_2 = 0$ and 15.4% of VKA-treated patients had a $CHADS_2 = 0$. The highest proportion of patients with $CHADS_2$ score > 2 is in the VKA + antiplatelet group.

Patients treated with antiplatelets and VKA + antiplatelets have higher scores in the HAS-BLED bleeding classification.

Table 2 shows that patients with antithrombotic treatment had more cardiovascular comorbidities when compared with non-treated patients, and patients in the dual therapy VKA + antiplatelet cohort had more comorbidities. Hypertension was the most frequent comorbidity, followed by dyslipidemia. Coronary artery disease was found in 34.8% of the patients in the VKA + antiplatelet cohort, with a high frequency of previous myocardial infarction (MI). Non-treated individuals had better eGFR than patients initiated on antithrombotic therapy, except for dabigatran (84.4% of dabigatran patients had eGFR > 60 mL/min/1.73m^2). However, there were more missing values in that group.

Table 2. Baseline comorbidities

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
CARDIOVASCULAR COMORBIDITIES (%)					
Hypertension	48.1	65.1	59.5	67.8	64.1
Years of evolution (m, SD)	7.4	6.8	6.8	7.1	5.9
Type 2 diabetes mellitus	14.4	18.5	16.7	26.4	16.3
Years of evolution (m, SD)	6.9	6.9	6.4	6.5	9.4
Dyslipidemia	24.8	33.2	31.7	38.3	31.4
Peripheral arterial disease	0.9	1.1	1.5	4.0	2.6
Coronary artery disease	4.3	2.8	5.7	34.8	3.9
MI	1.4	0.7	2.1	17.2	0.7
Angina	1.1	1.0	1.6	7.5	2.0
Heart failure	7.7	10.0	8.1	13.2	5.2
Previous stroke	4.8	7.2	5.3	14.1	8.5
TIA	1.0	1.6	1.8	5.3	4.6
BLEEDING (%)					
Previous bleeding	6.0	4.5	5.1	4.0	7.8
Cerebral haemorrhage	1.0	0.4	0.8	0.4	2.0
Gastrointestinal	3.6	2.5	2.9	1.3	3.9
Eye	0.4	0.7	0.6	0.4	0.0
Other	1.3	0.9	1.0	1.8	2.6
Peptic ulcer	3.6	3.7	3.8	2.2	2.6
RENAL IMPAIRMENT (%)					
eGFR (MDRD)					
<30 mL/min/1.73m^2	2.4	1.9	2.4	1.6	0.0
30-60	25.4	27.7	28.7	36.0	15.6
>60	72.2	70.4	68.9	62.4	84.4
Missing values	*35.0*	*18.1*	*19.1*	*16.7*	*28.8*
HEPATIC IMPAIRMENT (%)	3.2	1.7	1.6	2.2	0.7
Charlson comorbidity index [25] **(%)**					
0-2	88.6	90.6	89.1	88.5	92.2
>2	11.4	9.4	10.9	11.5	7.8

*BP, blood pressure. MI, myocardial infarction. TIA, transitory ischemic attack. eGFR, estimated glomerular filtration rate.

Disease control parameters and laboratory data of interest are described in Table 3. Around two thirds of patients had good control of BP, HbA1c and c-LDL levels without differences between cohorts.

Table 3. Disease control parameters and laboratory data

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
Blood pressure					
Systolic BP (m, SD)	132.5 (19.3)	133.3 (18.5)	133.5 (18.4)	132.3 (18.3)	131.6 (17.7)
Diastolic BP (m, SD)	76.6 (11.7)	78.0 (11.8)	77.2 (11.4)	77.0 (11.9)	77.5 (11.8)
Good BP control (<140/90 mmHg; %)	64.6	61.5	61.3	63.7	65.9
Missing values	*22.5*	*6.8*	*10.0*	*5.3*	*11.8*
HbA1c (m, SD)	1.4	1.3	1.3	1.3	1.1
HbA1c < 7% (%)	70.5	65.5	69.7	55.7	74.0
Missing values	*77.8*	*66.5*	*69.2*	*57.3*	*67.3*
Total cholesterol (mg/dL) (mean, SD)	195.7 (40.8)	198.3 (39.5)	195.1 (39.5)	183.3 (42.5)	199.0 (36.6)
HDL	53.0 (15.1)	53.1 (14.3)	53.9 (15.1)	51.1 (14.0)	54.3 (14.6)
LDL	120.9 (34.3)	121.6 (33.8)	119.3 (33.5)	109.1 (36.1)	125.1 (28.2)
n, % c-LDL < 130 mg/dL	61.0	61.0	63.5	72.4	59.6
Missing values of total cholesterol (%)	*35.4*	*18.7*	*19.7*	*15.9*	*29.4*

We describe medications of interest in use at baseline in Table 4. Patients with antithrombotic prescribed at baseline received more comedication than non-treated patients, since they had more comorbidity. Antihypertensive drugs, statins and proton pump inhibitors were the most frequent comedication.

All baseline characteristics were significantly different among the five groups.

Table 4. Medications in use at baseline (% of patients)

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
Digoxin	4.4	20.3	13.5	11.9	10.5
Amiodarone	7.9	18.3	14.6	23.3	9.2
Flecainide	4.3	4.4	6.1	3.1	9.2
Dronedarone	0.3	0.7	0.6	0.0	0.7
Other antiarrhythmic agents	1.9	1.9	2.2	0.9	2.0
Diuretics					
Low-ceiling diuretics	10.3	25.6	20.4	29.1	11.8
Thiazides	4.8	9.3	8.4	4.8	7.2
Aldosterone antagonists	1.8	3.4	2.2	5.3	0.7
Beta blockers	11.3	30.4	23.0	48.5	38.6
Calcium channel blockers					
Dihydropiridines	6.1	11.9	9.9	15.0	7.2
Verapamil	1.0	1.6	1.1	0.4	0.7
Diltiazem	1.8	9.3	5.0	5.7	6.5
ACEI	13.9	30.1	26.2	40.1	24.2
ARB	10.6	22.3	17.2	19.4	27.5
Other antihypertensive drugs	1.8	4.3	3.1	5.7	4.6
Nitrates	1.4	2.4	4.4	19.4	0.0
Trimetazidine	1.5	1.8	2.6	2.2	2.0
Ivabradine	0.1	0.1	0.3	0.9	0.0
Other vasodilator agents	0.2	0.4	0.3	0.4	0.0
Statins	11.3	24.3	22.7	52.4	22.2
Other lipid modifying agents	1.4	2.0	1.8	4.0	2.0
Oral antidiabetic agents	5.8	12.8	10.3	21.1	12.4

Insulins	1.4	2.4	2.2	4.0	1.3
Proton pump inhibitors	25.5	42.9	53.7	69.2	32.7
NSAIDs	15.5	19.0	20.6	18.5	8.5

*ACEI, angiotensin converter enzyme inhibitors. ARB, angiotensin receptor blockers. NSAID, non-steroidal anti-inflamatory drugs.

DISCUSSION

The ESC-FA study was designed as a retrospective observational cohort study on the effectiveness and safety of antithrombotic therapy in patients with non-valvular AF under use in clinical conditions in Catalonia. In this article we report the baseline socio-demographic and clinical characteristics of 22,585 non-valvular AF patients and discuss the main differences between non-treatment and usual treatments for prevention of stroke and thromboembolic events. The patients included in the study have been divided into five cohorts according to the antithrombotic treatment prescribed at the time of diagnosis.

This is an observational study performed with data obtained from an electronic database. Therefore, it is subject to certain limitations inherent in all such studies, such as the collection of non-randomized data, missing or incomplete information and possible confounders. The strengths of our study are the large number of patients included, representativeness of the general population (SIDIAP information comes from ICS, which manages more than 80% of the Catalan population), complete socio-demographic and health records and real clinical practice data.

