Effectiveness and safety of thromboembolic prevention in patients with non-valvular atrial fibrillation: ESC-FA study. A cohort from a Primary Healthcare electronic database

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Abstract

Atrial fibrillation (AF) is the most common chronic arrhythmia. It is associated with a variety of cardiovascular conditions and the most important clinical consequences are higher risks of stroke and mortality than general population.

AF management increasingly takes place in Primary Healthcare settings and it is based in stroke prevention, pharmacological control of heart rate and rhythm and handling of concomitant cardiovascular diseases.

This thesis is part of the ESC-FA study (Effectiveness, Safety and Costs in AF), which is a population-based retrospective observational cohort study conducted with data from electronic health records from Primary Healthcare in Catalonia. ESC-FA study received funding through 2011 Grants for Independent Clinical Research from the Ministerio de Sanidad, Política Social e Igualdad from the Spanish Government.

ESC-FA consists in four sub-studies; I to IV, and this thesis includes studies I and II. Study I results are reported in one published paper (paper 1) and in another paper which is currently under review (paper 2). Study II results are published in paper 3.

The study population includes all individuals ≥18 years-old with a diagnosis of non-valvular AF registered in SIDIAP (Information System

for the Improvement of Research in Primary Care) database during 2007-2012, who started antithrombotic treatment (or remained without it) after AF diagnosis.

In study I we describe antithrombotic use in 22 585 patients with non-valvular AF and assess effectiveness and safety of these drugs in real-use conditions before the introduction of direct oral anticoagulants in the management of the disease. Our main results showed: a non-valvular AF population with socio-demographic and clinical features similar to those in other populations, a reduction of stroke risk in patients treated with vitamin K antagonists who have higher risks of stroke ($CHADS_2$ and CHA_2DS_2-VASc index ≥2), an increased risk of stroke and gastrointestinal haemorrhage with antiplatelets and a reduced risk of all-cause mortality with both vitamin K antagonists and antiplatelets, in comparison with patients who were not treated with any antithrombotics.

In study II we describe heart rate and rhythm pharmacological management in non-valvular AF patients. Mostly prescribed drugs were β-blockers, probably pointing out that rate control strategy is the most frequent alternative used, as widely recommended as first-line therapy for management of chronic AF.

Some strengths of our study are the large number of patients included, representativeness for the general population, complete socio-

demographic and health records, long follow-up, and real clinical practice data. This study has high relevance in our setting as it assesses the real number of patients treated with traditional antithrombotics and the clinical results of their use in terms of stroke, haemorrhages and mortality rates, before assessing these clinical results including direct oral anticoagulants, which have been authorized for non-valvular AF in the last years.

Some weaknesses of observational studies conducted with electronic health records are missing or incomplete information, under-register of some health conditions, non-registered information of some personal circumstances of patients and possible confounders. These limitations have been minimized using the appropriate statistical techniques described in the papers included.

Keywords

Atrial fibrillation, electronic health records, primary healthcare, stroke, haemorrhage, cerebral haemorrhage, gastrointestinal haemorrhage, vitamin K antagonists, platelet-aggregation inhibitors, heart rate, hearth rhythm.

Resum

La fibril·lació auricular (FA) és l'arítmia crònica més freqüent. S'associa amb una àmplia varietat de malalties cardiovasculars i les seves conseqüències clíniques més importants són un major risc d'ictus i mortalitat respecte a la població general.

El maneig de la FA es porta a terme principalment des de l'Atenció Primària i està basat en la prevenció de l'ictus, el control farmacològic de la freqüència i del ritme cardíac i el maneig de les patologies cardiovasculars concomitants.

Aquesta tesi forma part de l'estudi ESC-FA (Efectivitat, Seguretat i Costos en FA), que és un estudi de cohorts retrospectiu de base poblacional amb dades procedents dels registres electrònics de la història clínica d'Atenció Primària a Catalunya. L'estudi ESC-FA va rebre finançament amb els ajuts a la Recerca Clínica Independent del 2011 del Ministerio de Sanidad, Política Social e Igualdad del Govern Espanyol. L'ESC-FA és un estudi amb quatre fases o subestudis; I a IV, i la tesi inclou els estudis I i II. Els resultats de l'estudi I es descriuen en un article publicat (article 1) i en un altre actualment en revisió per la seva publicació (article 2). Els resultats de l'estudi 2 estan publicats a l'article 3.

La població d'estudi inclou totes les persones ≥18 anys amb diagnòstic de FA no valvular registrat a la base de dades SIDIAP (Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària) durant el període 2007-2012, i que van iniciar tractament antitrombòtic (o van romandre sense aquest tractament) just després del diagnòstic de la FA.

A l'estudi I es descriu l'ús d'antitrombòtics en 22 585 pacients amb FA no valvular, i s'avaluen l'efectivitat i seguretat d'aquests fàrmacs en condicions reals d'ús, abans de la introducció dels anticoagulants orals directes en el maneig d'aquesta patologia. Els nostres resultats principals inclouen: una població amb FA no valvular de característiques sociodemogràfiques i clíniques semblants a la població inclosa en altres estudis, una reducció del risc d'ictus en pacients tractats amb antagonistes de vitamina K i amb elevat risc de patir aquest esdeveniment (puntuacions de $CHADS_2$ i CHA_2DS_2-VASc ≥2), un augment del risc d'ictus i d'hemorràgia digestiva en els pacients tractats amb antiagregants plaquetaris, i una reducció del risc de mortalitat per qualsevol causa tant amb antagonistes de vitamina K com amb antiagregants; respecte al grup de pacients no tractats amb antitrombòtics.

A l'estudi II es descriu el maneig farmacològic de la freqüència i ritme cardíac en FA no valvular. El grup de fàrmacs més utilitzat van ser els β-blocadors, indicant probablement que l'estratègia de control de la freqüència cardíaca és l'alternativa més usada, tal i com es recomana com a teràpia d'elecció en el maneig de la FA crònica.

Algunes fortaleses del nostre estudi inclouen la gran mostra de pacients estudiats, l'elevada representativitat de la població general, dades sociodemogràfiques i clíniques molt completes i llargs períodes de seguiment; tot en condicions reals d'ús. Es tracta d'un estudi molt rellevant al nostre entorn, donat què avalua el nombre real de pacients tractats amb antitrombòtics i els resultats clínics que se'n deriven del seu ús en termes d'incidència d'ictus, hemorràgies cerebrals i digestives, i mortalitat per qualsevol causa; abans d'avaluar aquests resultats incloent el grup d'anticoagulants orals directes que s'han començat a utilitzar en els últims anys.

Algunes limitacions dels estudis desenvolupats amb dades procedents de registres electrònics de la història clínica són la informació faltant, l'infrarregistre, la informació no recollida sobre certes circumstàncies dels pacients en aquest tipus de registres, i els possibles confusors. La majoria d'aquestes limitacions es poden minimitzar amb l'ús de les

tècniques estadístiques adequades, descrites als articles inclosos a la tesi.

Paraules clau

Fibril·lació auricular, registres electrònics de la història clínica, atenció primària, ictus, hemorràgia, hemorràgia cerebral, hemorràgia gastrointestinal, antagonistes de vitamina K, antiagregants plaquetaris, freqüència cardíaca, ritme cardíac.

1. Index

1.1. Index of tables and figures

Annex 2

2. List of abbreviations and acronyms

ADP	Adenosine diphosphate
AMPc	Adenosine monophosphate cyclic
ATP	Adenosine triphosphate
AF	Atrial fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$CHADS_2$	Stroke-risk score which includes congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA/TE (2 points)
CHA_2DS_2-VASc	Stroke risk score which includes congestive heart failure, hypertension, age ≥75 (2 points), diabetes mellitus, stroke/TIA/TE (2 points), vascular disease, age 65-74, female sex.
CI	Confidence interval
COX1	Cyclooxygenase 1
CrCl	Creatinine clearance
DM	Diabetes mellitus
DOAC	Direct oral anticoagulants
ESC-FA	Effectiveness, safety and costs in atrial fibrillation
GI	Gastrointestinal

GMPc	Guanosine monophosphate cyclic
GPIIb/IIIa	Glycoprotein IIb/IIIa
GPRD	General Practice Research Database
HAS-BLED	Hypertension (systolic blood pressure ≥160mmgHg), abnormal kidney and/or liver function, stroke, bleeding, labile INR, elderly, drugs (antiplatelets) and/or alcohol.
HF	Heart failure
HR	Hazard ratio
ICH	Intracranial haemorrhage
INR	International normalized ratio (measure of the extrinsic pathway of coagulation)
MI	Myocardial infarction
NOAC	New oral anticoagulants
OAC	Oral anticoagulants
PGH_2	Prostaglandin H_2
PGI_2	Prostacyclin
PHC	Primary Healthcare
RR	Relative risk
SBP	Systolic blood pressure
SIDIAP	Information System for the Improvement of Research in Primary Care
SD	Standard deviation
TE	Thromboembolism

TIA	Transient ischaemic attack
TXA_2	Thromboxane A_2
ULN	Upper limit of normal
VKA	Vitamin K antagonists

3. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] It is caused by atrial electrophysiological abnormalities, structural abnormalities, or a combination of these. Extrinsic factors, such as the autonomic nervous system, are often involved as well. AF can result in structural and electrical remodelling and changes in the autonomic nervous system.[2] The surface electrocardiogram is the cornerstone of diagnosis for cardiac rhythm disturbances.[3]

AF prevalence in the general population in North America and Europe is 1-2%,[4,5] and it increases with age, ranging from 0.5-1% in less than 50 years-old population[5–7] to more than 17% in older than 80.[6,7] A recent study in our area indicates an AF prevalence of up to 24.4% in patients older than 85.[8] The yearly incidence of new AF has been reported to be about 1.6% in population older than 65.[1]

Men are more often affected by AF than women, although women have a higher risk of suffering a stroke.[9]

AF represents an increasing healthcare burden, because of an ageing population and improved survival from other cardiovascular disorders.[1]

Management of AF increasingly takes place in Primary Healthcare (PHC) settings. It aims symptoms reduction and prevention of associated complications by rate control, rhythm control, prophylaxis of stroke and thromboembolic events and management of concomitant cardiovascular diseases.[1,9]

AF is clinically classified in five types, depending on the presentation and duration of the arrhythmia:[9]

- Firstly diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms. For every patient who presents with AF for the first time.
- Paroxysmal AF. Self-terminating arrhythmia, usually within 48 hours. It may continue for up to 7 days.
- Persistent AF. When an AF episode either lasts longer than 7 days or requires termination by cardioversion.
- Long-standing persistent AF. AF has lasted for ≥1 year when it is decided to adopt a rhythm control strategy.
- Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Rhythm control interventions are, by definition, not pursued in patients with permanent AF.

AF progresses from short to longer and more frequent episodes. Over years, many patients will develop sustained forms of AF.[9]

3.1. Risk factors

Numerous well-established and validated risk factors contribute to the development of AF.[9] The most prevalent risk factor for AF is hypertension. Some authors have reported that more than 70% of AF patients are diagnosed with hypertension.[2,6,7] Heart failure, which is present in 30% of the patients; chronic kidney disease, in 10-15% of AF patients; and type 2 diabetes mellitus (DM), present in around 20% of the patients, are also highly prevalent risk factors for AF.[10–12]

Traditionally, some other risk factors have been described, such as previous myocardial infarction (MI), valvular heart disease, hyperthyroidism, smoking, extreme physical activity, chronic obstructive pulmonary disease, obstructive sleep apnoea, obesity or excessive alcohol consumption.[4,10]

In the last years, some serum biomarkers have been proposed as AF risk factors. Although validation in large real-world patients is pending, for example natriuretic peptides may help to assess AF risk. It has been also said that C-reactive proteins or troponin I may increase the risk for stroke in AF patients.[10,11,13,14]

3.2. Atrial fibrillation consequences

AF may be asymptomatic, especially in elderly population. When symptoms occur, they include palpitations, shortness of breath, fatigue, dizziness and syncope.[2]

Suffering AF has multiple consequences. For instance, it confers a high risk of mortality, as it doubles death rates.[1,4,11] AF also increases the risk of heart failure, left ventricular dysfunction, degraded quality of life, reduced exercise capacity or hospitalizations.[9]

The most important clinical consequences of AF are stroke, cerebrovascular events and other thromboembolic events. AF confers a five-fold risk of stroke, one in five of all strokes is attributed to this arrhythmia and AF-related strokes are more severe, with patients less likely to survive and be free of disability.[1,9]

Moreover, women have higher stroke risk than men, despite AF incidence is higher in men.[9]

The four risk factors identified as the strongest predictors of stroke are: previous stroke and/or transient ischaemic attack, hypertension, type 2 DM and advanced age.[1,9]

The most important risk factors for stroke are included in the scores used to measure individual risk, $CHADS_2$[1,15] and CHA_2DS_2-VASc[4,16] index. Some stroke risk factors are also bleeding factors, which are measured by HAS-BLED index.[17–19] These scores are explained in detail in section *3.4. Antithrombotics for stroke prevention*.

3.3. Rate and rhythm control

Acute management of patients newly diagnosed with AF consists in stroke prophylaxis and acute improvement of cardiac function. The severity of AF-symptoms should drive the decision for acute restoration of sinus rhythm (in severely compromised patients) or acute management of the ventricular rate.[9]

For acute control of ventricular rate in stable patients, the target rate should be 80-100 beats per minute. Acute initiation for rate control therapy should usually be followed by a long-term rate control strategy. The main drugs are β-blockers, non-dihydropyridine calcium-channel antagonists, digoxin, dronedarone or amiodarone.[9]

In patients who remain symptomatic despite adequate rate control or in whom rhythm control therapy is pursued, pharmacological cardioversion of

AF may be initiated by a bolus administration of an antiarrhythmic drug, as flecainide, propafenone or amiodarone.[9]

In patients with mild symptoms, the use of rhythm control pharmacotherapy has not demonstrated mortality decrease, quality of life improvement, and reduction of heart failure incidence or thromboembolic complications. Rhythm control is recommended for restoring and maintaining sinus rhythm with electrical cardioversion and/or antiarrhythmic agents. Antiarrhythmic therapy is recommended for paroxysmal and persistent AF. The most widely used antiarrhythmic agents in patients with severe symptoms are amiodarone, sotalol or flecainide.[1,9,20]

3.4. Antithrombotics for stroke prevention

Stroke is a term used to describe an abrupt onset of focal neurologic deficit that lasts at least 24 hours and is presumed to be of vascular origin. Stroke can be either ischaemic or haemorrhagic in origin. The major modifiable risk factors for stroke are hypertension and AF.[3]

Ischemic strokes account for 88% of all strokes and are due either to local thrombus formation or to emboli that occlude a cerebral artery. The final result of both thrombus formation and embolism is arterial occlusion,

decreasing cerebral blood flow and causing ischaemia and ultimately infarction distal to the occlusion.[3]

The drugs aimed at decreasing the risk of stroke and thromboembolic events in patients with non-valvular AF are antithrombotics: oral anticoagulant drugs (OAC) and platelet-aggregation inhibitors or antiplatelets. They have the inconvenience of increasing bleeding risk.[4]

The OAC drugs traditionally used are the vitamin K antagonists (VKA); acenocoumarol in Spain and warfarin in the USA and most European countries.

In the last years, new OAC (NOAC), also known as direct OAC (DOAC), have been authorized for stroke prevention in non-valvular AF (in Spain dabigatran in 2011, rivaroxaban in 2012, apixaban in 2013 and edoxaban in 2015, although is not marketed yet).

The antiplatelets most commonly used are aspirin and clopidogrel.

The decision of using OAC or antiplatelets used to depend on the individual risk of stroke and bleeding. Some of the bleeding risk factors are also stroke risk factors.[1,21] Nowadays, most guidelines recommend using OAC, which have shown superiority over platelet-aggregation inhibitors.[4,22,23]

To assess individual risk of stroke and bleeding, risk stratification scores have been designed; $CHADS_2$ and CHA_2DS_2-VASc index for stroke risk and HAS-BLED for bleeding risk.