With regard to AF diagnosis, our data are supported by previous studies [18–21] which validate our findings and indicate that the study population is representative of the

population in Catalonia and thus it can be used in epidemiologic studies in our setting. More specifically, the diagnosis of AF has been validated in our population in the study published by García-Gil MDM et al.[22]

The diagnosis is sometimes registered in the patients' electronic health records after the real diagnosis has been made and the start of antithrombotic treatment is registered before or after the diagnosis register. To overcome this inconsistency, the cohorts have been constructed taking into account antithrombotic treatments registered during the interval of ± 3 months of diagnostic date.

Regarding the pharmacy invoicing register, we have excluded 7.3% of the 41,468 patients with non-valvular AF due to inconsistencies in the register of treatments, such as three or more antithrombotic drugs at baseline or only one dispensed package of antithrombotic agents.

Although most patients are treated with VKA, INR data are not described at baseline because two different methods of INR determination are used in Catalonia: by laboratory standard determination, which is performed in a low proportion of patients; or through a point-of-care rapid INR determination carried out during primary care visits or in hospitals in most cases. Since we do not have access to hospital records, a high number of INR had missing values. Therefore, INR has not been included in the HAS-BLED calculation. However, at this stage it should not make a significant difference, since INR is only determined in VKA-treated patients during follow-up and we present the data at baseline, when the INR has not yet been determined and the "L" for HAS-BLED is 0, the same as in patients not treated with VKA. Nonetheless, we

will conduct a validation for the INR during the follow-up period, as it is an essential parameter in the clinical management of VKA-treated patients.

Regarding socio-demographic characteristics, the proportion of men and women in our study is quite balanced (51.6% of men) and it is similar to prior registries.[15,26,27]

We found that patients treated with any antithrombotic drug are older, have more comorbidities at baseline and receive more comedication than non-treated individuals. In agreement with similar studies, we found high prevalence of hypertension, dyslipidemia, diabetes mellitus and heart failure in all AF patients.[26,28–30]

The number of patients included in the VKA + antiplatelet cohort is low, possibly due to the short interval of time used to consider a situation of dual therapy (two consecutive registers of both drugs at baseline). The number of patients included in the dabigatran cohort is also low, since this drug was authorised for non-valvular AF in Spain at the end of 2011 and we only include data up to 2012. Moreover, dabigatran is subject to restricted conditions for its prescription in our setting. Data for rivaroxaban are not shown, since there were only a few registers during 2012. Data for apixaban are not shown either, as it was authorised in Spain for non-valvular AF in 2013. VKA prescription rate in non-valvular AF patients at baseline is similar to other studies.

Kirchhof et al.[28] conducted an observational study (PREFER-AF) including 7,243 patients in seven European countries between January 2012 and January 2013. In the cross-sectional description their results suggest much better adherence to evidence and recommendations than previous reports of similar registries: VKA were prescribed in 66.3% of the patients included, antiplatelets in 11.2%, VKA + antiplatelet dual

therapy in 10.9% and dabigatran in 6.1%. They reported 17.7% of non-treated individuals. Results from a prospective follow-up study have not been published yet.

Kakkar et al.[29] conducted the GARFIELD study in different primary care settings, which described VKA prescription in 45.2% of AF patients, antiplatelet agents in 25.3%, dual therapy VKA + antiplatelet in 10.6% and dabigatran in 4.5%. They included 10,614 patients enrolled throughout 2009 and 2011. This study reported similar VKA and antiplatelet prescription rates to those found in our setting.

Scowcroft et al.[30] conducted a cohort study of 81,381 AF patients from the General Practice Research Database, diagnosed between 2000-2009. They found differences in VKA prescription according to group of age: in the 60-69 years-old group, VKA was prescribed in 57% of patients; in the 70-79 group, 55% of patients were receiving VKA; and only 32% of patients older than 80 were treated with VKA. Although this study was carried out with data from an electronic database, which makes possible the analysis of a large set of patients, the results are not easily comparable to ours, since we have not stratified patients by age group. In our study 51.1% of the VKA group are over 75 years of age.

Observational studies conducted in our setting described different proportions of patients treated with VKA [14,15,27] than those found in our study. Nevertheless, we described the situation only at baseline date and our patients could start antithrombotic treatment during follow-up. Moreover, these studies included small numbers of patients. Some of these studies analyse OAC prescription according to stroke risk; Barrios et al.[27] found 46.8% of patients with $CHADS_2 = 0$ treated with VKA and 31.9% with antiplatelets, and 57% of patients with $CHADS_2 \geq 2$ with VKA and 12.7%

with no antithrombotic treatment. In our study, 29.6% of patients with $CHADS_2 = 0$ or 44.9% of patients with $CHADS_2 \geq 3$ were treated with VKA, but 17.2% of this high-risk group ($CHADS_2 \geq 2$) were untreated. In conclusion, the decision of prescribing OAC did not appear to be related to stroke risk assessment in our setting.

Although it is difficult to compare our study with prior reports, even if the prescription of OAC in our setting appears to be low, it is nonetheless similar to other studies.

Conclusions

We describe the actual use of antithrombotic agents for stroke and thromboembolism prevention in a large number of non-valvular AF patients in Catalonia.

Age, gender and comorbidities in non-valvular AF patients were similar to those reported in previous studies. The prescription rates of patients initiated on VKA and on platelet aggregation inhibitors were similar to those reported in other studies.

We cannot establish any conclusion about dabigatran use, since only 153 patients had been initiated on this new OAC because its approval for use in AF patients took place in latter 2011. This is expected to change during follow-up, when more patients will have been included in the dabigatran cohort and will have started treatment with rivaroxaban and apixaban as well.

The next step in ESC-FA study is to assess effectiveness and safety of antithrombotic treatments by analysing stroke and other thromboembolic events and haemorrhage rates in our patients. These data would show changes in the management of non-

valvular AF patients in Catalonia due to modifications in antithrombotic treatment during follow-up and the introduction of the new OAC.

FIGURE LEGENDS

Figure 1. Study flowchart.

Patients included and excluded from the study.

AF: atrial fibrillation

SIDIAP: Information System for the Development of Research in Primary Care

VKA: vitamin K antagonist

Figure 2. Distribution of new diagnoses of atrial fibrillation per year and cohort

Percentage of patients newly diagnosed with AF per year in each cohort in the figure, number of patients in the table below.

Vitamin K antagonists (n=9057)

Antiplatelets (n=7424)

VKA + antiplatelet (n=227)

Dabigatran (n=153)

No antithrombotic treatment (n=5724)

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin converter enzyme inhibitors
AF	Atrial fibrillation
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blockers
ATC	Anatomic Therapeutic Chemical Classification System
BMI	Body mass index
BP	Blood pressure
CMBD-AH	Database that contains diagnoses at hospital discharge
eCAP	Electronic clinical records in Primary Care in ICS
eGFR	Estimated glomerular filtration rate
GP	General Practitioners
ICD	International Classification of Diseases
ICS	Catalan Health Institute
ICH	Intracranial haemorrhages
IDIAP	Institute in Primary Care Research
INR	International normalized ratio (measure of the extrinsic pathway of coagulation)
IQR	Interquartile range
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drugs
OAC	Oral anticoagulants
SD	Standard deviation
SIDIAP	Information System for the Development of Research in Primary Care
TIA	Transitory ischemic attack
VKA	Vitamin K antagonists

ANNEX OF CODES

ICD-10 codes list

AF: I48, excluding valvular aetiology. Hypertension: I10, I11, I12, I13, I15. Diabetes mellitus: E10, E11, E12, E13, E14. Angina: I20. MI: I21, I22, I23. Coronary heart disease: I24, I25. Cerebrovascular accidents: I63, I64, I67. TIA: G45, G46. Peripheral arterial disease: I73.8, I73.9. Heart failure: I50. Aortic-coronary bypass: Z95.1. Renal insufficiency: N17, N18, N19. Hepatic insufficiency: K72, K73, K74, R17. Dyslipidemia: E78.0, E78.2, E78.4, E78.5, E78.8, E78.9. Peptic ulcers, including bleeding ulcers: K22.1, K25, K26, K27, K28. Bleeding events: H11.3, H35.6, I60, I61, I62, K29.0, K22.8, K62.5, K92.0, K92.1, K92.2, R04.0, R58, S06.4.