$CHADS_2$ index is the most widely used score to assess thrombotic risk in non-valvular AF patients. According to their stroke risk, patients are classified as having low ($CHADS_2$ = 0), moderate ($CHADS_2$ = 1) or high ($CHADS_2 \geq 2$) risk of stroke.[1,15]

Table 1. $CHADS_2$ score

$CHADS_2$	**Description**	**Score**
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75	1
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
Maximum score		6

TIA, transient ischemic attack; TE, thromboembolism.

Source: Lip GYH et al. *Lancet* 2012;379(9816):648-61.[1]

CHA_2DS_2-VASc index was designed to complement $CHADS_2$. It identifies better patients with truly low risk of stroke[1,16,23] and it is the score currently recommended by European guidelines.[4,22,23]

Table 2. CHA_2DS_2-VASc score

CHA_2DS_2-VASc	Description	Score
C	Congestive HF/left ventricular dysfunction	1
H	Hypertension	1
A_2	Age ≥ 75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE previously	2
V	Vascular disease: previous MI, peripheral artery disease, complex aortic plaque	1
A	Age 65-74	1
S	Sex category, female	1
Maximum score		9

HF, heart failure; TIA, transient ischaemic attack; TE, thromboembolism; MI, myocardial infarction.

Source: Lip GYH et al. *Lancet* 2012;379(9816):648-61.[1]

According to their stroke risk, patients are classified as having low (CHA_2DS_2-VASc = 0), moderate (CHA_2DS_2-VASc = 1) or high (CHA_2DS_2-VASc ≥ 2) risk of stroke.

It is generally recommended to offer OAC to all patients with $CHADS_2$ or CHA_2DS_2-VASc ≥ 2.[4,22,23]

Thromboembolism risk distribution has been described in *Olesen et al*.[24] For patients with $CHADS_2$ = 0, the rate for thromboembolic events per year

ranges between 0.84% (if their CHA_2DS_2-VASc score is 0), 1.75% (CHA_2DS_2-VASc = 1) and 3.2% (CHA_2DS_2-VASc = 2).

Thromboembolism risk has also been studied according to $CHADS_2$ and CHA_2DS_2-VASc scores by *Rodríguez-Mañero et al.*[25] They conducted an observational study which included 1 544 AF patients: 77.9% had $CHADS_2 \geq 2$, 18.7% had $CHADS_2 = 1$ and 3.4% had $CHADS_2 = 0$. Around 16% of low-moderate risk patients became high risk patients when CHA_2DS_2-VASc score was calculated. Therefore, the recommendation to start OAC therapy changed in these patients.

Thus, it is recommendable to use CHA_2DS_2-VASc index in patients with low risk of stroke. If CHA_2DS_2-VASc is still 0, it is reasonable to omit antithrombotic therapy. If the score is 1, treatment with an OAC or aspirin may be considered according to USA guidelines,[26] although European guidelines recommend only anticoagulation.[4,22,23] With CHA_2DS_2-VASc ≥ 2, stroke and thromboembolism prevention is always recommended with OAC drugs to achieve a INR target of 2.0-3.0.[9,22]

In order to ascertain bleeding risk, HAS-BLED score is the recommended index.[17–19] It is considered that HAS-BLED = 0 means low risk for bleeding, 1-2 means moderate risk and ≥ 3 is a high risk. Strict follow-up is advisable in patients with a high bleeding risk, independently of the antithrombotic treatment received.[18,19]

Table 3. HAS-BLED score

HAS-BLED	Description	Score
H	Hypertension. Not controlled, with SBP ≥ 160 mmHg	1
A	Abnormal kidney function (chronic dyalisis, renal transplant or serum creatinine ≥ 200 µmol/L) or abnormal liver function (cirrhosis or biochemical data indicating hepatic impairment, bilirubin > 2-fold ULN, AST/ALT > 3-fold ULN)	1 or 2
S	Previous stroke	1
B	Previous bleeding	1
L	Unstable/high or labile INR	1
E	Elderly. Age ≥ 65	1
D	Drugs affecting haemostasy (aspirin, clopidogrel...) and/or alcohol intake ≥ 8 alcoholic drinks per week	1 or 2
Maximum score		9

SBP: Systolic blood pressure. ULN: upper limit of normal. AST: aspartate aminotransferase. ALT: alanine aminotransferase. INR: International Normalized Ratio. Labile INR: less than 60% of time within therapeutic range *(INR = 2-3)*[18].

Source: Pisters et al. *Chest* 2010;138(5):1093-100.[19]

3.4.1. Platelet-aggregation inhibitors

3.4.1.1. Platelet aggregation and mechanism of action of platelet-aggregation inhibitors

Aggregation involves platelet-to-platelet adhesion, and is necessary for effective haemostasis following the initial adhesion of platelets to the site of injury. Following adhesion, platelets are activated by a number of agonists

such as adenosine diphosphate (ADP) and collagen present at the sites of vascular injury.[27,28]

After the activation, there is an increase of platelet free calcium concentration, which results in a number of structural and functional changes of the platelet and a stimulation of membrane phospholipase A_2 activity, which liberates arachidonic acid from membrane phospholipids. Arachidonic acid is converted to prostaglandin H_2 (PGH_2) by the enzyme cyclooxygenase 1 (COX-1). PGH_2 is further metabolized to thromboxane (TXA_2) by thromboxane synthase and to prostacyclin (PGI_2) by prostacyclin synthase. TXA_2 is a potent activator of platelets and PGI_2 inhibits platelet activation and is an effective vasodilator.[27]

A main adhesion molecule involved in platelet aggregation is the membrane protein, GPIIb/IIIa complex, an integrin receptor present at high density on platelets. After platelet activation, GPIIb/IIIa binds soluble plasma fibrinogen. The receptor-bound fibrinogen acts as a bridge between two GPIIb/IIIa molecules on adjacent platelets. This is the final common pathway of platelet aggregation induced by platelet chemical agonists.[27]

Platelet-aggregation inhibitors act on different targets in the pathway described above to interfere with platelet function. Inhibitors of TXA_2 production, such as aspirin, inhibit COX1 irreversibly. This should cause a decrease in TXA_2 and PGI_2, but in fact, low doses of aspirin inhibit TXA_2

more than PGI_2. Aspirin doses for antiaggregation are normally 50-300 mg/day.[28]

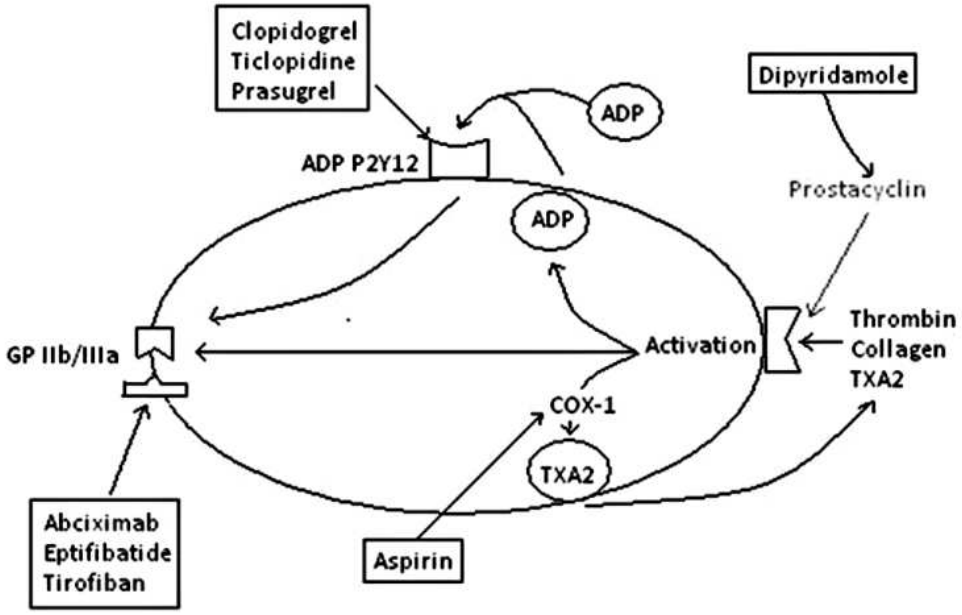
Dipyridamole inhibits aggregation through phosphodiesterase inhibition, which decreases AMPc and GMPc inside the platelets, causing an increase in ADP. It is normally used in dual therapy with aspirin.[28]

Other drugs inhibit ADP-dependent mechanisms, such as ticlopidine, prasugrel or clopidogrel, which is one of the most used antiplatelets. Clopidogrel is a prodrug. One of its metabolites selectively inhibits ADP binding to its platelet receptor, P2y, and the posterior activation of GPIIb/IIIa complex. This binding is irreversible, so the platelet-aggregation is inhibited for the rest of the platelet life (approximately 7-10 days).[28,29]

GPIIb/IIIa receptor is blocked by drugs as abciximab.[28]

Figure 1 shows the platelet-aggregation mechanisms and the sites where main platelet-aggregation inhibitors work.

Figure 1. Mechanism of action of antiplatelet agents



Source: Mohanty S, Vaidyanathan B. *Ann Pediatr Card* 2013;6:59-64[30]

3.4.1.2. Scientific evidence on antiplatelets for stroke prevention

a. Antiplatelet therapy vs. placebo

A meta-analysis performed by Hart et al.[21] which ascertained antithrombotic therapies for stroke prevention in AF, included eight independent randomized controlled studies comparing antiplatelets to placebo, together including 4 876 patients, 37% of them where women and had a mean age of 69 years-old. These clinical trials explored the prophylactic effects of antiplatelet therapy, most commonly aspirin, compared with placebo, on the

risk of thromboembolism in patients with AF. When aspirin alone was compared with placebo or no treatment in seven trials (3 990 patients), treatment with aspirin was associated with a non-significant 19% (95% CI, 1-35) reduction in the incidence of stroke. There was an absolute risk reduction of 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention by using aspirin. When only strokes classified as ischaemic were considered, aspirin resulted in a 21% (95% CI, 1–38) reduction in strokes. When data from all comparisons of antiplatelets and placebo or control groups were included in the meta-analysis, antiplatelet therapy reduced stroke by 22% (95% CI, 6–35). The dose of aspirin differed markedly between the studies, ranging from 50 to 1300 mg daily. Much of the beneficial effect of aspirin was driven by the results of one single positive trial, SPAF-I, which suggested a 42% stroke risk reduction with aspirin 325 mg vs. placebo.

The magnitude of stroke reduction from aspirin vs. placebo in the meta-analysis (19%) is broadly similar to that seen when aspirin is given to vascular disease subjects. Given that AF commonly coexists with vascular disease, the modest benefit seen for aspirin in AF is likely to be related to its effects on vascular disease. More recent cardiovascular primary prevention trials in non-AF cohorts have not shown a significant benefit from aspirin in reducing risk of cardiovascular events.

b. Dual therapy of antiplatelet and oral anticoagulant

About those patients requiring a dual therapy consisting of antiplatelet + OAC, there is no real consensus and the evidence comes from cohort data.[31] Adding aspirin to VKA does not reduce the risk of stroke and thromboembolism, but substantially increases bleeding events, so it is not generally recommended,[9] even in patients with stable coronary artery disease.[32]

3.4.2. Vitamin K antagonists

3.4.2.1. Anticoagulation and mechanism of action of Vitamin K antagonists

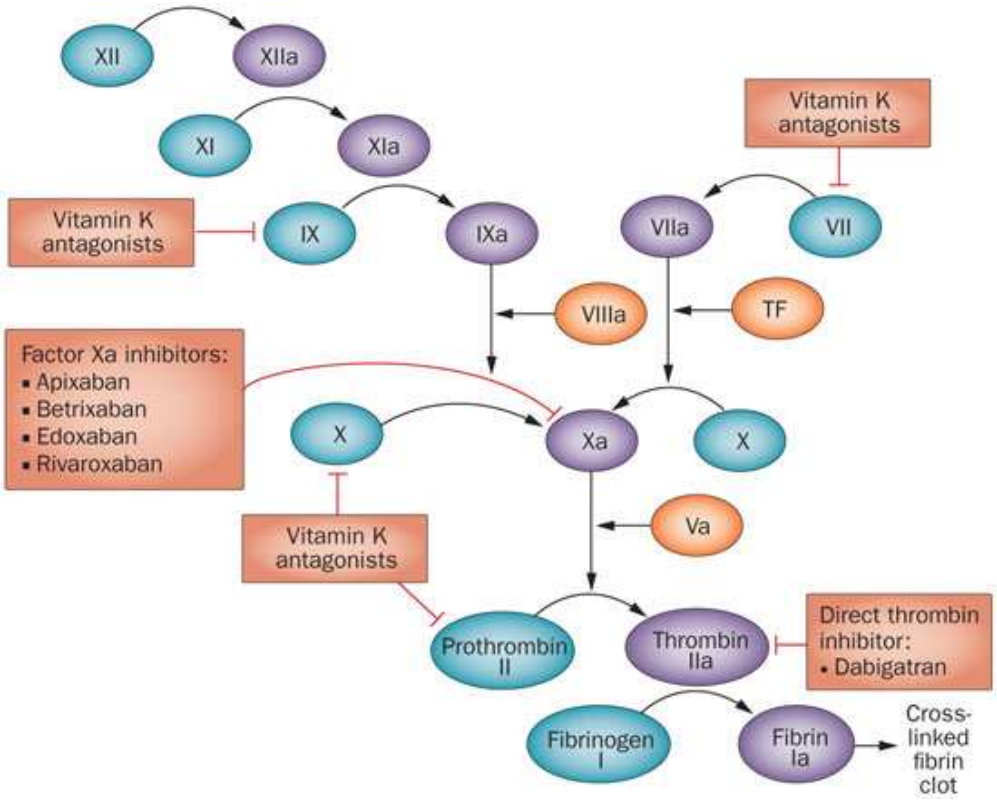
Coagulation involves the regulated sequence of proteolytic activation of a series of zymogens to achieve appropriate and timely haemostasis in an injured vessel, in an environment that overwhelmingly favours an anticoagulant state. In the non-pathological state, the inciting event involves exposure of circulating factor VII/VIIa to extravascularly expressed tissue factor, which brings into motion the series of steps which results in amplification of the initial stimulus, culminating in the conversion of fibrinogen to fibrin and clot formation. The precisely synchronized cascade of events is counter-balanced by a system of anticoagulant mechanisms, which serve to ensure that the haemostatic effect is regulated and does not extend inappropriately. Conversely, in pathological states, these events can escape

normal control mechanisms, due to either inherited or acquired defects, which lead to thrombosis.[33]

VKA produce an alteration of vitamin K, which is essential to hepatic synthesis of four coagulation factors; II, VII, IX, and X.[28] Figure 2 shows the coagulation cascade and the mechanism of action of VKA and DOAC.

Until the authorization of the DOAC in the past years, the pharmacological group used for stroke prevention were VKA, being acenocoumarol the most used in Spain despite warfarin is the most studied in clinical trials.

Figure 2. Mechanism of action of oral anticoagulants



Source: Makaryus John N., Halperin Jonathan L. & Lau. *Nature Reviews Cardiology* 2013;10:397-409[34]

3.4.2.2. Scientific evidence on vitamin K antagonists for stroke prevention

Numerous studies have provided an extensive evidence base for the use of antithrombotic therapy in AF. On the one hand, VKA have been assessed in different clinical trials vs placebo or other control treatments, and we present

a meta-analysis by Hart et al.[35] which conclude VKA are superior to placebo for stroke prevention in non-valvular AF.

On the other hand, several clinical trials and observational studies have assessed efficacy, effectiveness and safety of VKA vs. antiplatelets for stroke prevention. In section *b. Vitamin K antagonists vs. antiplatelets* there is a summary of two clinical trials, one meta-analysis and seven cohort studies which evaluated these outcomes. They may also be found in Tables A1 and A2 of Annex 2.

a. Vitamin K antagonists vs. placebo

In a meta-analysis conducted by Hart et al.[35] in 1999, the authors included six randomized clinical trials with 2 900 participants of 69 years-old, 71% of men and 20% of them had had a previous stroke. Five trials were primary prevention studies, and one was a secondary prevention trial. The patients were randomized to receive dose-adjusted warfarin or placebo. The average stroke rate was 4.5% per year for primary prevention and 12% per year for secondary prevention among patients assigned to the placebo or control groups. According to meta-analysis, adjusted-dose warfarin was associated with a 67% (95% CI, 54-77) reduction in ischaemic stroke. There were no new clinical trials included in the posterior meta-analysis conducted by the same authors in 2007.[21] Many strokes in the VKA-treated patients occurred when patients were not taking therapy or were sub-therapeutically

anticoagulated. All-cause mortality was significantly reduced (26%) by adjusted-dose VKA vs. control. The risk of intracranial haemorrhage was small.[9]

This meta-analysis concludes VKA are superior to placebo for stroke prevention in non-valvular AF.

b. Vitamin K antagonists vs. antiplatelets

Two clinical trials and one meta-analysis of clinical trials evaluated VKA efficacy and safety in comparison with antiplatelets for stroke prevention in AF. They are summarized in Table A1 in Annex 2.

Seven cohort studies assessed similar outcomes for VKA vs. comparators. They are summarized in Table A2 in Annex 2.

The first clinical trials of Mant et al.[36] randomly assigned 973 AF patients older than 75 to warfarin or aspirin and analysed (intention-to-treat analysis) stroke, ICH or clinically significant arterial embolism as a primary endpoint in the BAFTA study. Patients were followed-up during 2.7 years (SD 1.2). $CHADS_2$ score was 1-2 in 72% of them. Yearly risk for all events was 1.8% with warfarin and 3.8% with aspirin, RR 0.48 (95%CI 0.28-0.80, p=0.0027). No differences were found in the RR of major haemorrhages. These data showed that warfarin is more effective than aspirin in stroke prevention in people with AF who are older than 75.

The second clinical trial conducted by Connolly et al.[37] randomized 6 706 patients to receive OAC (50.3%) or clopidogrel + aspirin (49.7%) in ACTIVE-W clinical trial, which included patients with AF plus one or more risk factor for stroke. Median age was 70.2 and median $CHADS_2$ score was 2.0. The primary outcome was stroke, non-central nervous system systemic embolus, MI, or vascular death. Analyses were conducted by intention-to-treat. The study was stopped early because of clear evidence of superiority of OAC. The annual risk of primary outcomes was 5.60% with clopidogrel plus aspirin and 3.93% with OAC; RR 1.44 (95% CI, 1.18-1.76; p=0.0003).

In the meta-analysis conducted by Van Walraven et al,[38] 4 052 non-valvular AF patients from six clinical trials had been randomly assigned to OAC or aspirin with or without OAC. The OAC group were less likely to experience any stroke (HR 0.55, 95% CI, 0.43-0.71, p<0.001), ischaemic stroke (HR 0.48, 95% CI, 0.37-0.63, p<0.001), or cardiovascular events (HR 0.71, 95% CI, 0.59-0.85, p<0.001) but were more likely to experience major bleeding (HR 1.71, 95% CI, 1.21-2.41, p=0.02). Compared with aspirin, OAC significantly decreased the risk of all strokes, ischaemic strokes, and cardiovascular events for patients with non-valvular AF but modestly increased the absolute risk of major bleeding.

To sum up, clinical trials which assessed efficacy and safety of VKA vs. antiplatelets, demonstrated VKA superiority in the risk reduction of stroke, without significantly increasing major haemorrhages (Table A1 in Annex 2).

Regarding observational studies, seven cohort studies analysed VKA effectiveness and safety in comparison with platelet-aggregation inhibitors for stroke prevention in non-valvular AF. Two of them were for secondary prevention.

Three of these studies included two treatment groups, warfarin-treated and non-warfarin treated. They were three different cohort studies which included patients from ATRIA study,[39] which is a cross-sectional study evaluating rates and predictors of warfarin use in PHC patients with non-valvular AF.

Four studies conducted with real-use data included VKA, antiplatelets and no antithrombotic groups; three of them were conducted with electronic health records data and one with hospital discharge register data.

All seven cohort studies found superiority of VKA over antiplatelets or no antithrombotic treatment in risk reduction of stroke. These cohort studies are described below and can also be found in Table A2 from Annex 2.

In the observational study conducted linking three Danish databases by Nielsen et al,[40] event rates after 1-year of follow-up were assessed in 1 752 AF patients whit incident intracranial haemorrhage (ICH) and who were receiving OAC, antiplatelet or no antithrombotic treatment after ICH. The adjusted hazard ratio (HR) of ischaemic stroke, systemic embolism and all-cause mortality was 0.55 (95% CI, 0.39-0.78) in patients on OAC in comparison with no treatment. The HR of all-cause mortality was 0.55 (95% CI, 0.37-0.82).

In a different cohort study conducted with the three Danish databases, Lip et al.[41] studied 39 400 patients with 0 (male) or 1 (female) CHA_2DS_2-VASc risk factor; 23 752 (59.8%) untreated, 5 353 (13.6%) on aspirin and 10 475 (26.6%) on warfarin. In the intention-to-treat analysis and one year follow-up of patients with no risk factors, HR for ischaemic stroke was 1.85 (CI95% 1.11-3.07) for warfarin versus untreated, and 1.05 (CI95% 0.55-2.02) for warfarin versus aspirin. HR for ICH were 1.09 (CI95% 0.39-3.04) and 1.71 (CI95% 0.33-8.97) for warfarin versus untreated and aspirin, respectively. HR for death were 0.61 (CI95% 0.47-0.80) and 0.72 (CI95% 0.51-1.02) also for warfarin versus untreated and aspirin. The authors concluded that low-risk patients have a truly low risk for stroke and haemorrhages. With one risk factor-increase (CHA_2DS_2-VASc male =1, CHA_2DS_2-VASc female=2), at one year stroke increased 3.01-fold, bleeding 2.35-fold and death 3.12-fold.

Forslund et al.[42] evaluated the benefits of warfarin, aspirin or no treatment in a cohort study of 41 810 AF patients. Patients treated with warfarin had lower risk of stroke than untreated (HR 0.55, CI95% 0.37-0.81). Those treated with aspirin had an increased risk of suffering stroke and thromboembolism and an increased bleeding risk. Warfarin patients had lower mortality rates than aspirin or untreated patients (all-cause death during 2010: 3.6%, 12.4% and 10.3%, respectively. HR 0.56, CI95% 0.44-0.71, for warfarin versus untreated; HR 0.87, CI95% 0.72-1.04, for aspirin versus untreated). They indicate this reflects confounding by indication (decisions not to treat frail patients with warfarin) rather than therapeutic

effects of aspirin, which would lead to more complications than with warfarin, or very large effects of warfarin treatment on mortality.

Friberg et al.[43] assessed effectiveness and safety of warfarin versus no treatment in 170 292 AF subjects in a cohort study. Ischaemic stroke rates increased with increasing CHA_2DS_2VASc scores from 0 to 12% annually in patients without warfarin and to 7% in patients with warfarin at baseline. ICH occurred at an annual rate of 0.6% in warfarin-treated and untreated patients alike, whereas bleeding of any type occurred at an annual rate of 2.3%. So the risk of ischaemic stroke without OAC is higher than the risk of ICH with OAC treatment.

In the cohort study of Singer et al,[44] the authors assessed stroke and ICH rates in a cohort of 13 559 AF patients, 46.9% untreated and 53.1% receiving warfarin. They described an overall unadjusted rate of stroke and thromboembolism of 1.27% (95% CI, 1.19-1.44) and an overall unadjusted rate of ICH of 0.58% (95% CI, 0.51-0.68); with an adjusted net clinical benefit of warfarin over no-warfarin therapy of 0.68% per year, although patients in no-warfarin group could be on antiplatelets treatment. There was no mortality assessment.

In the cohort study conducted by Go et al,[45] they reported a 51% lower risk of thromboembolism with warfarin compared with no warfarin therapy (either no antithrombotic or aspirin). Warfarin was associated with a nearly 2-fold adjusted increased risk of ICH (HR 0.49, CI95% 0.40-0.61), so it showed

being effective for preventing ischaemic stroke in patients with AF in clinical practice while the absolute increase in ICH risk was small (HR 1.97, CI95% 1.24-3.13). They also found a 31% decrease in the risk of all-cause mortality with warfarin (HR 0.69, CI95% 0.61-0.77).

Hylek et al.[46] assessed stroke rates in a cohort of 13 559 AF patients; 596 (4.4%) suffered a stroke during 20 months of follow-up. 32% were treated with warfarin, 27% with aspirin and 42% were untreated. Independent factors associated with stroke severity were being untreated, receiving warfarin and having an INR < 2.0, age and heart failure.

In summary, all seven cohort studies demonstrated clinical benefits of VKA over comparators when used for stroke prevention in non-valvular AF patients (Table A2, Annex 2).

3.4.3. Direct oral anticoagulants

3.4.3.1. Mechanism of action of direct oral anticoagulants

DOAC block the activity of one single step in coagulation and they are classified into two classes depending on the mechanism of action; thrombin inhibitors and factor Xa inhibitors (Figure 2).[4] Oral direct thrombin (factor IIa) inhibitors include dabigatran etexilate, a pro-drug which is rapidly absorbed and converted to dabigatran by hydrolysis after its oral administration.[47] Oral direct factor Xa inhibitors include rivaroxaban, apixaban and edoxaban.[4]

Dabigatran (2011), rivaroxaban (2012), apixaban (2013) and edoxaban (2015, not still marketed in Spain, commercialization expected during 2016) have recently received authorization for stroke prevention in non-valvular AF patients. They have predictable pharmacological effects and relatively few drug and food interactions compared with VKA. This feature has allowed them to be developed using fixed doses without the need for routine anticoagulation monitoring.[48] An antidote for dabigatran is already available.[49,50]

3.4.3.2. Scientific evidence on direct oral anticoagulants for stroke prevention

DOAC have shown non-inferiority in stroke prevention compared with warfarin in their respective pivotal clinical trials.[51–54] They have not been

compared in head-to-head clinical trials, but some indirect comparisons have been performed.[55–57] Stroke rates with DOAC are lower than with warfarin, so they may represent valid therapeutic alternatives in non-valvular AF patients.[55–57]

Dabigatran efficacy and safety were assessed through RE-LY clinical trial,[51] which compared two blinded doses of dabigatran (110 mg or 150 mg twice daily) with open-label adjusted-dose warfarin in 18 113 patients with non-valvular AF (mean age 71 years, mean $CHADS_2$ = 2.1). Dabigatran 150 mg was superior to warfarin for stroke prevention. Dabigatran 110 mg was non-inferior to warfarin. Rates of haemorrhagic stroke and ICH were lower with both doses of dabigatran, but gastrointestinal bleeding was increased with dabigatran 150 mg.

Rivaroxaban was assessed in ROCKET-AF clinical trial,[52] which included 14 264 AF patients (mean age 73 years, mean $CHADS_2$ = 3.5) to compare rivaroxaban with warfarin. Rivaroxaban was non-inferior to warfarin in stroke prevention. There was no reduction in rates of mortality or ischaemic stroke, but a significant reduction in haemorrhagic stroke and ICH. Major bleeding was not significantly different between rivaroxaban and warfarin.

Apixaban was assessed in ARISTOTLE clinical trial[53] compared with warfarin in 18 201 patients (mean age 70 years, mean $CHADS_2$ = 2.1). There was a significant reduction in stroke and thromboembolic events by 21% with apixaban, 31% reduction in major bleeding and 11% reduction in

all-cause mortality. Rates of haemorrhagic stroke and ICH were significantly lower with apixaban than with warfarin. Gastrointestinal haemorrhages were similar between the two groups.

ENGAGE AF-TIMI 48 clinical trial[54] included 21 105 AF patients (mean age 72 years, mean $CHADS_2$ = 2.8) and compared two blinded doses of edoxaban once daily (60 mg or 30 mg) with dose-adjusted warfarin. In the intention-to-treat analysis, there was a trend favouring high-dose edoxaban versus warfarin and an unfavourable trend with low-dose edoxaban versus warfarin for stroke prevention. Both edoxaban doses were associated with significantly lower rates of bleeding and cardiovascular mortality.

Changes in utilization of OAC in AF should arise after the authorization of these molecules, although there is still insufficient evidence to recommend one DOAC over another as some patient characteristics, drug compliance, tolerability and cost may be important considerations in the choice of agent.[4]

3.5. Drug utilization studies with real-use data on antithrombotic therapy for stroke prevention

We have seen that most guidelines recommend starting antithrombotic treatment depending on individual risk of suffering a stroke or thromboembolic events and individual risk of bleeding.[4,26] The prevalence for OAC contraindications has been reported in previous studies, being 7.8% up to 20%.[42,58,59] Therefore, OAC use should be around 80-90%.

Nevertheless, the real situation is different. There are several studies which have assessed VKA use in patients with non-valvular AF and have found underuse of these drugs[6,60–62] in AF patients. This is thought to be caused by VKA-associated risk of haemorrhage, multiple interactions (drug-drug, food-drug or alcohol-drug), high inter- and intra-individual variability in INR values because of pharmacogenetic differences and the need of monitoring within a narrow therapeutic INR range and VKA dosage changes associated.[9,59,63,64]

Some authors in Europe have studied OAC utilization in AF patients.[11,58,60] PREFER[11] and GARFIELD[58] studies are both international descriptive studies which assess use of antithrombotics prescribed after AF diagnosis. The study conducted by Scowcroft et al.[60] examined warfarin-treated vs untreated in different age groups.

The three utilization studies are described now and can also be found in Table A3 from Annex 2.

Kirchhof et al.[65] conducted an observational study (PREFER in AF) in 7 243 patients in hospital and PHC settings from seven European countries. They found that over 80% of patients were receiving VKA or DOAC for stroke prevention at baseline (VKA 66.3%, VKA + antiplatelet 11.2%, Dabigatran 6.1%, antiplatelets 11.2% and no antithrombotic treatment 17.7%).

In the observational GARFIELD registry performed in PHC, Kakkar et al.[58] included 10 614 patients and reported that VKA were frequently not used according to stroke risk scores, as they found overuse in patients at low risk and underuse in those at high risk (52.8% patients with $CHADS_2$ = 0-1 and 61.9% with $CHADS_2$ = 2-6 were receiving VKA).

In the study performed with General Practice Research Database (GPRD) data, Scowcroft et al.[60] found warfarin underuse in older than 80 (32% of >80 were receiving warfarin) and in women compared with men with the same stroke risk factors, not explained by increased comorbidity or increased bleeding risk.

There is also a systematic review conducted by Ogilvie et al.[61] that compared current treatment practices for stroke prevention in AF with published guidelines. They analysed 54 studies (clinical trials excluded) on stroke risk stratification or prior stroke. Nine of them stratified by $CHADS_2$ score, and found underuse of OAC in patients with $CHADS_2 \geq 2$ (<70% of

patients were anticoagulated). Twenty-one studies used other risk stratification and 29 included patients who had suffered a previous stroke.

In Spain, some studies on OAC utilization have been conducted in hospital and in PHC settings, with heterogeneous methodologies. The prevalence of use of OAC is approximately 65%, although some of the studies did not estimate stroke risk scores, so anticoagulation might not be always indicated. [6,25,62,66–70]

3.6. Justification of ESC-FA study

Ageing population increases the incidences of AF and stroke, but elderly patients are not generally included in most phase-III randomized clinical trials on anticoagulation. In addition, the number of patients treated with antithrombotics in our setting is unknown, as, to our knowledge, there are no population-based studies published and there are no data about their use in clinical conditions. Moreover, acenocoumarol is the main VKA used in Spain, which has not been studied as much as warfarin, although they are considered equivalents.

Effectiveness of antithrombotics used to prevent stroke and safety issues as haemorrhagic events have not been assessed in real-use conditions in our

population either. Therefore, the net clinical benefit obtained by the patients treated with these drugs is also unknown.

Rate and rhythm control pharmacological therapies employed in AF patients need to be studied in our population too.

It is necessary to estimate all the economic costs originated from AF management after describing drug utilization in this condition and clinical results associated.