ICD9 codes list

Cerebrovascular and thromboembolic events: 433.9, 434.0, 434.1, 434.9, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.9, 438.0, 438.9, 046.3. Bleeding events: 362.81, 372.72, 431, 432.1, 432.9, 530.8, 530.9, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 532.4, 532.6, 534.0, 534.2, 534.4, 534.6, 535.0, 569.3, 578.0, 578.1, 578.9.

ATC codes list

Antithrombotic drugs: B01A. Rate and rhythm control therapy: C01AA, C01B. Cardiovascular agents: C01DA, C01EB, C01DX12, C02DB02, C02CA, C03AA, C03AB, C03AX, C03BA, C03CA, C03DA, C07, C08, C09, C10. Drugs used in diabetes mellitus: A10. Proton pump inhibitors: A02BC. NSAID: M01AB, M01AC, M01AE, M01AH, N02BA, N02BB.

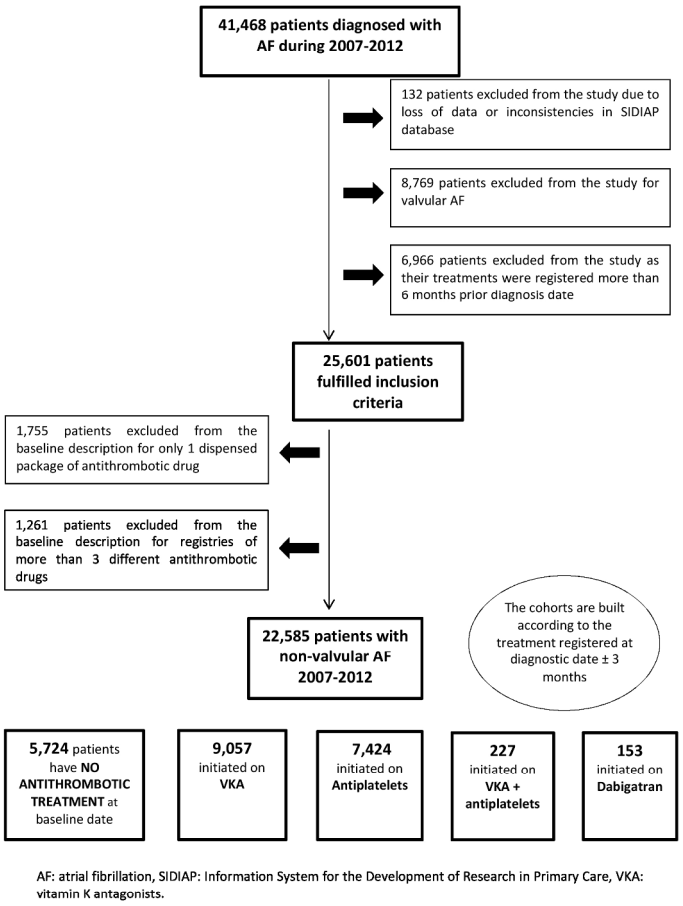
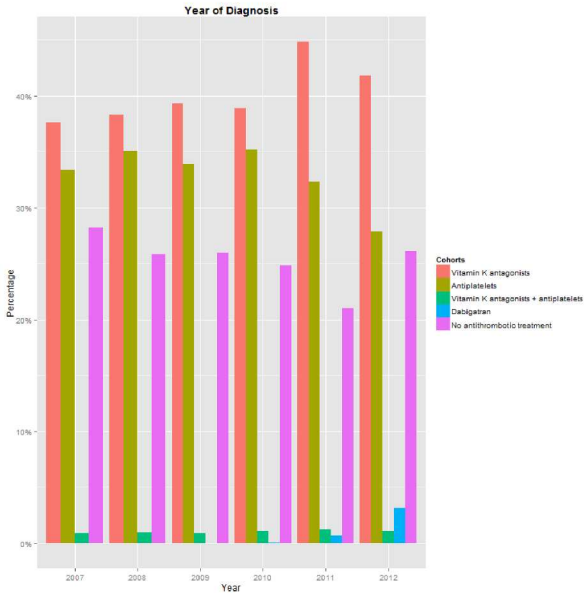


Figure 1. Study flowchart.
Patients included and excluded from the study.
AF: atrial fibrillation
SIDIAP: Information System for the Development of Research in Primary Care
VKA: vitamin K antagonist
209x297mm (300 x 300 DPI)

Figure 2. Distribution of new diagnoses of atrial fibrillation per year and cohort

Percentage of patients newly diagnosed with AF per year in each cohort in the figure, number of patients in the table below.



n	No treatment	VKA	Antiplatelets	VKA + antiplatelets	Dabigatran	Overall
2007	1088	1446	1285	34		3853
2008	911	1348	1236	34		3529
2009	954	1444	1246	31	1	3676
2010	931	1457	1318	40	3	3749
2011	797	1694	1223	46	25	3785
2012	1043	1668	1116	42	124	3993
Overall period	5724	9057	7424	227	153	**22585**

Figure 2. Distribution of new diagnoses of atrial fibrillation per year and cohort
Percentage of patients newly diagnosed with AF per year in each cohort in the figure, number of patients in the table below.
Vitamin K antagonists (n=9057)
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Effectiveness, Safety and Costs of Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation: Phase I ESC-FA Protocol Study and Baseline Characteristics of a Cohort from a Primary Care Electronic Database

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Secondary Subject Heading:	Epidemiology, Health services research, Cardiovascular medicine

Keywords:	atrial fibrillation, electronic health records, Anticoagulation < HAEMATOLOGY, platelet aggregation inhibitors, Bleeding disorders & coagulopathies < HAEMATOLOGY, Stroke medicine < INTERNAL MEDICINE

Effectiveness, Safety and Costs of Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation: Phase I ESC-FA Protocol Study and Baseline Characteristics of a Cohort from a Primary Care Electronic Database.

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Keywords: atrial fibrillation, electronic health records, anticoagulants, platelet aggregation inhibitors, stroke, bleeding

Word count: 3782

Effectiveness, Safety and Costs of Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation: Phase I ESC-FA Protocol Study and Baseline Characteristics of a Cohort from a Primary Care Electronic Database.

ABSTRACT

Purpose

Atrial fibrillation is the most common arrhythmia. Its management aims to reduce symptoms and to prevent complications through rate and rhythm control, management of concomitant cardiac diseases and prevention of related complications, mainly stroke.

The main objective of ESC-FA study is to analyse the drugs used for the management of the disease in real-use conditions, in particular antithrombotic agents for stroke prevention. The aim of this work is to present the study protocol of Phase I of the ESC-FA study and the baseline characteristics of newly diagnosed patients with atrial fibrillation in Catalonia, Spain.

Participants

The data source is SIDIAP database. The population included are all patients with non-valvular atrial fibrillation diagnosis registered in the electronic health records during 2007-2012.

Findings to date

A total of 22,585 patients with non-valvular atrial fibrillation were included in the baseline description. Their mean age was 72.8 years and 51.6% were men. The most commonly prescribed antithrombotics were vitamin K antagonists (40.1% of patients) and platelet aggregation inhibitors (32.9%); 25.3% had not been prescribed antithrombotic treatment. Age, gender, comorbidities and comedication at baseline were similar to those reported for previous studies.

Future plans

The next steps in the ESC-FA study will be assessing effectiveness and safety of antithrombotic treatments, analysing stroke events and bleeding episodes' rates in our patients (rest of phase I), describing the current management of the disease and its costs in our setting, and assessing how the introduction of new oral anticoagulants changes the stroke prevention in non-valvular atrial fibrillation.

Limitations and strengths

The limitations inherent to these studies are the collection of non-randomized data or missing information. Regarding possible infra-register of atrial fibrillation diagnosis, we have confirmed that prevalence in our setting is comparable to the prevalence reported in the available literature. About inconsistencies found in the pharmacy invoice registers, they have made us to exclude a high number of patients. Nevertheless, we were not sure about the validity of these data and that is why they

were excluded. Thus, we can confirm that the information on drugs in this work is completely reliable.

Regarding the strengths of this study, it is necessary to emphasise the large number of patients included and the coverage of our database and the representativeness of the general population (SIDIAP information comes from electronic health records of 5.8 million people – more than 80% of the Catalan population –), complete socio-demographic data, and real clinical practice data. Moreover, this is the first population study in our setting which assesses the number of patients treated with the different pharmacological options traditionally used for stroke prevention in atrial fibrillation in a real clinical practice scenario and, in the following step of the study, which analyses effectiveness and safety of these treatments in terms of stroke and haemorrhages rates.

INTRODUCTION

Atrial fibrillation (AF) is the most common chronic arrhythmia, with increasing health-care burden because of an ageing population and improved survival from cardiovascular events.[1] Its estimated prevalence is approximately 1-2% of general population.[1,2] AF increases with age, from 0.5% in people under 50 [2] to 10-15% in people over 80 years of age.[3]

AF is associated with various cardiovascular conditions such as hypertension, symptomatic heart failure or heart valve disease. It increases the risk of stroke by 5-fold, and one in five strokes is attributed to this arrhythmia.[4]

Management of patients with AF aims to reduce symptoms by means of rate and rhythm control and management of concomitant cardiac diseases, and to prevent AF complications such as stroke and thromboembolism.[4] Antithrombotic drugs used for stroke prevention in non-valvular AF are oral anticoagulants (OAC), specifically vitamin K antagonists (VKA), and antiplatelet agents.[4] Recently, new OAC have received marketing authorisation in the European Union for this indication: dabigatran received authorisation in Spain in October 2011; rivaroxaban in June 2012 and apixaban in August 2013.

The use of OAC and/or antiplatelet therapy depends on patient's risk of developing thromboembolic and bleeding events,[5,6] taking into account that some risk factors for bleeding are also risk factors for stroke.[1] It is generally recommended to assess stroke risk with the $CHADS_2$ [7,8] and CHA_2DS_2-VASc [1,9] scores, and bleeding risk with the HAS-BLED score.[2,10,11]

Net clinical benefit of antithrombotic prophylaxis in AF patients has been demonstrated in some studies.[12,13] However, studies on OAC conducted in our setting indicate underuse,[3,5,14–17] possibly because of the VKA risk for bleeding; significant interactions with other drugs, food and alcohol; need of frequent INR monitoring and high inter- and intra-individual variability in INR.[1,4] In fact, the current number of AF patients under antithrombotic treatment in our setting is unknown. Also, no data on adequacy of prescription based on stroke and bleeding risk exist. Similarly, no studies on antithrombotic effectiveness in stroke prevention in our setting have been published.

Therefore, the ageing population, which increases AF and stroke incidences;[2,3] the recent approval of new OAC for stroke prevention in non-valvular AF; and the need to assess use of OAC and their clinical results through population studies of the VKA most used in our setting (acenocoumarol instead of warfarin, which has been evaluated in most clinical trials); underscore the need for the ESC-FA (Effectiveness, Safety and Costs in Atrial Fibrillation) study.

The main objective of ESC-FA study is to analyse the drugs used for the management of non-valvular AF, in particular antithrombotic agents for stroke prevention.

The study is divided in four different phases. The specific objectives of phase I are: 1) to describe the antithrombotic management in AF in our setting, 2) to assess the effectiveness of antithrombotics in real-use conditions according to stroke rates and 3) to assess the safety of antithrombotic according to bleeding events rates.

The specific objective of phase II is to describe the management of rhythm and rate control. The specific objective of phase III is to estimate the cost of managing non-

valvular AF in our setting. The specific objective of phase IV is to assess changes of effectiveness, safety and costs associated with the introduction of new OAC.

In this paper we present the protocol of phase I of the ESC-FA study, with the description of baseline characteristics of patients with non-valvular AF and the drugs currently used for stroke and thromboembolism prevention in our setting.

METHODS

Study design

The ESC-FA study is a retrospective observational cohort study in ≥ 18 years-old individuals with a diagnosis of non-valvular AF registered in the electronic health records throughout 2007 and 2012 in all Primary Care Centres of the Catalan Health Institute (ICS). The ICS is the main provider of health services in Catalonia and it manages 274 Primary Care practices with a catchment population of 5,835,000 patients (80% of the Catalan population, or more than 10% of the Spanish population).

Data source

The data source is SIDIAP database (Information System for the Development of Research in Primary Care). SIDIAP contains anonymized clinical information that originates from different data sources:[18–22] 1) eCAP™ (electronic health records in Primary Care of the ICS); which includes information since 2006 on socio-demographic characteristics, health conditions registered as ICD10 codes, General Practitioners' (GP) prescriptions, clinical parameters and toxic habits. 2) Laboratory data. 3) Prescriptions

and their corresponding pharmacy invoice data; available since 2005: information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions, by ATC codes. 4) The CMBD-AH database, which includes diagnoses at hospital discharge registered as ICD9 codes.

Study population

Inclusion criteria: all patients older than 18 years with a new diagnosis of non-valvular AF registered in SIDIAP from 2007 to 2012.

Exclusion criteria: valvular AF and antithrombotic treatment registered more than 6 months before the AF diagnosis. .

The cohorts were defined according to the antithrombotic treatment registered in the pharmacy invoice database at the time of diagnosis, considering an overall 6 month-period for the definition of baseline date (± 3 months between diagnosis date and antithrombotic treatment date). All patients with more than one dispensed package of antithrombotic registered in this period of time were included in the study.

To define dual therapy at baseline (VKA + antiplatelet, or aspirin + another antiplatelet), we considered at least two consecutive entries in the pharmacy invoice database for both drugs during the baseline period.

Two consecutive entries are all those separated by a period of time equal to the period of supply of a drug package. For instance, for 1-month treatment packages,

consecutive entries are those separated by a 1-month interval in the pharmacy invoice register.

Study variables

At baseline the following variables were collected: gender, age at diagnosis, MEDEA Index (deprivation index which shows the social or material disadvantage of a person or group respect their city/region/country, according to census data in Catalonia. The higher it is, the worse the deprivation [23]), smoking status (last register before diagnosis), alcohol intake (last register before diagnosis), body mass index (BMI, nearest value to diagnosis date, within an interval of ± 2 years of diagnosis date), stroke and bleeding risk ($CHADS_2$ and HAS-BLED were calculated at baseline with the information registered in SIDIAP. For bleeding risk, HAS-BLED was calculated without "L: labile INR" item, since INR values were missing in most patients); comorbidities of interest and cardiovascular risk factors registered before AF diagnosis (cardiovascular comorbidities, previous bleedings, and kidney and liver function; as ICD10 codes specified in the ICD10 codes list in supplementary file), laboratory data (the nearest value to diagnosis date, within an interval of ± 1 year of diagnostic date), blood pressure (BP, the nearest values of systolic and diastolic BP to diagnosis date, within an interval of ± 1 year of diagnosis date), antithrombotic drugs registered in the pharmacy invoicing database within ± 3 months from diagnosis date (registered as ATC codes specified in the ATC codes list in supplementary file), concomitant drug therapy of interest registered in the pharmacy invoicing database within ± 3 months from diagnosis date (rate and rhythm control drugs, other cardiovascular medication,

diabetes treatments, proton pump inhibitors, and non-steroidal anti-inflammatory drugs [NSAID]; as ATC codes specified in the ATC codes list in supplementary file), stroke and other thromboembolic events rates and bleeding episodes (cerebral, gastrointestinal, eye and other haemorrhages) rates registered at CMBD-AH before AF diagnosis in order to confirm the stroke and bleeding rates registered at SIDIAP (as ICD9 codes specified in the ICD9 codes list in supplementary file).