At last, due to the marketing authorization of DOAC for stroke prevention in non-valvular AF in the recent years, it is necessary to study their benefits, risks and costs and to compare them with the traditional antithrombotic agents, as DOAC would probably change anticoagulation recommendations in non-valvular AF patients.

All these facts justify the need to conduct the ESC-FA population study.

ESC-FA (effectiveness, safety and costs in atrial fibrillation) study is a population-based retrospective observational cohort study conducted with data from electronic health records from PHC. It is divided in four sub-studies; I to IV, with different objectives. This thesis includes studies I and II.

4. Study hypotheses

4.1. Study I

As ageing population increases incidences of AF and stroke, we expect to find higher proportions of elderly patients treated with VKA than in previous studies, although we are not aware of the real number of overall patients treated with VKA for stroke prevention in our setting.

A positive net clinical benefit of VKA treatment compared with antiplatelets and no antithrombotic treatment would be expected as previous publications have demonstrated the superiority of warfarin preventing stroke compared to antiplatelets or no antithrombotic treatment, and warfarin is considered equivalent to acenocoumarol.

4.2. Study II

A similar therapeutic management of rate and rhythm control to that found in previous publications and according to current guidelines is expected to be found in our setting.

5. Objectives

5.1. Main objective of ESC-FA study

To assess the use of drugs prescribed for non-valvular AF, particularly antithrombotic agents for stroke prevention.

5.2. Specific objectives of Study I

- To describe the antithrombotic management in non-valvular AF before the authorization of DOAC (paper 1)
- To assess antithrombotic effectiveness in real-use conditions, according to stroke rates (paper 2, under review, annex 1)
- To assess antithrombotic safety in real-use conditions, according to major bleeding events rates (paper 2)

5.3. Specific objectives of Study II

To describe rate and rhythm control drugs used in non-valvular AF (paper 3).

6. Methods and results

In order to carry out the studies I and II, the work from study I has been divided in two different articles, 1 and 2. Paper 2 is currently under review and it may be found at annex 1. Study II is presented in paper 3.

6.1. Paper 1

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BMJ Open

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 Effectiveness, Safety and Costs in Atrial Fibrillation (ESC-FA) study is to analyse the drugs used for the management of the disease in real-use conditions, particularly the 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 System for the Improvement of Research in Primary Care (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 co-medication at baseline were similar to those reported for previous studies.

Future plans: The next phase in the ESC-FA study will involve assessing the 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.

Strengths and limitations of this study

- The limitations inherent in these studies are the collection of non-randomised data or missing information. Regarding the possible infraregister of atrial fibrillation diagnosis, we have confirmed that prevalence in our setting is comparable to the prevalence reported in the available literature. Given the inconsistencies found in the pharmacy invoice registers, we had to exclude a high number of patients. We were not sure about the validity of these data and that is why they were excluded. Therefore, 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 (System for the Improvement of Research in Primary Care (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; subsequently the study analyses the effectiveness and safety of these treatments in terms of stroke and haemorrhage rates.

INTRODUCTION

Atrial fibrillation (AF) is the most common form of chronic arrhythmia, with increasing healthcare burden due to an ageing

population and improved survival rate 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 fivefold, and one in five strokes is attributed to this type of arrhythmia.[4]

Management of patients with AF aims to reduce symptoms by means of rate and rhythm control, and the management of concomitant cardiac diseases 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 stroke prevention: 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 the 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 Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke ($CHADS_2$)[7 8] and Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, Stroke, Vascular disease, Age 65-74, female Sex (CHA_2DS_2-VASc)[1 9] scores, and bleeding risk with the Hypertension, Abnormal kidney and/or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs and/or alcohol (HAS-BLED) score.[2 10 11]

Net clinical benefit of antithrombotic prophylaxis in patients with AF has been demonstrated in some studies.[12 13] However, studies on OAC conducted in our setting indicate underuse[3 5 14–17] that is possibly due to the VKA risk for bleeding; significant interactions with other drugs, food and alcohol; need for frequent INR monitoring and the high interindividual and intraindividual variability in INR.[1 4] In fact, the current number of patients with AF under antithrombotic treatment in our setting is unknown. Also, no data on the adequacy of prescriptions 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 Effectiveness, Safety and Costs in Atrial Fibrillation (ESC-FA) study.

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

The study is divided into four different phases. The specific objectives of phase I are: (1) to describe the antithrombotic management of 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 antithrombotics use 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 in effectiveness, safety and costs associated with the introduction of a 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 of ≥18-year-old individuals with a diagnosis of non-valvular AF and 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 System for the Improvement of Research in Primary Care (SIDIAP) database. SIDIAP contains anonymised 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 sociodemographic characteristics, health conditions registered as International Classification of Diseases (ICD)10 codes, general practitioners' prescriptions, clinical parameters and toxic habits; (2) laboratory data; (3) prescriptions and their corresponding pharmacy invoice data that are available since 2005, with information on all pharmaceutical products dispensed by community pharmacies for Catalan Health System prescriptions, by Anatomic Therapeutic Chemical Classification System (ATC) codes; (4) the CMBD-AH database that 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 by 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 an 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; Mortalidad en áreas pequeñas Españolas y Desigualdades socioEconómicas y Ambientales (MEDEA) Index (deprivation index which shows the social or material disadvantage accruing to a person or group in accordance to their city/region/country, as given in the census data in Catalonia. The higher this is, the worse the deprivation[23]; smoking status (last register before diagnosis); alcohol intake (last register before diagnosis); body mass index (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 given as ICD10 codes specified in the ICD10 codes list; see online 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; see online supplementary file); concomitant drug therapy of interest registered in the pharmacy invoice 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 listed as ATC codes specified in the ATC codes list; see online 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; see online 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 taken 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 annualised rate of thromboembolic events prevented minus the annualised rate of intracranial haemorrhages (ICHs) induced multiplied by a weighting factor of 1.5; this reflects the relative impact, in terms of disability, of an ICH while receiving VKA (studied with warfarin) versus experiencing an ischaemic stroke while not receiving VKA:

$$\text{Net clinical benefit} = (\textit{st}\text{roke rate off} - \text{VKA} - \text{stroke rate on} - \text{VKA}) - 1.5 \times (\text{ICH rate on} - \text{VKA} - \text{ICH rate off} - \text{VKA})$$

Statistical analysis

Descriptive statistics were used to summarise the data. Categorical variables were expressed as frequencies (percentage) and quantitative variables as mean (SD) or median (IQR) for non-normally distributed variables. The differences between cohorts were tested using analysis of variance or Kruskal-Wallis test, χ^2 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 sociodemographic 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 who change from one cohort to another during the follow-up and censoring according to the patient's change of cohort.

All statistical tests were two-tailed using a significance level of 5%. The analyses were performed using Stata V.11 (Stata Corp, Collage Station, Texas, USA) and R V.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.

Regarding the data contained in the databases and as per 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 anonymised and identified by an internal code, which makes it impossible to identify the individuals included. Thus, it is not necessary to ask for informed consent from the participants. Each individual is identified through an encrypted, anonymised 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=1755) and patients with ≥3 different antithrombotic drugs registered (n=1261), as this is a group that is 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 5724 (25.3%) of patients with no antithrombotic treatment registered at baseline. The most prescribed treatment were VKA (9057 patients, 40.1%), followed by platelet aggregation inhibitors (7424, 32.9%). The remaining patients were initiated on VKA + antiplatelet (1.0%) or on dabigatran (0.7%).

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

The baseline characteristics of our patients, including percentages of patients with missing data, are described in tables 1–4.

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; however, 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.

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); 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 dyslipidaemia. Coronary artery disease was found in 34.8% of the patients in the VKA + antiplatelet cohort, with a high frequency of previous myocardial infarction. Non-treated individuals had better estimated glomerular filtration rate (eGFR) than patients initiated on antithrombotic therapy, except for dabigatran (84.4% of dabigatran patients had eGFR >60 mL/min/1.73 m^2). However, there were more missing values in that group.

Disease control parameters and laboratory data of interest are described in table 3. Around two-thirds of patients had good control of BP, glycated haemoglobin and low-density lipoprotein cholesterol levels without differences between cohorts.

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

All baseline sociodemographic characteristics and comorbidities were significantly different among the five groups.

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

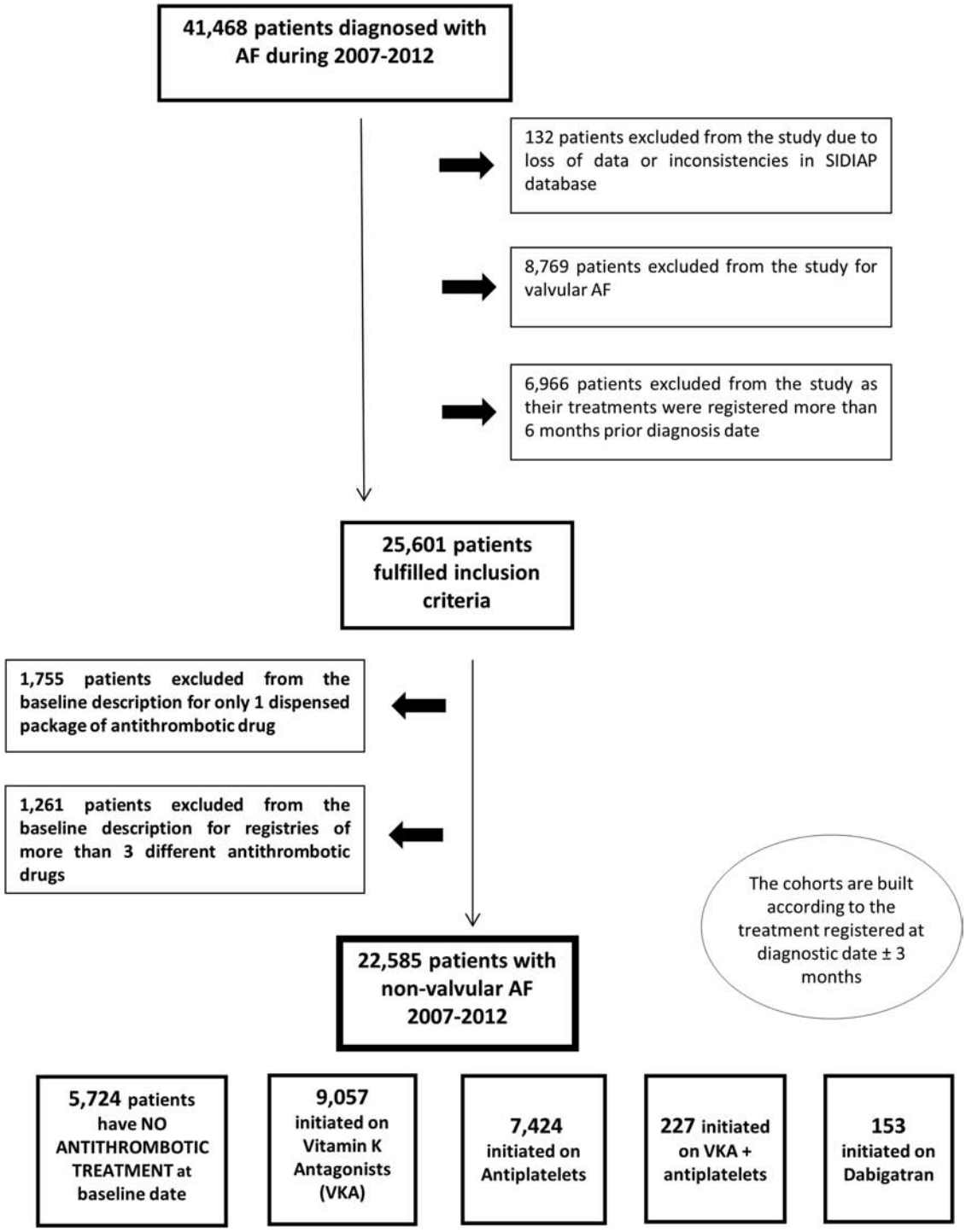

Figure 1 Study flow chart. Patients included and excluded from the study. AF, atrial fibrillation; SIDIAP, System for the Improvement of Research in Primary Care; VKA, vitamin K antagonist.

that was in use under clinical conditions in Catalonia. In this article, we report the baseline sociodemographic and clinical characteristics of 22 585 patients with non-valvular AF 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-randomised 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),

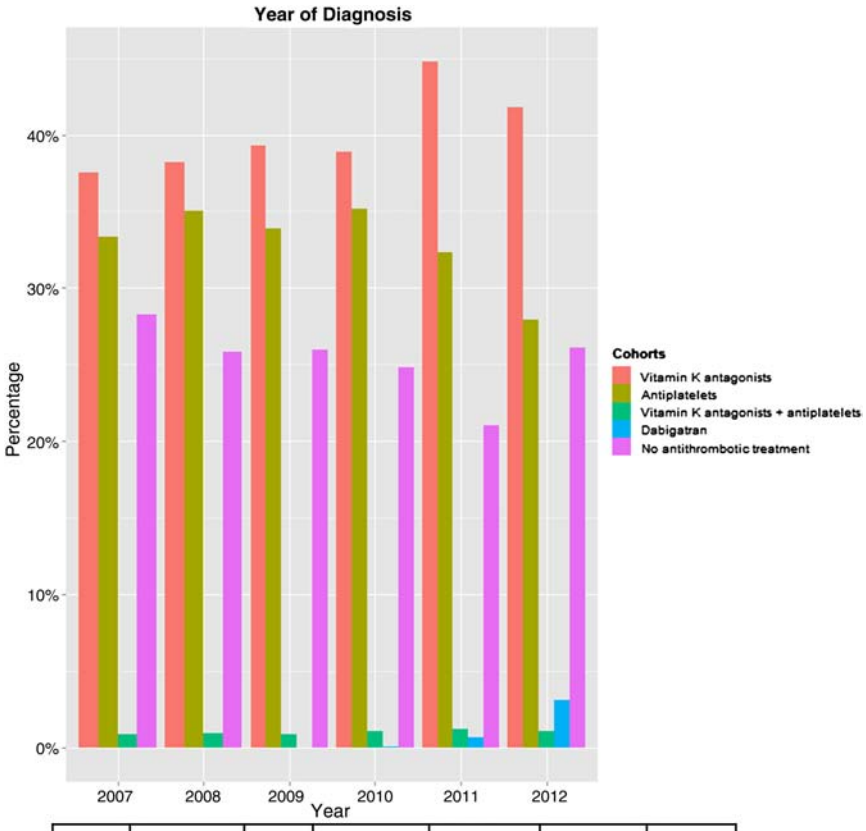

Figure 2 Distribution of new diagnoses of atrial fibrillation (AF) per year and cohort. Percentage of patients newly diagnosed with AF per year in each cohort in the figure, number of patients in the table below. Vitamin K antagonists (VKA; n=9057); antiplatelets (n=7424); VKA + antiplatelet (n=227); dabigatran (n=153); no antithrombotic treatment (n=5724).

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

complete sociodemographic 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 can be used in epidemiological studies in our setting. More specifically, the diagnosis of AF has been validated in our population in the study published by García-Gil Mdel *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 from the 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 1261 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 another 1755 patients from the baseline description of the cohort because they only had one package of antithrombotic medication 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

Table 1 Sociodemographic characteristics and cardiovascular, stroke and bleeding risk factors

n=22 585	No antithrombotic treatment 5724	VKA 9057	Antiplatelet agents 7424	VKA + antiplatelet 227	Dabigatran 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/m^2; 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

BMI, body mass index; VKA, vitamin K antagonists.

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 sociodemographic characteristics, the proportion of men and women in our study is quite balanced (51.6% of men) and this is similar to that in prior registries.[15 27 28]

We found that patients treated with any antithrombotic drug are older, have more comorbidity at baseline and receive more co-medication than non-treated individuals. In agreement with similar studies, we found high prevalence of hypertension, dyslipidaemia, diabetes mellitus and heart failure in all patients with AF.[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 patients with non-valvular AF at baseline is similar to those in other studies.

Kirchhof *et al*[29] conducted an observational study (PREvention oF thromboemolic events—European Registry in Atrial Fibrillation, PREFER-AF) including 7243 patients in seven European countries between January 2012 and January 2013. In the cross-sectional

Table 2 Baseline comorbidities

n=22 585	No antithrombotic treatment 5724	VKA 9057	Antiplatelet agents 7424	VKA + antiplatelet 227	Dabigatran 153
Cardiovascular comorbidity (%)					
Hypertension	48.1	65.1	59.5	67.8	64.1
Years of evolution (mean, 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 (mean, SD)	6.9	6.9	6.4	6.5	9.4
Dyslipidaemia	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/1.73 m^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

eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; TIA, transitory ischaemic attack; VKA, vitamin K antagonists.

Table 3 Disease control parameters and laboratory data

n=22 585	No antithrombotic treatment 5724	VKA 9057	Antiplatelet agents 7424	VKA + antiplatelet 227	Dabigatran 153
BP					
Systolic BP (mean, SD)	132.5 (19.3)	133.3 (18.5)	133.5 (18.4)	132.3 (18.3)	131.6 (17.7)
Diastolic BP (mean, 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 mm Hg; %)	64.6	61.5	61.3	63.7	65.9
Missing values	*22.5*	*6.8*	*10.0*	*5.3*	*11.8*
HbA1c (mean, 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, per cent of 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*

BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; c-LDL, low-density lipoprotein-cholesterol; VKA, vitamin K antagonists.

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

n=22 585	No antithrombotic treatment 5724	VKA 9057	Antiplatelet agents 7424	VKA + antiplatelet 227	Dabigatran 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
β-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

ARB, angiotensin receptor blockers; NSAID, non-steroidal anti-inflammatory drugs.

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 as yet.

Kakkar *et al*[30] conducted the GARFIELD study in different primary care settings, which described VKA prescription in 45.2% of patients with AF, 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 patients with AF from the General Practice Research Database, diagnosed with AF between 2000 and 2009. They found differences in VKA prescription

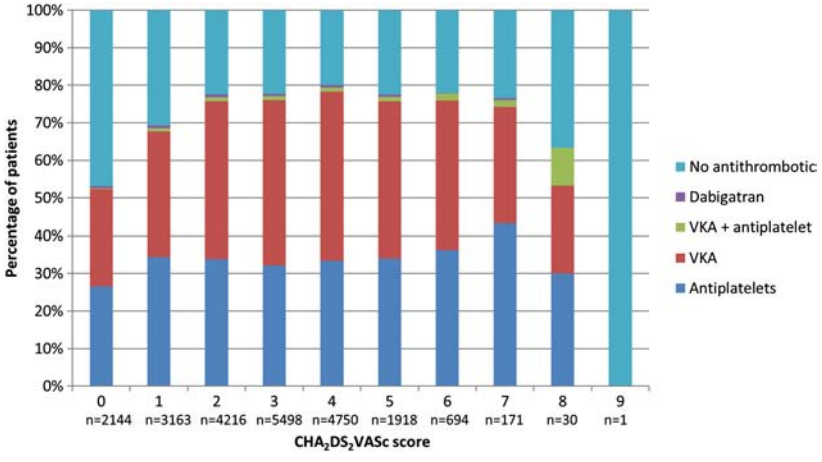

Figure 3 CHA_2DS_2VASc scores in the treatment cohorts. Percentage of patients from each cohort by stroke risk according to CHA_2DS_2VASc score. VKA, vitamin K antagonist.

according to the age group: in the 60–69 years age group, VKA was prescribed to 57% of the patients; in the 70–79 years age group, 55% of patients were receiving VKA; and only 32% of patients older than 80 years 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; 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, by 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 patients with non-valvular AF in Catalonia.

Age, gender and comorbidity in patients with non-valvular AF 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 as its approval for use in patients with AF 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 patients with non-valvular AF in Catalonia due to modifications in antithrombotic treatment during follow-up and the introduction of the new OAC.

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Contributors RM, DC, XC were involved in study design. MG-S, CVU, RM were involved in writing and editing the manuscript. JM[a]E was involved in data extraction from SIDIAP. AR-L was involved in statistical analysis. MG-S, CVU, RM, DC, XC, IF-G, ATM, ED, MC, BB, CV were involved in review and final approval of the manuscript. This article is part of the article compendium for the PhD thesis of MG-S.

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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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Notes

6.2. Paper 3

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Drug Therapy for Rate and Rhythm Control in Nonvalvular Atrial Fibrillation: A Cross-sectional Study With Electronic Health Records in a Primary Care Cohort

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ABSTRACT

Purpose: The purpose of this study is to describe the pharmacologic management of rate and rhythm and assess which factors are associated with the prescription of these drugs in patients with nonvalvular atrial fibrillation (AF) from the Effectiveness, Safety, and Costs in Atrial Fibrillation study.

Methods: This retrospective, cross-sectional study describes the pharmacologic rate and rhythm control management strategies adopted during 2012 in all patients diagnosed as having nonvalvular AF in 2007 to 2011. The data source is the Information System for the Improvement of Research in Primary Care database, which is based on primary care electronic health records. To answer the study objectives, 3 multivariate regression models to assess the independent factors associated with the prescription of these drugs were conducted for 2012. The rate and rhythm control drugs assessed were β-blockers, nondihydropyridine calcium channel blockers, antiarrhythmic agents, and digoxin.

Findings: A total of 21,304 patients were diagnosed as having nonvalvular AF; 11,638 (54.6%) had at least one heart rate measure during 2012. Of them, 7777 (66.8%) received one or more rate and/or rhythm control drugs during 2012. Most patients (5751 [73.9%] of 7777) received only one drug for rate and/or rhythm control. Rate control agents were the most frequently used in 2012, with β-blockers the most prescribed group (4091 patients [52.6%]). A variety of different variables were associated with the prescription of rate and/or rhythm control drugs in the multivariate regression models.

Implications: The most used pharmacologic treatment of rate and rhythm control in our AF population is β-blockers, indicating that a rate control strategy is preferred in our setting, as widely recommended. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: adrenergic β-antagonists, antiarrhythmia agents, atrial fibrillation, electronic health records, heart rate, rate control drugs.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent chronic arrhythmia, with an estimated prevalence of 1.5% to 2% of the general population in the developed world.[1,2]

Long-term general management of patients with AF aims to reduce symptoms and prevent complications through rate and rhythm control, management of concomitant cardiac diseases, and prevention of stroke and thromboembolic events.[3]

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Several studies in patients with AF have compared the strategy of rhythm control with the strategy of heart rate (HR) control.[4–7] The rhythm control strategy consists of cardioversion and treatment with antiarrhythmic drugs, such as flecainide or amiodarone, to maintain sinus rhythm. It can improve symptoms and reduce the incidence of stroke but may lead to an increased risk of adverse events due to negative inotropic and proarrhythmic effects.[1] Antiarrhythmic agents are not more effective in preventing serious complications and have considerable toxicity.[8]

The rate control strategy, which allows AF to persist, may have fewer adverse events.[4] Ventricular rate control is now widely used as first-line therapy for management of chronic AF. Lenient rate control (resting HR <110 beats/min) is easier to achieve and appears to be as effective as strict rate control (resting HR <80 beats/min).[9] Adrenergic β-antagonists or nondihydropyridine calcium channel blockers are the initial choice for ventricular rate control in most patients; sometimes digoxin can be added.[2,10]

The Effectiveness, Safety, and Costs in Atrial Fibrillation (ESC-FA) study was designed to describe AF management. As the population ages, AF and stroke incidences increase,[1] but elderly patients are not usually included in clinical trials. Population studies of the pharmacologic management of AF and the use of oral anticoagulants (OACs) and vitamin K antagonists (acenocoumarol instead of warfarin, which has been evaluated in most clinical trials) have not been described in our setting, and the recent approval of new OACs for stroke prevention in nonvalvular AF may be introducing changes in the management of the disease.

The ESC-FA study is divided into 4 phases. The specific objectives of Phase I are to describe the antithrombotic management in AF in our setting, to assess the effectiveness of antithrombotic agents in real-use conditions according to stroke rates, and to assess the tolerability of antithrombotics according to bleeding event rates. The specific objective of Phase II is to describe rhythm and rate control management. The specific objective of Phase III is to estimate costs of the general management of nonvalvular AF in our setting. The specific objective of Phase IV is to assess how the introduction of new OACs affects treatment changes, effectiveness, tolerability, and costs. The objective of this article is to describe rate and rhythm control management and assess which factors are associated with the prescription of these drugs in patients with nonvalvular AF in the ESC-FA study cohort (Phase II).

PATIENTS AND METHODS

Study Design

This is a population-based, retrospective, cross-sectional study that describes the pharmacologic management of rate and rhythm in 2 different moments during the study period (at baseline, defined as time of diagnosis, and during the year 2012) in all patients with nonvalvular AF diagnosed between 2007 and 2011 at all primary care practices of the Catalan Health Institute (ICS). The ICS is the main provider of health services in Catalonia, and it manages 274 primary care practices, including 5,835,000 patients (80% of the Catalan population, or >10% of the Spanish population).

Data Source

The data source is the Information System for the Improvement of Research in Primary Care (SIDIAP) database, which contains anonymized clinical information that originates from different data sources[11–15]: (1) eCAP (electronic health records in primary care of the ICS), which includes information since 2006 on sociodemographic characteristics, health conditions registered as *International Classification of Diseases, Tenth Revision* (ICD-10) codes, general practitioners' prescriptions, clinical parameters, and toxic habits; (2) laboratory data; (3) prescriptions and their corresponding pharmacy invoice data (available since 2005), including information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions by ATC codes; and (4) the Conjunto Mínimo de Datos Básicos al Alta Hospitalaria (CMBD-AH) database, which includes diagnoses at hospital discharge registered as *International Classification of Diseases, Ninth Revision* (ICD-9) codes.

Study Population

The study included all patients aged >18 years with a new diagnosis of nonvalvular AF registered in 2007 to 2011, with at least one record of HR measure in the SIDIAP database during 2012.

Patients with valvular AF and patients without HR measures registered during 2012 were excluded from the study.

Study Variables

Information on the following variables was collected: sex, age at diagnosis, 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), HR (highest value registered during all of 2012), comorbidities of interest registered before AF diagnosis (as ICD-9 and ICD-10 codes), cardioversion during the study period (ICD-9 code), and the following drug therapies (as ATC codes): drugs for rate and rhythm control, antithrombotic agents, and concomitant drug therapy of interest (all of them registered in the pharmacy invoice database at the time of diagnosis [considering a period of ±3 months between diagnosis date and treatment date] and during 2012).

The HR measures are registered in a specific site in the electronic health records. The method of measuring HR is unknown. We classified the patients into 2 subgroups, according to their HR values (<100 or ≥100 beats/min), to compare their baseline characteristics, considering ≥100 beats/min as a high HR.

For diagnoses of type 2 diabetes mellitus (DM), dyslipidemia, and coronary artery disease (CAD), patients were included if the ICD-10 code was registered in the database and/or if they had records in the pharmacy invoice database for antidiabetic agents and/or insulin, statins, or other lipid-lowering drugs and nitrates, respectively.

The independent variables for the multivariate regressions were sex, age, hypertension, DM, dyslipidemia, peripheral artery disease, CAD, heart failure (HF), chronic kidney disease, HR, and treatment with OACs, antiplatelets, and drugs affecting the renin-angiotensin system (eg, angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blocker [ARB]).

The dependent variables for the multivariate regressions were the prescription of the drugs from the next pharmacologic groups: (1) β-blockers (adrenergic β-antagonists) and nondihydropyridine calcium channel blockers, verapamil, and diltiazem as rate-reducing drugs; (2) antiarrhythmic agents, classes Ic and III, used to control heart rhythm (amiodarone, flecainide, dronedarone, disopyramide, hydroquinidine, mexiletine, propafenone); and (3) digoxin.

Statistical Analysis

Baseline characteristics were compared between HR groups using the χ^2 test for the dichotomous variables and the t test for the continuous ones. Medication use at baseline and 2012 was compared using the McNemar test for paired proportions. Statistical significance was set at 0.05.

To assess the independent factors associated with the prescription of the different drugs used for rate and rhythm control, we conducted 3 multivariate regression analyses for the 3 therapeutic groups prescribed in 2012, using logistic regression models to find out the independent study variables (demographic, comorbidities, HR, and other treatments) associated with the fact of being treated with each of the 3 types of drugs for rate and rhythm control. For each drug group, we computed bivariate and multivariate models. The multivariate models were built using a stepwise procedure.

All the analyses were performed using R, version 3.0.2, and Stata/SE, version 13, for Windows (Stata Corp, College Station, Texas).

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 the SIDIAP are always anonymized and identified by an internal code, which makes it impossible to identify the individuals included. Thus, it is not necessary to ask for informed consent from the participants. Each patient is identified through an encrypted, anonymized code.

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

Table I. Baseline characteristics of patients diagnosed as having atrial fibrillation during 2007-2011, according to HR values measured in 2012.

Characteristic	Patients With HR <100 beats/min (n=10,349)	Patients With HR ≥100 beats/min (n=1289)	P*
Sociodemographic data			
Sex, %			0.021
Female	49.1	52.5	
Male	50.9	47.5	
Age			
Mean (SD), y*	72.7 (11.0)	72.3 (11.4)	0.145
>75 years old, %	47.9	46.7	0.425
BMI			
Mean (SD), kg/m^2	29.8 (5.1)	30.4 (5.4)	<0.001
BMI ≥30 (obesity), %	43.6	48.8	0.001
Missing values, %	20.8	18.9	
Smoking status, %			0.080
Nonsmoker	70.4	70.0	
Current smoker	10.6	12.6	
Ex-smoker	19.0	17.3	
Missing values	18.1	17.7	
Alcohol intake, %			0.775
Nonconsumer	69.5	68.7	
Mild-moderate	28.0	28.5	
Alcohol abuse	2.5	2.9	
Missing values	29.7	29.9	
HR, mean (SD), beats/min	76.5 (11.8)	111.5 (13.6)	
Comorbidities, %			
Hypertension	65.9	64.8	0.440
Type 2 DM†	22.1	25.3	0.009
Dyslipidemia†	47.8	46.2	0.271
Peripheral artery disease	1.2	0.9	0.415
Coronary artery disease†	8.0	5.5	0.002
Heart failure	7.7	8.3	0.456
Chronic kidney disease	4.8	5.3	0.419

BMI = body mass index; DM = diabetes mellitus; HR = heart rate.
*Comparison of proportions using the χ^2 test, except for age; means compared by the *t* test.
†International Classification of Diseases, Tenth Revision (ICD-10) code or specific pharmacologic agents.

RESULTS

A total of 21,304 patients with a nonvalvular AF diagnosis registered during 2007 to 2011, and 11,638 (54.6%) had at least one HR determination during 2012. Their mean (SD) age was 72.7 (11.1) years, and 50.5% of them were men.

Of the 11,638 patients included, 3853 (33.1%) had only one HR measure, 2579 (22.2%) had 2 measures, and 5206 (44.7%) had ≥3 measures. Most of the patients, 10,349 (88.9%) had HR values <100 beats/min during 2012. In 671 patients (5.8%), cardioversion was applied as a rhythm control strategy during the study period.

Table II. Medication prescribed at baseline and during 2012 to 7777 patients diagnosed as having atrial fibrillation during 2007-2011.

Medication	Treatments at Baseline*	Treatments in 2012	P†
Rate and rhythm control treatments, %			
β-Blockers	37.8	52.6	<0.001
Verapamil	2.2	2.2	0.856
Diltiazem	10.2	12.1	<0.001
Amiodarone	22.2	16.7	<0.001
Flecainide	7.6	11.4	<0.001
Dronedarone	0.9	1.9	<0.001
Other antiarrhythmic agents	3.2	3.2	0.732
Digoxin	26.0	30.7	<0.001
No rate and rhythm control treatment	18.3	0	
Co-treatments			
Oral anticoagulants	56.2	67.9	<0.001
VKAs	55.6	64.7	<0.001
New OACs	0.8	4.7	<0.001
Antiplatelets	32.5	30.7	0.002
Aspirin	29.9	28.0	0.001
Other antiplatelets	3.9	4.0	0.909
No antithrombotic treatment	18.9	8.4	<0.001
ACEIs	30.6	30.2	0.370
ARBs	23.7	27.8	<0.001

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; OACs = oral anticoagulants; VKAs = vitamin K antagonists.
*Baseline refers to the date of atrial fibrillation diagnosis (2007-2011).
†Comparison of paired proportions using the McNemar test.