During follow-up the following variables will be assessed for objectives 2 and 3: stroke and bleeding risk calculated during follow-up; stroke and other thromboembolic events and haemorrhages rates; antithrombotic drugs during follow-up to assess treatment changes, new treatments or end of treatment and analysis of effectiveness and safety of the main treatment options – VKA, antiplatelet drugs and no antithrombotic treatment –; through the variable "net clinical benefit".

"Net clinical benefit" has been defined in a previous publication [24] as the annualized rate of thromboembolic events prevented minus the annualized rate of intracranial haemorrhages (ICH) induced multiplied by a weighting factor of 1.5; which reflects the relative impact, in terms of disability, of an ICH while receiving VKA (studied with warfarin) versus experiencing an ischemic stroke while not receiving VKA:

Net clinical benefit =

(Stroke rate off-VKA – Stroke rate on-VKA) – 1.5 x (ICH rate on-VKA – ICH rate off-VKA)

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical variables were expressed as frequencies (percentage) and quantitative variables as mean (Standard deviation, SD) or median (interquartile range, IQR) for non-normally distributed variables. The differences between cohorts were tested using Analysis of variance (ANOVA) or Kruskal-Wallis test, Chi square or Fisher exact test for unadjusted comparison, as appropriate.

Incidence rates and incidence rate ratios of stroke and bleeding events during the follow-up will be estimated using Poisson regression. The resulting person-time value will be used as an offset variable. Time-to-event analysis will be performed using non-parametric methods like Kaplan-Meier and log-rank test. Multivariate Cox proportional-hazards regression models will be fitted, adjusting for baseline socio-demographical characteristics and confounding and predictive factors of each event. Extended Cox models will be used when the model's proportional hazards assumption does not hold.

Sensitivity analysis will be carried out excluding patients that change from one cohort to another during the follow-up and censoring by patient's change of cohort.

All statistical tests were two-tailed using a significance level of 5%. The analyses were performed using Stata ver. 11 (Stata Corp., Collage Station, TX) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical and legal issues

The present study follows national and international regulations: Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and Good Research Practice principles and guidelines.

The IDIAP Jordi Gol Clinical Research Ethics Committee, the reference institution for research in Primary Care of the ICS, approved the study protocol.

Regarding the data contained in the databases and according to Spanish legislation about confidentiality and data protection (Ley Orgánica 15/1999 de 13 de diciembre de Protección de Datos de Carácter Personal), data included in SIDIAP are always anonymized and identified by an internal code, which makes impossible to identify the individuals included. Thus, it is not necessary to ask for informed consent to the participants. Each individual is identified through an encrypted, anonymized code.

For the linkage with CMBD database (or other databases), SIDIAP uses a "trusted third party" in order to ensure confidentiality when linking both data sources. This third party has no access to clinical information, only to codes and IDs.

COHORT DESCRIPTION AND FINDINGS TO DATE

There were 41,468 patients with a new AF diagnosis registered in SIDIAP between 2007 and 2012. Of the newly diagnosed patients, 25,601 (61.7%) fulfilled the inclusion criteria and none of the exclusion criteria (Figure 1). Study cohorts were based on antithrombotic treatment registered at the time of AF diagnosis (± 3 months interval). Two treatment groups were excluded from the baseline description of the cohorts

(11.8% of patients included): patients with only 1 dispensed package of antithrombotic registered during study period (n=1,755) and patients with ≥ 3 different antithrombotic drugs registered (n= 1,261), as it is a group excessively heterogeneous.

We present the baseline characteristics of 22,585 individuals with non-valvular AF, diagnosed from 2007 to 2012. Their mean age was 72.8 (SD 13.1) years and 51.6% were men. The number of patients diagnosed per year with AF in each cohort is shown in Figure 2.

There were 5,724 (25.3%) of patients with no antithrombotic treatment registered at baseline. The most prescribed treatment were VKA (9,057 patients, 40.1%), followed by platelet aggregation inhibitors (7,424, 32.9%). The remaining patients were initiated on VKA + antiplatelet (1.0%) or on dabigatran (0.7%).

The proportion of patients with no antithrombotic treatment decreased during the study period from 28.2% in 2007 to 26.1% in 2012, while the proportion of VKA-treated increased from 37.5% in 2007 to 41.8% in 2012. A decrease in the prescription of antiplatelet agents was observed, form 33.4% in 2007 to 27.9% in 2012.

The baseline characteristics of our patients, including percentages of patients with missing data, are described in Tables 1, 2, 3 and 4.

Table 1 shows higher proportions of men in all cohorts except in the antiplatelet group. Patients treated with any antithrombotic drug were older than non-treated patients. There were more patients over 75 years in the group of antiplatelets. There were more current smokers in the group of patients with no antithrombotic treatment,

but this group had a higher percentage of missing values than the rest of the groups.

There was also a high percentage of missing values in alcohol intake.

Table 1. Socio-demographic characteristics and cardiovascular, stroke and bleeding risk factors

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
Gender					
Female (%)	46.9	48.3	50.3	36.6	38.6
Male (%)	53.1	51.7	49.7	63.4	61.4
Age (years; mean, SD)	69.6 (16.4)	73.4 (10.3)	74.6 (12.9)	72.4 (9.9)	71.4 (11.0)
> 75 years (%)	45.5	51.1	53.6	43.6	39.2
MEDEA[23] (mean, SD)	0.44 (0.92)	0.52 (0.90)	0.50 (0.91)	0.51 (0.82)	0.29 (0.97)
≥ 4th quintile (%)	36.6	39.4	39.1	41.0	29.9
BMI (kg/m2; mean, SD)	28.6 (5.1)	30.2 (5.3)	29.2 (5.2)	30.1 (5.5)	29.5 (4.4)
BMI ≥30: obesity (%)	34.7	46.8	38.8	44.4	40.2
Missing values (%)	*46.4*	*25.3*	*33.9*	*25.6*	*39.9*
Smoking status (%)					
Non smoker	65.7	70.0	70.3	62.8	66.2
Current smoker	16.9	10.3	11.8	12.2	9.6
Ex-smoker	17.4	19.7	17.9	25.0	24.2
Missing values	*30.9*	*19.5*	*18.4*	*17.2*	*11.1*
Alcohol intake (%)					
Non consumer	71.8	70.3	70.4	67.5	63.3
Mild-moderate	25.7	27.3	27.2	31.3	32.7
Alcohol abuse	2.5	2.4	2.4	1.2	4.1
Missing values	*49.0*	*29.0*	*35.2*	*26.9*	*35.9*
$CHADS_2$ score[7] **(%)**					
0	31.7	15.3	19.9	11.9	18.3
1	29.6	31.9	32.6	31.3	38.6
2	24.8	34.8	30.6	27.8	26.1
≥3	14.0	18.0	16.9	29.1	17.0
CHA_2DS_2VASc score [25] **(%)**					
0-1	34.5	17.8	22.3	13.6	24.2

2	16.5	19.5	19.2	18.5	24.8
3	21.4	26.6	23.8	26.4	20.3
≥4	27.6	36.0	34.7	41.3	36.8
HAS-BLED score[10,11] **(%)**					
0	16.3	6.6	0.0	0.0	4.1
1-2	63.6	68.9	42.5	34.3	81.6
≥3	20.2	24.4	57.4	65.7	14.3

Considering only the three main cohorts (no treatment, VKA, antiplatelets) and according to a $CHADS_2$ score ≥2, 52.8% of the patients from the VKA cohort would be considered as "adequately anticoagulated". According to a CHA_2DS_2VASc score ≥2, 62.6% of VKA patients would be "adequately anticoagulated" and at least 6.1% of patients in the same group ($CHA_2DS_2VASc=0$) would be "inadequately anticoagulated" as their stroke risk is low (Figure 3).

On the other hand, there are 38.8% patients in the no-treatment group with a $CHADS_2$ score ≥2, so they should be receiving VKA. This percentage is 65.5% if we take into account the CHA_2DS_2VASc score (≥2) and, thus, only 34.5% patients with a low-moderate stroke risk are not treated with antithrombotics.