Table I gives the baseline characteristics of the patients included. We present their characteristics according to HR values in 2012. The group with HRs ≥100 beats/min had a higher percentage of women, obese patients, and patients with type 2 DM than in the group with HRs <100 beats/min and a lower percentage of patients with CAD. There were no other significant differences.

At the time of diagnosis, 4283 (36.8%) of the patients included were not taking rate or rhythm control drugs. During 2012, 7777 patients (66.8%) received treatment for rate and/or rhythm control, and 3861 (33.2%) patients were not receiving these treatments. The drugs for rate and rhythm control, stroke prevention, and other co-treatments prescribed at baseline and during 2012 in these 7777 patients are listed in Table II.

Of these 7777 patients, 5751 (73.9%) received only one drug (Figure 1), with β-blockers the most frequently used drug, and 2026 (26.1%) received more than one drug for rate and/or rhythm control (Figure 2). The most frequent combinations in these patients were β-blockers and digoxin, β-blockers and amiodarone, and β-blockers and flecainide. In the first multivariate model (Table III), hypertension, dyslipidemia, CAD, HF, OAC treatment, antiplatelet treatment, and ACEI plus ARB treatments were associated with the use of β-blockers and nondihydropyridine calcium channel blockers during 2012. Male sex or increasing age were not associated with the prescription of these drugs.

In the second multivariate model for antiarrhythmic agents (Table IV), we found a positive association between dyslipidemia, OAC treatment, and antiplatelet treatment and the use of these drugs, and an inverse association between male sex, age,

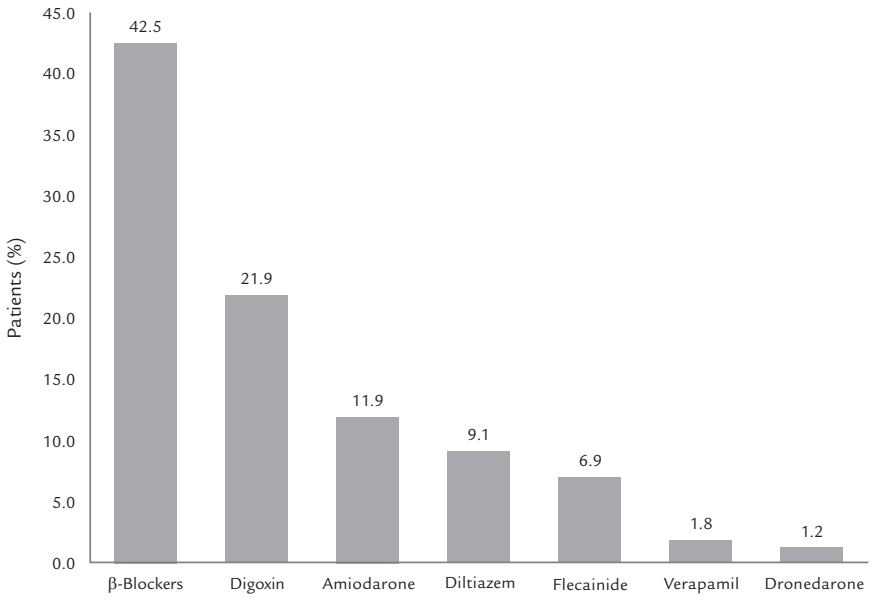

Figure 1. Frequencies of rate and rhythm control treatments used as monotherapy in 2012. Of the 7777 patients receiving drug therapy for rate and/or rhythm control, 5751 (73.9%) were treated with monotherapy.

hypertension, type 2 DM, HF, and HR and the use of these antiarrhythmics. In the third multivariate model for digoxin (Table V), we observed a positive association between age, type 2 DM, HF, HR, OAC treatment, and antiplatelet treatment and the use of digoxin and an inverse association with male sex, hypertension, dyslipidemia, and chronic kidney disease.

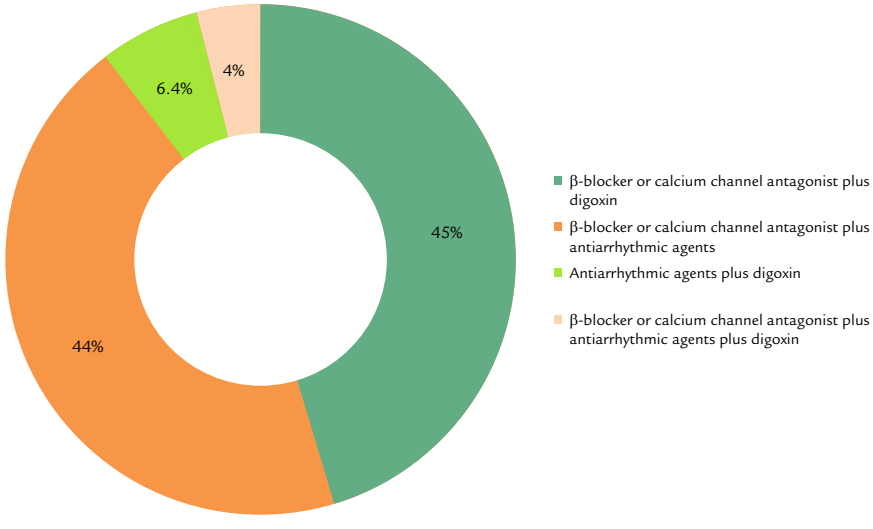

Figure 2. Percentage of patients treated with each combination during 2012. Of the 7777 patients, 2026 (26.1%) were receiving more than one drug for rate and/or rhythm control.

Table III. Independent factors associated with prescription of β-blockers and nondihydropyridine calcium channel blockers in 7777 patients diagnosed as having atrial fibrillation in 2007-2011 and receiving these rate and/or rhythm control therapies during 2012.

	Bivariate model		Multivariate model	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	0.89 (0.82–0.95)	0.001	0.77 (0.71–0.84)	<0.001
Age*	0.92 (0.90–0.93)	<0.001	0.86 (0.84–0.88)	<0.001
Hypertension	1.27 (1.17–1.37)	<0.001	1.13 (1.03–1.23)	0.009
Type 2 DM	1.11 (1.01–1.21)	0.023		
Dyslipidemia	1.52 (1.41–1.63)	<0.001	1.31 (1.21–1.41)	<0.001
Peripheral artery disease	1.29 (0.92–1.81)	0.146		
Coronary artery disease	1.84 (1.60–2.11)	<0.001	1.69 (1.46–1.96)	<0.001
Heart failure	1.60 (1.40–1.84)	<0.001	1.63 (1.41–1.88)	<0.001
Chronic kidney disease	0.91 (0.76–1.08)	0.265		
Heart rate	1 (0.99–1.03)	0.514		
Heart rate ≥100 beats/min†	1.17 (1.04–1.31)	0.009		
OAC treatment	2.05 (1.90–2.22)	<0.001	2.73 (2.46–3.03)	<0.001
Antiplatelet treatment	0.87 (0.80–0.94)	<0.001	1.60 (1.44–1.78)	<0.001
ACEI plus ARB treatment	1.65 (1.53–1.78)	<0.001	1.45 (1.34–1.58)	<0.001

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DM = diabetes mellitus; OAC = oral anticoagulant; OR = odds ratio.
*Per each 5 years.
†Per each 10 beats/min.

DISCUSSION

Phase II of the ESC-FA study describes HR and rhythm management in patients with nonvalvular AF in Catalonia through a cross-sectional design. We describe 11,638 patients, 66.8% of them treated with rate and rhythm control drugs during 2012 and most of them with HR values <100 beats/min.

The most important limitation of the study is the lack of information about the condition regarding the heart rhythm of our patients. This information is not usually registered in electronic health records, so it is an inherent limitation of studies conducted in this type of databases. At the time of diagnosis, patients may present with an episode of arrhythmia, but we are not able to ascertain how many patients continued to have AF or how many patients whose heart rhythm is normal (sinus rhythm) in 2012.

Regarding rate and rhythm control treatments, 36.8% of patients were not given any of these drugs at baseline, which may indicate that they were under sinus rhythm and did not need a prescription for rhythm control drugs. However, as we pointed out before, we do not have this information.

During 2012, 33.2% of patients were not receiving any rate or rhythm control treatment. However, we cannot evaluate why they did not receive these treatments because we do not know their rhythm status.

Nevertheless, the main objective of this study was to describe the pharmacologic management of rate and rhythm in patients with AF under clinical conditions in our setting in a definite moment through a cross-sectional design.

Another important limitation of the study is the low number of HR measures registered per patient because SIDIAP database only allows the extraction of HR measures codified in a specific section and not the HR measures registered as text. With the inclusion of patients with at least one measure of HR during 2012, we only describe 11,638 patients (53.4%) diagnosed as having AF. If we had included patients with at least 2 measures, we could only have described 7788 patients (36.7%). Therefore, we included all patients

Table IV. Independent factors associated with prescription of amiodarone, flecainide, dronedarone and other antiarrhythmic agents in 7777 patients diagnosed as having atrial fibrillation in 2007-2011 and receiving these rate and/or rhythm control therapies during 2012.

	Bivariate model		Multivariate model	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	0.96 (0.88–1.05)	0.410	0.70 (0.64–0.77)	<0.001
Age*	0.81 (0.79–0.82)	<0.001	0.79 (0.77–0.80)	<0.001
Hypertension	0.73 (0.66–0.80)	<0.001	0.88 (0.80–0.98)	0.016
Type 2 DM	0.78 (0.70–0.87)	<0.001	0.82 (0.73–0.93)	0.001
Dyslipidemia	1.19 (1.09–1.30)	<0.001	1.17 (1.06–1.28)	0.001
Peripheral artery disease	0.73 (0.46–1.16)	0.181		
Coronary artery disease	1.06 (0.90–1.25)	0.479		
Heart failure	0.63 (0.52–0.76)	<0.001	0.78 (0.64–0.95)	0.013
Chronic kidney disease	0.81 (0.65–1.01)	0.061		
Heart rate	0.87 (0.85–0.90)	<0.001	0.87 (0.85–0.90)	<0.001
Heart rate ≥100 beats/min†	1.00 (0.87–1.15)	0.979		
OAC treatment	0.97 (0.89–1.06)	0.542	1.69 (1.50–1.91)	<0.001
Antiplatelet treatment	1.38 (1.25–1.51)	<0.001	1.83 (1.62–2.07)	<0.001
ACEI plus ARB treatment	0.97 (0.89–1.06)	0.553		

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DM = diabetes mellitus; OAC = oral anticoagulant; OR = odds ratio.
*Per each 5 years.
†Per each 10 beats/min.

with HR measures to report the maximum number of patients and the real situation in our setting.

As indicated in Table II, there were differences between 2012 and diagnostic time for the 7777 patients treated. The most frequent prescription of rate control drugs, such as β-blockers, diltiazem, or digoxin, in 2012 may be due to the choice of this strategy as recommended for chronic AF.[6,7,9,10] Flecainide was introduced in the guidelines in our setting in 2011 as first-line treatment for pharmacologic cardioversion, which may be the reason for the increase in its prescription. Amiodarone might be more prescribed at baseline if the patients had atrial fibrillation, but, as noted, we do not know their rhythm status.

Regarding antithrombotic treatments, OACs are more frequently used, whereas the use of antiplatelets and nonantithrombotic alternatives has been slightly reduced in 2012. Current available evidence reveals OAC superiority over antiplatelets and nonantithrombotics in preventing stroke and thromboembolic events,[1,16–18] so changes in guidelines for stroke prevention may be causing these prescription changes.

Of these 7777 patients treated with rate and/or rhythm control agents, most received only one drug, with β-blockers the most frequently used drug (Figure 1). The rest of the patients received more than one drug for rate or rhythm control (Figure 2). In both groups, β-blockers are the most commonly prescribed medicines, so the most frequent strategy in our population is the rate control strategy, which is now recommended and widely used as first-line therapy for management of chronic AF.[6,7,9,10]

Different independent factors were associated with the prescription of the different pharmacologic groups used for rate and rhythm control, as found in the multivariate regression analyses (Tables III, IV, and V). The strongest factor associated with β-blockers, verapamil, or diltiazem treatment was OAC use, followed by CAD, HF, antiplatelet use, ACEI plus ARB treatments, dyslipidemia, and hypertension.

Table V. Independent factors associated with prescription of digoxin in 777 patients diagnosed as having atrial fibrillation in 2007-2011 and receiving this rate and/or rhythm control therapy during 2012.

	Bivariate model		Multivariate model	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	0.59 (0.54–0.65)	<0.001	0.70 (0.63–0.77)	<0.001
Age*	1.21 (1.19–1.24)	<0.001	1.19 (1.16–1.22)	<0.001
Hypertension	1.10 (1.00–1.21)	0.049	0.87 (0.78–0.96)	0.006
Type 2 DM	1.30 (1.17–1.44)	<0.001	1.27 (1.14–1.42)	<0.001
Dyslipidemia	0.82 (0.75–0.90)	<0.001	0.79 (0.72–0.87)	<0.001
Peripheral artery disease	0.92 (0.60–1.42)	0.717		
Coronary artery disease	1.12 (0.95–1.32)	0.184		
Heart failure	2.75 (2.39–3.17)	<0.001	2.31 (1.99–2.68)	<0.001
Chronic kidney disease	0.80 (0.64–1.00)	0.053	0.60 (0.48–0.76)	<0.001
Heart rate	1.19 (1.16–1.22)	<0.001	1.17 (1.14–1.20)	<0.001
Heart rate ≥100 beats/min†	1.86 (1.64–2.12)	<0.001		
OAC treatment	2.47 (2.23–2.74)	<0.001	2.61 (2.28–2.99)	<0.001
Antiplatelet treatment	0.64 (0.58–0.71)	<0.001	1.16 (1.01–1.33)	0.037
ACEI plus ARB treatment	1.18 (1.07–1.29)	<0.001		

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DM = diabetes mellitus; OAC = oral anticoagulant; OR = odds ratio.
*Per each 5 years.
†Per each 10 beats/min.

The first choices for rate control management in patients with associated diseases, such as hypertension or CAD, are β-blockers, verapamil or diltiazem. For HF, the recommendations include β-blockers and digoxin.[2,10] A few variables were strongly associated with antiarrhythmic drugs use. There was no positive association with male sex, age, hypertension, type 2 DM, HF, and HR. The lack of association with variables included in the multivariate model may indicate that these drugs are frequently prescribed for the reversion of the arrhythmia so their prescription is not related to patient characteristics. The lack of association with age may indicate that they are most frequently prescribed in younger patients. In fact, rhythm control is more frequently prescribed in symptomatic patients, those <65 years old, and those with no hypertension or HF.[2]

The strongest factors associated with digoxin use were OAC use, HF, DM, age, HR, and antiplatelet use. Digoxin is the recommended rate control drug in patients with inactive lifestyle (elderly people, associated comorbidities) or with HF, and it can be added to β-blockers or to calcium channel blockers in patients with uncontrolled ventricular rates.[3] Digoxin was inversely associated with chronic kidney disease. In fact, it should be used cautiously in these patients.[2,3]

Apart from the limitations indicated above regarding rhythm condition and the number of HR measures registered in the database, this study is subject to certain limitations inherent in all observational studies conducted with databases based on electronic health records, such as the collection of nonrandomized data, missing information, and possible confounders. These limitations are normally minimized with the use of appropriate statistical techniques, such as multivariate regression models adjusted for sociodemographic characteristics and possible confounders and predictive factors. The strengths of the study are the large number of patients included, representativeness of the general population, complete sociodemographic and clinical records, and real clinical practice data.