Patients treated with antiplatelets and VKA + antiplatelets have higher scores in the HAS-BLED bleeding classification.

Table 2 shows that patients with antithrombotic treatment had more cardiovascular comorbidities when compared with non-treated patients, and patients in the dual therapy VKA + antiplatelet cohort had more comorbidity. Hypertension was the most frequent comorbidity, followed by dyslipidemia. Coronary artery disease was found in 34.8% of the patients in the VKA + antiplatelet cohort, with a high frequency of previous myocardial infarction (MI). Non-treated individuals had better eGFR than patients initiated on antithrombotic therapy, except for dabigatran (84.4% of dabigatran patients had eGFR > 60 mL/min/1.73m^2). However, there were more missing values in that group.

Table 2. Baseline comorbidities

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
CARDIOVASCULAR COMORBIDITY (%)					
Hypertension	48.1	65.1	59.5	67.8	64.1
Years of evolution (m, SD)	7.4	6.8	6.8	7.1	5.9
Type 2 diabetes mellitus	14.4	18.5	16.7	26.4	16.3
Years of evolution (m, SD)	6.9	6.9	6.4	6.5	9.4
Dyslipidemia	24.8	33.2	31.7	38.3	31.4
Peripheral arterial disease	0.9	1.1	1.5	4.0	2.6
Coronary artery disease	4.3	2.8	5.7	34.8	3.9
MI	1.4	0.7	2.1	17.2	0.7
Angina	1.1	1.0	1.6	7.5	2.0
Heart failure	7.7	10.0	8.1	13.2	5.2
Previous stroke	4.8	7.2	5.3	14.1	8.5
TIA	1.0	1.6	1.8	5.3	4.6
BLEEDING (%)					
Previous bleeding	6.0	4.5	5.1	4.0	7.8
Cerebral haemorrhage	1.0	0.4	0.8	0.4	2.0
Gastrointestinal	3.6	2.5	2.9	1.3	3.9
Eye	0.4	0.7	0.6	0.4	0.0
Other	1.3	0.9	1.0	1.8	2.6
Peptic ulcer	3.6	3.7	3.8	2.2	2.6
RENAL IMPAIRMENT (%)					
eGFR (MDRD)					
<30 mL/min/1.73m^2	2.4	1.9	2.4	1.6	0.0
30-60	25.4	27.7	28.7	36.0	15.6
>60	72.2	70.4	68.9	62.4	84.4
Missing values	*35.0*	*18.1*	*19.1*	*16.7*	*28.8*
HEPATIC IMPAIRMENT (%)	3.2	1.7	1.6	2.2	0.7
Charlson comorbidity index [26] **(%)**					
0-2	88.6	90.6	89.1	88.5	92.2
>2	11.4	9.4	10.9	11.5	7.8

*BP, blood pressure. MI, myocardial infarction. TIA, transitory ischemic attack. eGFR, estimated glomerular filtration rate.

Disease control parameters and laboratory data of interest are described in Table 3. Around two thirds of patients had good control of BP, HbA1c and c-LDL levels without differences between cohorts.

Table 3. Disease control parameters and laboratory data

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
Blood pressure					
Systolic BP (m, SD)	132.5 (19.3)	133.3 (18.5)	133.5 (18.4)	132.3 (18.3)	131.6 (17.7)
Diastolic BP (m, SD)	76.6 (11.7)	78.0 (11.8)	77.2 (11.4)	77.0 (11.9)	77.5 (11.8)
Good BP control (<140/90 mmHg; %)	64.6	61.5	61.3	63.7	65.9
Missing values	*22.5*	*6.8*	*10.0*	*5.3*	*11.8*
HbA1c (m, SD)	1.4	1.3	1.3	1.3	1.1
HbA1c < 7% (%)	70.5	65.5	69.7	55.7	74.0
Missing values	*77.8*	*66.5*	*69.2*	*57.3*	*67.3*
Total cholesterol (mg/dL) (mean, SD)	195.7 (40.8)	198.3 (39.5)	195.1 (39.5)	183.3 (42.5)	199.0 (36.6)
HDL	53.0 (15.1)	53.1 (14.3)	53.9 (15.1)	51.1 (14.0)	54.3 (14.6)
LDL	120.9 (34.3)	121.6 (33.8)	119.3 (33.5)	109.1 (36.1)	125.1 (28.2)
n, % c-LDL < 130 mg/dL	61.0	61.0	63.5	72.4	59.6
Missing values of total cholesterol (%)	*35.4*	*18.7*	*19.7*	*15.9*	*29.4*

We describe medications of interest in use at baseline in Table 4. Patients with antithrombotic prescribed at baseline received more comedication than non-treated patients, since they had more comorbidity. Antihypertensive drugs, statins and proton pump inhibitors were the most frequent comedication.

All baseline socio-demographic characteristics and comorbidities were significantly different among the five groups.

Table 4. Medications in use at baseline (% of patients)

	No antithrombotic treatment	VKA	Antiplatelet agents	VKA + Antiplatelet	Dabigatran
n = 22585	**5724**	**9057**	**7424**	**227**	**153**
Digoxin	4.4	20.3	13.5	11.9	10.5
Amiodarone	7.9	18.3	14.6	23.3	9.2
Flecainide	4.3	4.4	6.1	3.1	9.2
Dronedarone	0.3	0.7	0.6	0.0	0.7
Other antiarrhythmic agents	1.9	1.9	2.2	0.9	2.0
Diuretics					
Low-ceiling diuretics	10.3	25.6	20.4	29.1	11.8
Thiazides	4.8	9.3	8.4	4.8	7.2
Aldosterone antagonists	1.8	3.4	2.2	5.3	0.7
Beta blockers	11.3	30.4	23.0	48.5	38.6
Calcium channel blockers					
Dihydropiridines	6.1	11.9	9.9	15.0	7.2
Verapamil	1.0	1.6	1.1	0.4	0.7
Diltiazem	1.8	9.3	5.0	5.7	6.5
ACEI	13.9	30.1	26.2	40.1	24.2
ARB	10.6	22.3	17.2	19.4	27.5
Other antihypertensive drugs	1.8	4.3	3.1	5.7	4.6
Nitrates	1.4	2.4	4.4	19.4	0.0
Trimetazidine	1.5	1.8	2.6	2.2	2.0
Ivabradine	0.1	0.1	0.3	0.9	0.0
Other vasodilator agents	0.2	0.4	0.3	0.4	0.0
Statins	11.3	24.3	22.7	52.4	22.2
Other lipid modifying agents	1.4	2.0	1.8	4.0	2.0
Oral antidiabetic agents	5.8	12.8	10.3	21.1	12.4

Insulins	1.4	2.4	2.2	4.0	1.3
Proton pump inhibitors	25.5	42.9	53.7	69.2	32.7
NSAIDs	15.5	19.0	20.6	18.5	8.5

*ACEI, angiotensin converter enzyme inhibitors. ARB, angiotensin receptor blockers. NSAID, non-steroidal anti-inflamatory drugs.

DISCUSSION

The ESC-FA study was designed as a retrospective observational cohort study on the effectiveness and safety of antithrombotic therapy in patients with non-valvular AF under use in clinical conditions in Catalonia. In this article we report the baseline socio-demographic and clinical characteristics of 22,585 non-valvular AF patients recently diagnosed and discuss the main differences between non-treatment and usual treatments for prevention of stroke and thromboembolic events. The patients included in the study have been divided into five cohorts according to the antithrombotic treatment prescribed at the time of diagnosis.

This is an observational study performed with data obtained from an electronic database. Therefore, it is subject to certain limitations inherent in all such studies, such as the collection of non-randomized data, missing or incomplete information and possible confounders. The strengths of our study are the large number of patients included, representativeness of the general population (SIDIAP information comes from ICS, which manages more than 80% of the Catalan population), complete socio-demographic and health records and real clinical practice data.

With regard to AF diagnosis, our data are supported by previous studies [18–21] which validate our findings and indicate that the study population is representative of the

population in Catalonia and thus it can be used in epidemiologic studies in our setting. More specifically, the diagnosis of AF has been validated in our population in the study published by García-Gil MDM et al.[22]

The diagnosis is sometimes registered in the patients' electronic health records after the real diagnosis has been made and the start of antithrombotic treatment is registered before or after the diagnosis register. To overcome this inconsistency, the cohorts have been constructed taking into account antithrombotic treatments registered during the interval of ± 3 months of diagnostic date.

Regarding the pharmacy invoicing register, we have excluded 11.8% of the 25,601 patients with non-valvular AF due to inconsistencies in the register of treatments. We decided to exclude 1,261 patients as they had registers of three or more different antithrombotic drugs simultaneously at baseline and we assumed there might be errors in the pharmacy invoice database. We decided to exclude other 1,755 patients from the baseline description of the cohort because they only had one package of antithrombotic dispensed and there were dispensing errors.

Although most patients are treated with VKA, INR data are not described at baseline because two different methods of INR determination are used in Catalonia: by laboratory standard determination, which is performed in a low proportion of patients; or through a point-of-care rapid INR determination carried out during primary care visits or in hospitals in most cases. Since we do not have access to hospital records, a high number of INR had missing values. Therefore, INR has not been included in the HAS-BLED calculation. However, at this stage it should not make a significant difference, since INR is only determined in VKA-treated patients during follow-up and

we present the data at baseline, when the INR has not yet been determined and the "L" for HAS-BLED is 0, the same as in patients not treated with VKA. Nonetheless, we will conduct a validation for the INR during the follow-up period, as it is an essential parameter in the clinical management of VKA-treated patients.

Regarding socio-demographic characteristics, the proportion of men and women in our study is quite balanced (51.6% of men) and it is similar to prior registries.[15,27,28]

We found that patients treated with any antithrombotic drug are older, have more comorbidity at baseline and receive more comedication than non-treated individuals. In agreement with similar studies, we found high prevalence of hypertension, dyslipidemia, diabetes mellitus and heart failure in all AF patients.[27,29–31]

The number of patients included in the VKA + antiplatelet cohort is low, possibly due to the short interval of time used to consider a situation of dual therapy (two consecutive registers of both drugs at baseline). The number of patients included in the dabigatran cohort is also low, since this drug was authorised for non-valvular AF in Spain at the end of 2011 and we only include data up to 2012. Moreover, dabigatran is subject to restricted conditions for its prescription in our setting. Data for rivaroxaban are not shown, since there were only a few registers during 2012. Data for apixaban are not shown either, as it was authorised in Spain for non-valvular AF in 2013. VKA prescription rate in non-valvular AF patients at baseline is similar to other studies.

Kirchhof et al.[29] conducted an observational study (PREFER-AF) including 7,243 patients in seven European countries between January 2012 and January 2013. In the cross-sectional description their results suggest much better adherence to evidence and recommendations than previous reports of similar registries: VKA were prescribed

in 66.3% of the patients included, antiplatelets in 11.2%, VKA + antiplatelet dual therapy in 10.9% and dabigatran in 6.1%. They reported 17.7% of non-treated individuals. Results from a prospective follow-up study have not been published yet.

Kakkar et al.[30] conducted the GARFIELD study in different primary care settings, which described VKA prescription in 45.2% of AF patients, antiplatelet agents in 25.3%, dual therapy VKA + antiplatelet in 10.6% and dabigatran in 4.5%. They included 10,614 patients enrolled throughout 2009 and 2011. This study reported similar VKA and antiplatelet prescription rates to those found in our setting.

Scowcroft et al.[31] conducted a cohort study of 81,381 AF patients from the General Practice Research Database, diagnosed between 2000-2009. They found differences in VKA prescription according to group of age: in the 60-69 years-old group, VKA was prescribed in 57% of patients; in the 70-79 group, 55% of patients were receiving VKA; and only 32% of patients older than 80 were treated with VKA. Although this study was carried out with data from an electronic database, which makes possible the analysis of a large set of patients, the results are not easily comparable to ours, since we have not stratified patients by age group. In our study 51.1% of the VKA group are over 75 years of age.

Observational studies conducted in our setting described different proportions of patients treated with VKA [14,15,28] than those found in our study (Table 1 and Figure 3). Nevertheless, we described the situation only at baseline date and our patients could start antithrombotic treatment during follow-up. Moreover, these studies included small numbers of patients. The adequacy of anticoagulation is described in some of these studies; Kirchhof et al. [29] describe 85.6% of patients adequately

anticoagulated (CHA_2DS_2-VASc ≥2). In our study there are less patients adequately anticoagulated (62.6% of VKA patients had CHA_2DS_2-VASc ≥2), but only 6.1% of patients with truly low risk (CHA_2DS_2-VASc =0) received VKA at baseline, while this proportion of inadequate anticoagulation is higher in other studies [28,30].

Kakkar et al. [30] and Barrios et al. [28] describe 61.9% and 57% of patients adequately anticoagulated respectively, considering $CHADS_2$ score. On the other hand, Scowcroft et al. [31] included 90% of patients with a CHA_2DS_2-VASc score ≥2, but only 45.6% of the patients included received warfarin. Although it is difficult to compare our study with prior reports, even if the prescription of OAC in our setting appears to be low, it is nonetheless similar to other studies.

Conclusions

We describe the actual use of antithrombotic agents for stroke and thromboembolism prevention in a large number of non-valvular AF patients in Catalonia.

Age, gender and comorbidity in non-valvular AF patients were similar to those reported in previous studies. The prescription rates of patients initiated on VKA and on platelet aggregation inhibitors were similar to those reported in other studies.

We cannot establish any conclusion about dabigatran use, since only 153 patients had been initiated on this new OAC because its approval for use in AF patients took place in latter 2011. This is expected to change during follow-up, when more patients will have been included in the dabigatran cohort and will have started treatment with rivaroxaban and apixaban as well.

The next step in ESC-FA study is to assess effectiveness and safety of antithrombotic treatments by analysing stroke and other thromboembolic events and haemorrhage rates in our patients. These data would show changes in the management of non-valvular AF patients in Catalonia due to modifications in antithrombotic treatment during follow-up and the introduction of the new OAC.

FIGURE LEGENDS

Figure 1. Study flowchart.

Patients included and excluded from the study.

AF: atrial fibrillation

SIDIAP: Information System for the Development of Research in Primary Care

VKA: vitamin K antagonist

Figure 2. Distribution of new diagnoses of atrial fibrillation per year and cohort

Percentage of patients newly diagnosed with AF per year in each cohort in the figure, number of patients in the table below.

Vitamin K antagonists (n=9057)

Antiplatelets (n=7424)

VKA + antiplatelet (n=227)

Dabigatran (n=153)

No antithrombotic treatment (n=5724)

Figure 3. CHA_2DS_2VASc scores in the treatment cohorts.

Percentage of patients from each cohort by stroke risk according to CHA_2DS_2VASc score.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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DATA SHARING STATEMENT

Statistical code and dataset are available from the corresponding author.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin converter enzyme inhibitors
AF	Atrial fibrillation
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blockers
ATC	Anatomic Therapeutic Chemical Classification System
BMI	Body mass index
BP	Blood pressure
CMBD-AH	Database that contains diagnoses at hospital discharge
eCAP	Electronic clinical records in Primary Care in ICS
eGFR	Estimated glomerular filtration rate
ESC-FA	Effectiveness, Safety and Costs in Atrial Fibrillation
GP	General Practitioners
ICD	International Classification of Diseases
ICS	Catalan Health Institute
ICH	Intracranial haemorrhages
IDIAP	Institute in Primary Care Research
INR	International normalized ratio (measure of the extrinsic pathway of coagulation)
IQR	Interquartile range
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drugs
OAC	Oral anticoagulants
SD	Standard deviation
SIDIAP	Information System for the Development of Research in Primary Care
TIA	Transitory ischemic attack
VKA	Vitamin K antagonists

Figure 1.