CONCLUSIONS

In conclusion, we describe the pharmacologic management of rate and rhythm control in our population diagnosed as having AF; rate control drugs were the most frequently prescribed during 2012. Most patients (73.9%) received only one drug for rate or rhythm control. The rest of the patients (26.1%) received more than one drug. The principal pharmacologic alternative in both groups was β-blockers, probably indicating that rate control strategy is the most frequent alternative used, as widely recommended as first-line therapy for management of chronic AF.

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AUTHOR CONTRIBUTIONS

Rosa Morros and Dolors Capellà designed the whole ESC-FA study.

Maria Giner-Soriano, Cristina Vedia Urgell and Rosa Morros wrote and edited the manuscript.

Josep Maria Elorza-Ricart (acknowledgements) conducted the data extraction from SIDIAP.

Albert Roso-Llorach and Aina Casellas conducted the statistical analyses.

Maria Giner-Soriano, Albert Roso-Llorach, Cristina Vedia Urgell, Aina Casellas, Ignacio Ferreira-González, Dolors Capellà and Rosa Morros reviewed and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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7. Discussion

7.1. Study I

This is a cohort study which assessed use, effectiveness and safety of antithrombotics for stroke prevention in AF in real-use conditions.

ESC-FA study I is a retrospective observational population-based cohort study on the use, effectiveness and safety of antithrombotic therapy for stroke prevention in patients with non-valvular AF in real-use conditions. We included 22 585 patients newly diagnosed with non-valvular AF during 2007-2012.

Patients were divided into five cohorts according to the antithrombotic treatment prescribed at the time of diagnosis: non-treated, VKA, antiplatelets, dual therapy with VKA and an antiplatelet, and dabigatran. Effectiveness and safety were analysed within the three largest cohorts (n=22 205): VKA, antiplatelets and no antithrombotic treatment.

After AF diagnosis, 41% of patients initiated VKA, 33% initiated antiplatelets, and 26% remained untreated. This frequencies are similar to those in previous similar studies.[6,25,58]

From 2007 to 2012, there was an increase in VKA prescription (from 38% in 2007 to 42% in 2012) and patients initiated with antiplatelets or untreated decreased over the study period.

Age, gender, comorbidities and comedication at baseline were similar to those reported in previous comparable studies. Patients untreated were younger than those with any antithrombotic treatment prescribed after diagnosis.

Generally, treated patients presented more comorbidity and received more comedication than non-treated. The most frequent chronic conditions associated in these patients were hypertension, dyslipidaemia and type 2 DM. The most frequently prescribed drugs were proton-pump inhibitors and other frequent comedications were β-blockers (prescribed in most AF patients for rate control, as seen in study II), ACEI, ARB, diuretics or statins.

With regard to stroke risk stratification, when it was measured by CHA_2DS_2-VASc, there was a decrease in the number of patients with low-moderate risk (scores 0 to 1) and an increase in the number with high risk of stroke (score ≥2), compared to the risk measured by $CHADS_2$, as presented in

Table 4, adapted from Paper 1; showing that CHA_2DS_2-VASc score has the ability of better classifying patients at risk of stroke.[1,16]

Table 4. Stroke risk measured by $CHADS_2$ and CHA_2DS_2-VASc in the groups of non-treated, antiplatelets and vitamin K antagonists

	No antithrombotic n=5724	Antiplatelets n=7424	Vitamin K antagonists n=9057
$CHADS_2$ (%)			
0	31.7	19.9	15.3
1	29.6	32.6	31.9
≥2	38.8	47.5	52.8
CHA_2DS_2-VASc (%)			
0	17.5	7.7	6.1
1	17	11.7	14.6
≥2	65.5	82.2	77.7

Source: Paper 1 – Giner-Soriano M, Vedia Urgell C, Roso-Llorach A et al. *BMJ open* 2016;6:e010144. doi: 10.1136/bmjopen-2015-010144

Regarding the information in Table 4, it is important to emphasize that there is some inadequacy of anticoagulation in our cohort, as 82.2% of patients treated with antiplatelets and 65.5% of untreated have high risk of stroke (CHA_2DS_2-VASc ≥2), thus they should be anticoagulated, accordingly to guidelines.[4,22,23]

Observational studies conducted in Spain describe different proportions of patients treated with VKA[6,25,67] than those found in our study. Only Barrios et al.[6] described adequacy of anticoagulation; 57% of their patients were correctly anticoagulated, considering $CHADS_2$ score.

Different studies carried out in various countries have assessed the prescription and use of antithrombotics according to stroke risk, reporting the adequacy of anticoagulation,[58,60,65] considering that it is generally recommended to offer OAC to all patients with $CHADS_2$ or CHA_2DS_2-VASc ≥ 2.[4,22,23]

For example, Kirchhof et al.[65] study (PREFER-AF) suggests much better adherence to evidence and recommendations than previous reports: VKA were prescribed in 66.3% of the patients included, antiplatelets in 11.2%, VKA + antiplatelet dual therapy in 10.9%, dabigatran in 6.1%, and 17.7% of non-treated individuals. They described the adequacy of anticoagulation according to stroke risk, and 85.6% of patients were considered as adequately anticoagulated (CHA_2DS_2-VASc ≥2).

In our study there were fewer patients adequately anticoagulated, as 76% of the whole cohort had CHA_2DS_2-VASc score ≥2, but only 40.1% of overall patients were prescribed VKA at baseline. However, if we take into account $CHADS_2$ score which was the recommended stratification for stroke risk during the study period, the proportion of patients adequately anticoagulated

is higher, as only 47.4% of patients are considered as having high risk of stroke ($CHADS_2$ ≥2) and 40.1% of them were receiving VKA.

We found some level of inadequacy of anticoagulation, according to CHA_2DS_2-VASc score, and a frequent lack of correlation between stroke risk and antithrombotic treatment prescribed.

Those patients at high risk (CHA_2DS_2-VASc ≥2) who did not receive anticoagulation but antiplatelets may be responsible of what is known as confounding by indication, meaning that frail patients (elderly, with high stroke risk, with potential contraindications for OAC) would not be receiving treatment with OAC, and the increase of stroke risk seen with antiplatelets could be due to this bias, rather than their therapeutic effects.

We assessed effectiveness and safety of antithrombotic treatments within the cohorts of VKA, platelet-aggregation inhibitors and untreated patients, in terms of incidence of stroke, haemorrhages and all-cause mortality.

Patients with high risk of stroke who were treated with VKA showed reduction in stroke risk in comparison with untreated. This implies that patients correctly anticoagulated are benefited from the treatment.

We found reduction of stroke risk with VKA in patients with higher scores of $CHADS_2$ and CHA_2DS_2-VASc (≥2) in comparison with no antithrombotic treatment, with no significant increases in the risk of cerebral and digestive haemorrhages. We observed increased risks of stroke and gastrointestinal haemorrhage with antiplatelets when compared with untreated. Both VKA and antiplatelets showed lower rates of all-cause mortality.

All these findings are similar to those found in comparable cohort studies, as shown in Table A2 in Annex 2.[42–46] We found lower risk of stroke and mortality with VKA in comparison with no therapy, without significantly increasing bleeding risk, as shown in the previous studies.[42–46] There were no significant increases in cerebral haemorrhage risk, although there was a trend for VKA in increasing this risk, as previously seen in Forslund et al. or Friberg et al. studies.[42,43]

Treatment with antiplatelets increased the risk of stroke and gastrointestinal haemorrhages, the latest being a very well-known side effect of this pharmacological group.[31,42,71,72] The increased risk of stroke with antiplatelets could be pointing out a confounding by indication, meaning that frail patients

would not be receiving treatment with OAC but with antiplatelets, as shown in the study by Forslund et al.[42]

Inadequate treatment of patients who are candidate to receive anticoagulation may reduce treatment's effectiveness.

If we analyse the non-treated cohort in our study, we hypothesize it may include two different types of patients: better prognosis-patients, probably younger with low comorbidity and low risk of stroke, that might be in a status of sinus rhythm, so they do not need to be anticoagulated; and patients with worse prognosis, probably elderly with many comorbidities and high risk of stroke, who are not started on OAC because they are considered frail patients or present possible contraindications as dementia, bleeding history, frequent falls or particular social circumstances such as living alone.[21,42,73] In fact, all-cause mortality rates increased with age in all groups, and they were higher in the antiplatelets and in the non-treated group in comparison with VKA. Again, as in the antiplatelets group, patients with worse prognosis and high stroke risk would remain untreated, although OAC are indicated but they are not prescribed as patients are considered frail.[42] These frail patients would have higher mortality rates which could explain the higher all-cause mortality associated with the whole group of untreated.

To conclude study I discussion, we assessed use, effectiveness and safety of antithrombotics for stroke prevention in non-valvular AF through a population-based cohort study with real-use data. Age, gender, comorbidities and comedications at baseline were similar to previous comparable studies.

We found some level of inadequacy of anticoagulation, as 76% of our patients had high risk of stroke; however, only 40% of the cohort received VKA.

Patients adequately treated with VKA showed reduction in stroke risk in comparison with untreated. We found increased risks of stroke and gastrointestinal haemorrhage with antiplatelets vs. no treatment. Both VKA and antiplatelets showed lower rates of all-cause mortality.

VKA seem to be the best antithrombotic option for stroke prevention in non-valvular AF.

7.2. Study II

The second part of ESC-FA study describes the heart rate and rhythm pharmacological management in patients with non-valvular AF through a cross-sectional design. It includes a sample of patients from ESC-FA study,

diagnosed from 2007 to 2011 and with registries of heart rate measures in the electronic health records during 2012.

We described 11 638 patients, 66.8% of them were treated with rate and rhythm control drugs during 2012.

β-blockers were the most frequent group prescribed, as rate control is the recommended first-line therapy for management of chronic non-valvular AF.

We analysed different clinical factors involved in the prescription of the drugs used for the management of rate and rhythm control, such as β-blockers, calcium-channel blockers, antiarrhythmic agents and digoxin. Some independent factors such as OAC use, coronary artery disease or heart failure were associated with the prescription of β-blockers, verapamil and diltiazem. Most frequent prescription of rate control drugs may be due to the choice of this strategy as recommended for chronic AF in patients, also if they have hypertension or coronary artery disease.[9,62,74–76] For patients with heart failure, the recommendations include β-blockers and digoxin.[1,76]

Only a few variables were associated with antiarrhythmic drugs use. This may suggest that these drugs are frequently prescribed for the reversion of the arrhythmia and not for chronic management of AF, so their prescription

is not related with patients' characteristics. The inverse association with age may indicate that they are most frequently prescribed in younger patients. In fact, rhythm control is usually recommended for symptomatic patients, younger than 65, with no hypertension or heart failure.[1]

Some of the strongest factors associated with digoxin use were OAC use, heart failure, DM, or age. Digoxin is the recommended rate control drug in patients with inactive lifestyle (elderly people, associated comorbidities, etc.) or with heart failure, and it can be added to β-blockers or to calcium-channel blockers in patients with uncontrolled ventricular rates.[9] Digoxin was inversely associated with chronic kidney disease. In fact, it should be used cautiously in these patients.[1,9]

To sum up, we described utilization of drugs for rate and rhythm control in AF. β-blockers were the most frequently prescribed drugs, as widely recommended as first-line therapy for management of chronic non-valvular AF.

7.3. Strengths and limitations

The most important strengths of this study are the large number of patients included, representativeness for the general population, complete socio-demographic and health records, long follow-up, and real clinical practice data; all these characteristics are common strengths of studies conducted with electronic health records' data.

This study is of big relevance in our setting as it assesses the real number of patients treated with traditional antithrombotics and the clinical results of their use in terms of stroke, haemorrhages and mortality rates, before assessing these clinical results including DOAC, which have been authorized for non-valvular AF in the last years.

Some weaknesses of cohort studies conducted with electronic health records are missing or incomplete information, and possible confounders. To minimize missing information and confounders' effects, we used missing imputation techniques and fitting Cox regression models adjusted for socio-demographical characteristics and for possible confounders and predictive factors, respectively, as described in the statistical analysis sections in the papers.

Taking into account that the study was performed with PHC electronic health records, the prevalence of AF diagnosis depends on registries and we might find under-register of diagnosis.

Another important limitation with studies conducted with these data is the non-registered information of some personal circumstances of patients (individual socioeconomic circumstances, living alone, frail patients, frequent falls, etc.) which may affect the decisions of prescribing a specific treatment.

Another limitation is the lack of information about the heart rate or rhythm status of our patients. At the time of diagnosis, patients may present with an episode of arrhythmia, but we are not able to ascertain how many of them persist with the AF or how many are under sinus rhythm after being diagnosed. This information is not usually registered in electronic health records, so it is an inherent limitation of studies conducted in this type of databases. As a consequence, we cannot associate the rhythm status with the treatments prescribed for rate and rhythm control. Of course, we are not able to know either if patients are not initiated with antithrombotic drugs after AF diagnosis because they are under sinus rhythm and asymptomatic or because they are frail patients whose clinicians decided not to anticoagulate.

Despite the inherent limitations of database studies, the data of this study are supported by previous studies conducted in SIDIAP database,[77–80] which validate our findings and indicate that the study population is representative

of the population in Catalonia and thus can be used in epidemiological studies in our setting.

7.4. Future research plans

The main objective of ESC-FA study is to assess the use of drugs prescribed for non-valvular AF throughout four substudies. Studies I and II have been presented in this thesis and studies III and IV are currently ongoing.

Study III estimates annual costs per patient of disease management in the cohort of patients diagnosed of AF between 2007 and 2012 and who initiated antithrombotic therapy after diagnosis (n= 22 205). The variables included for the estimation of costs are: drug treatment dispensations, INR determinations, number of visits in PHC, number of hospitalizations, number of strokes, and number of major haemorrhages during the study period. Results are currently being analysed.

Study IV assesses effectiveness, safety and costs of all current antithrombotic agents, including DOAC. A cross-sectional study including patients with non-valvular AF who started OAC between 2011-2013 have recently been submitted for its publication. The objective of this work was to characterize the profile of patients with non-valvular AF who initiated OAC

with dabigatran and compare it with those who initiated VKA. An overall of 14 266 people have been included in this part of the study. Patients from dabigatran group were younger, with a lower risk of stroke and bleeding, fewer comorbidities and higher proportion of stroke and ICH in comparison to VKA group. The next step is to assess effectiveness and safety according to incidence of stroke and haemorrhages in these cohorts.

8. Conclusions

1. We described the use of antithrombotic agents used for stroke prevention in a large number of patients with non-valvular AF diagnosed from 2007 to 2012. Age, gender and comorbidity in non-valvular AF patients were similar to those reported in previous similar studies.

Taking into account that the study was conducted with PHC electronic health records, the prevalence of AF diagnosis and other comorbidities depends on registries and we might find under-register of diagnosis. However, our data are supported by previous studies[78–81] which indicate that prevalence for common chronic conditions in PHC registered in SIDIAP are equivalent to those described in the literature and thus validate our findings, so the study population is representative of the population in Catalonia and it can be used in epidemiologic studies in our setting, considering the potential limitations in order to minimize them.

2. The prescription rates for patients initiated on antithrombotic therapies after AF diagnosis were: 41% of patients received VKA, 33% received antiplatelets and 26% untreated.

These frequencies are similar to those reported in previous equivalent studies,[6,25,58] although more recent reports indicate higher proportions of patients receiving OAC.[65]

3. Regarding the clinical results in terms of stroke, we found reduction in stroke risk with VKA in patients with higher risk of stroke ($CHADS_2$ and CHA_2DS_2-VASc ≥2) in comparison with no antithrombotic treatment. No significant increases in the risk of cerebral and digestive haemorrhages were found with VKA therapy.

If patients with high risk of stroke who were treated with VKA showed reduction in stroke risk in comparison with untreated, we may assume that patients correctly anticoagulated are benefited from the treatment and we may conclude that anticoagulation is the best option for stroke prevention in non-valvular AF.

4. Increased risks of stroke and gastrointestinal haemorrhage were observed with antiplatelets when compared with untreated patients.