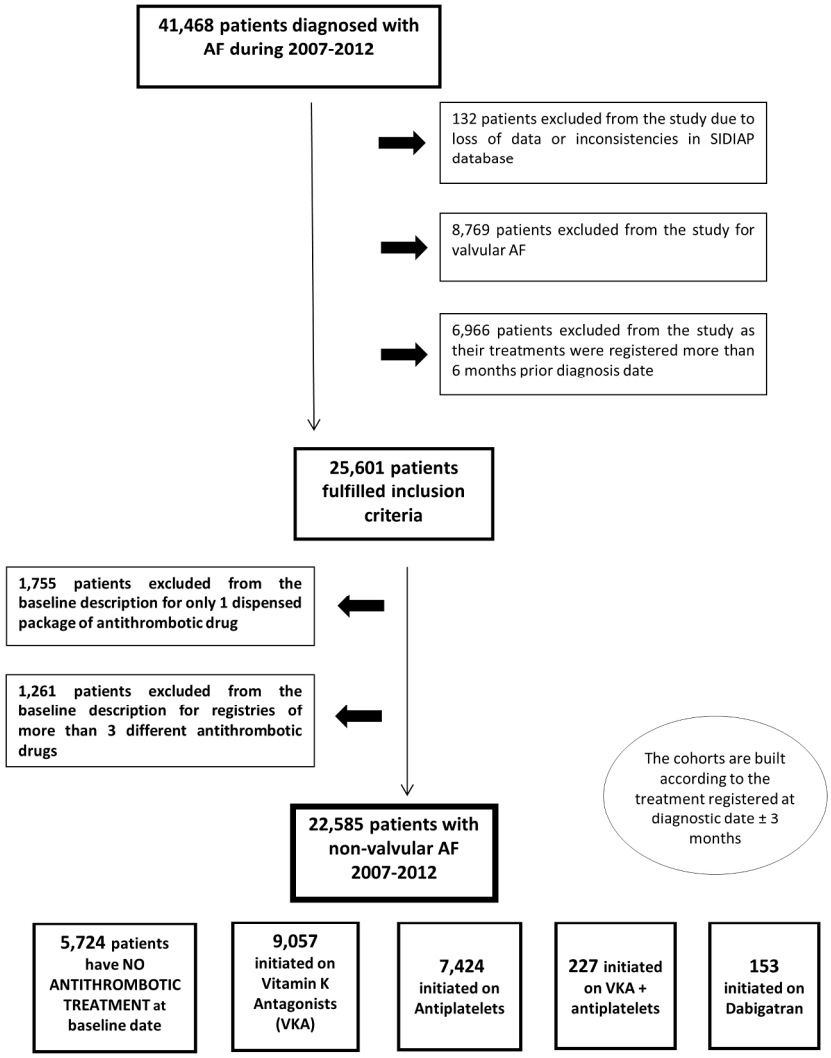
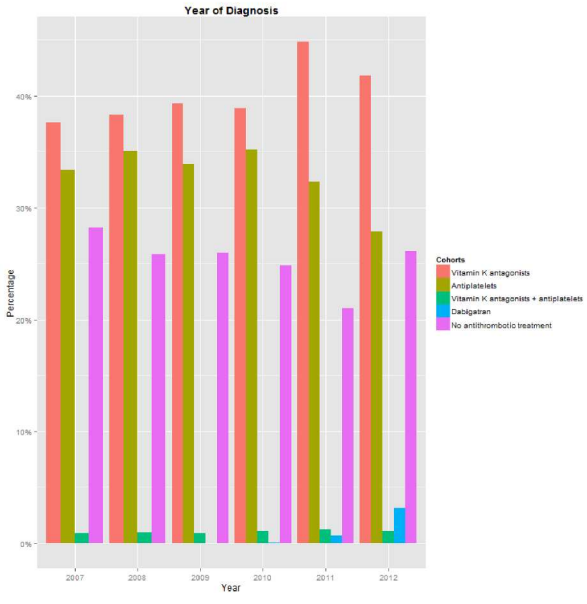


Figure 1. Study flowchart.
Patients included and excluded from the study.
AF: atrial fibrillation
SIDIAP: Information System for the Development of Research in Primary Care
VKA: vitamin K antagonist
190x254mm (300 x 300 DPI)

Figure 2. Distribution of new diagnoses of atrial fibrillation per year and cohort

Percentage of patients newly diagnosed with AF per year in each cohort in the figure, number of patients in the table below.



n	No treatment	VKA	Antiplatelets	VKA + antiplatelets	Dabigatran	Overall
2007	1088	1446	1285	34		3853
2008	911	1348	1236	34		3529
2009	954	1444	1246	31	1	3676
2010	931	1457	1318	40	3	3749
2011	797	1694	1223	46	25	3785
2012	1043	1668	1116	42	124	3993
Overall period	5724	9057	7424	227	153	**22585**

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Dabigatran (n=153)
No antithrombotic treatment (n=5724)
209x297mm (300 x 300 DPI)

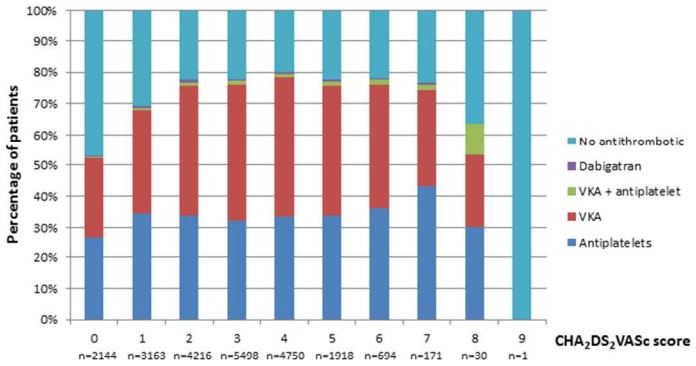

Figure 3. CHA2DS2VASc scores in the treatment cohorts.
Percentage of patients from each cohort by stroke risk according to CHA2DS2VASc score.
254x190mm (96 x 96 DPI)

ANNEX OF CODES

ICD-10 codes list

AF: I48, excluding valvular aetiology (I05, I08). Hypertension: I10, I11, I12, I13, I15. Diabetes mellitus: E10, E11, E12, E13, E14. Angina: I20. MI: I21, I22, I23. Coronary heart disease: I24, I25. Cerebrovascular accidents: I63, I64, I67. TIA: G45, G46. Peripheral arterial disease: I73.8, I73.9. Heart failure: I50. Aortic-coronary bypass: Z95.1. Renal insufficiency: N17, N18, N19. Hepatic insufficiency: K72, K73, K74, R17. Dyslipidemia: E78.0, E78.2, E78.4, E78.5, E78.8, E78.9. Peptic ulcers, including bleeding ulcers: K22.1, K25, K26, K27, K28. Bleeding events: H11.3, H35.6, I60, I61, I62, K29.0, K22.8, K62.5, K92.0, K92.1, K92.2, R04.0, R58, S06.4.

ICD9 codes list

Cerebrovascular and thromboembolic events: 433.9, 434.0, 434.1, 434.9, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.9, 438.0, 438.9, 046.3. Bleeding events: 362.81, 372.72, 431, 432.1, 432.9, 530.8, 530.9, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 532.4, 532.6, 534.0, 534.2, 534.4, 534.6, 535.0, 569.3, 578.0, 578.1, 578.9.

ATC codes list

Antithrombotic drugs: B01A. Rate and rhythm control therapy: C01AA, C01B. Cardiovascular agents: C01DA, C01EB, C01DX12, C02DB02, C02CA, C03AA, C03AB, C03AX, C03BA, C03CA, C03DA, C07, C08, C09, C10. Drugs used in diabetes mellitus: A10. Proton pump inhibitors: A02BC. NSAID: M01AB, M01AC, M01AE, M01AH, N02BA, N02BB.