The increased risk of stroke with antiplatelets could be pointing out a confounding by indication, meaning that frail patients would not be receiving treatment with OAC but with antiplatelets, as shown in previous studies.[42] So

inadequate treatment of patients who are candidate to be anticoagulated may reduce treatment's effectiveness.

5. Both VKA and antiplatelets showed lower rates of all-cause mortality in comparison with no antithrombotic therapy.

We have hypothesized that the untreated cohort may include two different types of patients: better prognosis-patients, and patients with worse prognosis, probably elderly with many comorbidities and high risk of stroke, who are not started on OAC because they are considered frail patients.[21,42,73] They would have higher mortality rates which could explain the higher all-cause mortality associated with the whole group of untreated.

6. About the drugs used for rate and rhythm control in our AF population, β-blockers were the most frequently prescribed drugs.

The most frequent prescription of β-blockers is pointing out that rate control is the preferred strategy in our setting, as widely recommended as first-line therapy for management of chronic non-valvular AF.

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10. Annex 1: Paper 2

Maria Giner-Soriano, Albert Roso-Llorach, Cristina Vedia Urgell, Xavier Castells, Dolors Capellà, Ignacio Ferreira-González, Josep Mª Elorza, Marc Casajuana, Amelia Troncoso Mariño, Eduard Diògene, Bonaventura Bolíbar, Concepció Violán, Rosa Morros. **Effectiveness and safety of drugs used for stroke prevention in a cohort of non-valvular atrial fibrillation patients from a Primary Care electronic database**. Under review.

Effectiveness and safety of drugs used for stroke prevention in a cohort of non-valvular atrial fibrillation patients from a Primary Care electronic database.

Running head: Stroke prevention in non-valvular atrial fibrillation

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Keywords: atrial fibrillation, electronic health records, stroke, haemorrhage, vitamin K antagonists, platelet-aggregation inhibitors.

Key points:

- Clinical trials and observational studies have assessed efficacy, effectiveness and safety of oral anticoagulants for stroke prevention in non-valvular atrial fibrillation.
- Many studies on anticoagulants use for stroke prevention indicate under-use of vitamin K antagonists.
- Vitamin K antagonists, particularly warfarin, have demonstrated a higher reduction in stroke and mortality risks in atrial fibrillation patients than platelet-aggregation inhibitors or no antithrombotic treatment.
- We assess effectiveness and safety of drugs traditionally used for stroke prevention in non-valvular atrial fibrillation before the introduction of direct anticoagulants through a population-based study conducted within an automated healthcare database originated from primary care electronic health records.

- We have seen a reduction of stroke and mortality risks with vitamin K antagonists, without significantly increasing bleeding risk. Despite reducing overall mortality risk, we have found an increase in stroke and gastrointestinal haemorrhage risks with platelet-aggregation inhibitors. Vitamin K antagonists seem to be the best antithrombotic option for stroke prevention in non-valvular atrial fibrillation.

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Conflict of Interest statement

All authors have completed the Conflict of Interest Disclosure Forms and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work, and no other relationships or activities that could influence the submitted work.

Abstract

Purpose

To assess effectiveness and safety of antithrombotics for stroke prevention in non-valvular atrial fibrillation in real-use conditions.

Methods

Population-based retrospective cohort study. Information emerges from SIDIAP, database containing anonymized information from electronic health records from 274 primary health care centres of the Catalan Health Institute, Catalonia (Spain), with a reference population of 5,835,000 people.

Population includes all adults with a new diagnosis of non-valvular atrial fibrillation registered in SIDIAP from 2007 to 2012.

The main outcome of antithrombotics' effectiveness was stroke. The main outcomes of safety were cerebral and gastrointestinal haemorrhages. We also estimated all-cause mortality. We used multivariable Cox proportional hazard models to examine association between antithrombotic treatment and main outcomes.

Results

We included 22,205 subjects with non-valvular atrial fibrillation; 40.8% initiated on vitamin K antagonists (VKA), 33.4% on antiplatelets and 25.8% untreated. We

found stroke risk reduction with VKA in patients with $CHADS_2$ ≥2, HR 0.75 (95% CI, 0.57-0.99) and CHA_2DS_2-VASc ≥2, HR 0.78 (95% CI, 0.61-0.98) and stroke risk increase with antiplatelets, HR 1.26 (95% CI, 1.02-1.56). We observed a higher risk of digestive bleeding with antiplatelets, HR 1.44 (95% CI, 1.10-1.89). Both VKA and antiplatelets were associated with reduction of all-cause mortality risk; HR 0.54 (95% CI, 0.48-0.61) and HR 0.87 (95% CI, 0.79-0.96) respectively.

Conclusions

This study found a stroke risk reduction associated with VKA and an increased risk of stroke and gastrointestinal bleeding associated with platelet-aggregation inhibitors in comparison with untreated patients. Both antithrombotic groups showed a reduction in all-cause mortality.

Keywords

Atrial fibrillation, electronic health records, stroke, cerebral haemorrhage, gastrointestinal haemorrhage, vitamin K antagonists, platelet-aggregation inhibitors, all-cause mortality, antithrombotic, primary health care

Introduction

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia. Its prevalence in the general population in North America and Europe is 1.5-2% and it increases with age.[1–3] It represents an increasing health-care burden due to an ageing population.[2] In Spain, Gómez-Doblas et al. reported a prevalence of 4.4% in population older than 40 attended in primary health care (PHC),[4] and Barrios et al. described a prevalence of 6.1% in general PHC population.[5] Both authors described a prevalence higher than 17% in older than 80. Clua-Espuny et al. described similar prevalence and an approximately 20% of undiagnosed cases.[6]

AF is associated with a variety of cardiovascular conditions such as hypertension, symptomatic heart failure, or stroke. In fact, it increases stroke risk by five-fold, and one in five strokes may be attributed to AF. Mortality rate is also increased in these patients.[7]

Management of AF patients increasingly takes place in PHC settings. It aims reduction of symptoms and prevention of associated complications by heart rate and rhythm control, handling of concomitant cardiovascular disorders and stroke prevention.[2,7] The drugs aimed at decreasing the risk of stroke and thromboembolic events in AF are antithrombotics: oral anticoagulant drugs (OAC) and platelet-aggregation inhibitors, also known as antiplatelets. Current available data have shown superiority of OAC over antiplatelets, so they are the recommended treatment in the guidelines for patients requiring antithrombotic

therapy, even though they have been frequently prescribed to patients considered as non-candidate for anticoagulation.[8–12]

Traditionally, OAC drugs used were vitamin K antagonists (VKA); acenocoumarol in Spain and warfarin in the US and some European countries. Recently, direct OAC received marketing authorization in the European Union for stroke prevention in non-valvular AF (dabigatran in 2011, rivaroxaban in 2012, apixaban in 2013 in Spain).

Apart from the clinical trials which demonstrated efficacy and safety of OAC in stroke prevention, their effectiveness has been assessed in some observational studies, where warfarin showed lower stroke risks than aspirin or other antiplatelets, or no antithrombotic treatment.[13–16]

There are some studies on OAC utilization in AF patients from Europe,[17–19] most of them indicating VKA under-use, and some published in PHC in Spain, although conducted within small sample sizes.[5,20–24]

To our knowledge, utilization of antithrombotic drugs for stroke prevention in AF and their effectiveness and safety in real-use conditions have not been assessed in our setting through population studies conducted with electronic health records.

A progressively ageing population, which in addition increases incidences of AF and thromboembolic events and a necessity of assessing effectiveness and safety of antithrombotic agents in real-use conditions before the introduction of direct OAC

in AF management, justify the need of conducting this study. Moreover, the most used VKA in our setting is acenocoumarol, which has not been studied as much as warfarin for stroke prevention in AF, although they are considered equivalents.

The main objective of this study is to assess the effectiveness of antithrombotics in real-use conditions according to stroke rates and to assess the safety of antithrombotics according to bleeding events rates before the introduction of the direct OAC. All-cause mortality will be also estimated.

Methods

ESC-FA study (Effectiveness, Safety and Costs in Atrial Fibrillation) is a population-based retrospective observational cohort study.

The study population were all individuals older than 18 years with a new diagnosis of non-valvular AF registered in SIDIAP database (Information System for the Improvement of Research in Primary Care)[25–31] from 2007 to 2012.

Data source

SIDIAP[31] contains anonymized clinical information of all PHC Centres of the Catalan Health Institute (ICS), main provider of health services in Catalonia, Spain, managing 274 PHC practices with a reference population of 5,835,000 patients (80% of the Catalan population). This information emerges from eCAP™, electronic health records in PHC of the ICS, and it includes socio-demographic characteristics,

health conditions registered as ICD10 codes, clinical parameters, toxic habits, laboratory data, and General Practitioners' (GP) prescriptions and their corresponding pharmacy invoice data.

SIDIAP may be linked with CMBD-AH ("minimum set of data at hospital discharge")[32], which contains diagnoses coded with ICD9 at hospital discharge from all hospitals in Catalonia, to obtain the data for the endpoints of the study (stroke, bleedings).

Variables

The variables assessed at baseline were: socio-demographic characteristics, stroke and bleeding risks by $CHADS_2$, CHA_2D_2VASc and HAS-BLED scores (HAS-BLED was calculated without "L: labile INR" item, since INR values were missing in most patients treated with VKA as they were new treatments and in all patients from the other two groups), comorbidities of interest before AF diagnosis (ICD9 and ICD10 codes, see supplementary file of codes), stroke and bleeding episodes registered before AF diagnosis (ICD9 and ICD10 codes, see supplementary file of codes), laboratory data, exposures to all antithrombotics and to concomitant drugs prescribed at the time of diagnosis (ATC codes).

The variables assessed during follow-up were: any stroke, haemorrhages, all-cause mortality rates and exposures to all antithrombotic drugs.

The main outcome to assess effectiveness of antithrombotic drugs during follow-up was stroke. The main outcome to assess safety was major bleeding, specifically cerebral and gastrointestinal haemorrhages. The rest of the overall haemorrhages included eye bleeding, genitourinary bleeding and other bleeding. All events of interest were concurrently identified through SIDIAP (ICD10) and CMBD-AH (ICD9) databases.

All-cause mortality during follow-up was assessed through SIDIAP database. We had access to date of death, but we were not able to know cause of death.

We obtained the information on drug exposures from the pharmacy invoice registry. As diagnosis and treatment start may be registered in different days in eCAP™, we allowed a time interval of ± 3 months from diagnosis date and start of treatment.

All variables and outcomes of interest were analysed in the patients initiated on VKA, antiplatelets or untreated, excluding patients receiving other antithrombotic therapies due to small sample size (as dual therapy with VKA and antiplatelets, n=227, or dabigatran, n=153).

We have recently published a detailed description of the ESC-FA study methodology and all baseline characteristics of patients.[33]

Statistical analysis

Descriptive statistics were used to summarize overall information. Categorical variables were expressed as frequencies (percentage) and quantitative variables as mean (Standard deviation, SD) or median (interquartile range, IQR).

For each event, we defined time to follow-up as the time between cohort entry and the event. Patients were followed until censored (died only for stroke and bleeding events, lost to follow-up or end of observation). Patients were also censored when they initiated a new antithrombotic treatment.

Incidence rates of stroke and bleeding events during follow-up were estimated for each cohort. Incident rates are presented per 1,000 patients-year and their correspondent 95% confidence intervals (CI).

Time-to-event analysis was performed using non-parametric methods like Kaplan-Meier and log-rank test.

Multivariate Cox proportional-hazards regression models were fitted, adjusting for the following baseline socio-demographical characteristics and confounding and predictive factors of each event: age, sex, Charlson index, creatinine clearance (<30, 30-60 or >60 mL/min/1.73m^2), previous stroke, MI, peripheral artery disease, hypertension, heart failure, diabetes mellitus, hepatic impairment, dyslipidaemia or statin treatment, previous bleeding, peptic ulcer disease, co-treatments with digoxin, β-blockers, verapamil, diltiazem, other antiarrhythmic drugs, angiotensin

converter enzyme inhibitors, angiotensin II receptor blockers, proton pump inhibitors, non-steroidal anti-inflammatory drugs.

All-cause mortality was also adjusted for MEDEA index (deprivation index which shows the social or material disadvantage accruing to a person or group in accordance to their city/region/country, as given in the census data in Catalonia. The higher it is, the worse the deprivation)[34] in the Cox model.

The no-treatment group was considered as the reference in all analysis. Extended Cox models were used when the model's proportional hazards assumption did not hold.

Multiple imputations with 10 imputed datasets were used to handle missing data. We included all the potential predictive variables and survival outcome terms in the imputation model. Our final Cox models were fitted using the multiply imputed datasets by using Rubin's rules to combine effect estimates and standard errors to allow for the uncertainty related to missing data.

All statistical tests were two-sided at the 5% significance level. The analyses were performed using Stata ver. 13 (Stata Corp., Collage Station, TX) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

From 2007 to 2012, 22,585 non-valvular AF patients were included in ESC-FA study. We analysed outcomes of interest in 22,205 patients who were prescribed the most frequent antithrombotic options or remained untreated at baseline; 9,057 (40.8%) patients initiated on VKA, 7,424 (33.4%) with antiplatelets and 5,724 (25.8%) untreated. These patients were 72.8 (13.1) years-old and 51.4% of them were men. The stroke risk measured by $CHADS_2$ was low-moderate (0-1) in 52.6% of them. We were able to calculate HAS-BLED in 14,161 patients, so there were 36.2% of patients with missing values. Main baseline characteristics are shown in Table 1.

All baseline characteristics for the 22,585 patients are shown in Tables S1 to S4 and Figure S1 in the Supporting information, and we have previously described them in a published paper recently.[33]

Effectiveness assessment

Among 22,205 patients, we identified 687 (3.1%) strokes. The total person-time during the follow-up was 44,017.6 person-years and stroke rate was 15.6 per 1,000 patients-years (95% CI 14.5-16.8). Stroke rates and per stroke risk in each cohort are presented in Table 2.

The Kaplan-Meier estimates of time to the event stroke during follow-up are presented in Figure 1.

Adjusted Cox models for stroke and the rest of the outcomes are shown in Figure 2. We found a stroke risk increase with antiplatelets, adjusted hazard ratio (HR) 1.26 (95% CI, 1.02-1.56, p=0.030). We found a non-significant reduction of stroke risk with VKA therapy, HR 0.86 (95% CI, 0.69-1.07, p=0.175), and it was statistically significant in patients with high risk of stroke; $CHADS_2$ score ≥2, HR 0.75 (95% CI, 0.57-0.99, p=0.042) and CHA_2DS_2-VASc score ≥2, HR 0.78 (95% CI, 0.61-0.98, p=0.033).

Safety assessment

Incidence rates of all haemorrhages for the three cohorts are shown in Table 3. All haemorrhages rate in the whole population was 22.9 per 1,000 person-years (95% CI, 21.6-24.4).

Cerebral haemorrhage rate in overall population was 2.8 per 1,000 person-years (95% CI, 2.4-3.3). No statistically significant differences were found in the adjusted HR for cerebral bleeding (Figure 2), although we observed a positive association for VKA and cerebral bleeding, HR 1.67 (95% CI 0.96-2.91, p=0.070).

Regarding gastrointestinal haemorrhage, the event rate in overall population was 10.7 per 1,000 person-years (95% CI, 9.8-11.7). We observed a higher risk of suffering digestive bleeding with antiplatelets, HR 1.44 (95% CI, 1.10-1.89, p=0.008) (Figure 2).

All-cause mortality

The cumulative time at risk for death was 44,757.1 person-years. A total of 2,480 patients died (11.2%); 12.7% of the untreated cohort, 15.2% of the antiplatelets group and 6.9% of the VKA group. Total all-cause mortality rates and per age groups for the three cohorts are shown in Table 4. We observed higher rates progressively increasing with age and different between groups.

Kaplan-Meier estimates of survival until the time of censoring are shown in Figure 3.

Both antiplatelets and VKA showed a significant reduction in the risk of all-cause mortality; 13% of reduction with antiplatelets, HR 0.87 (95% CI, 0.79-0.96, p=0.007) and 46% with VKA, HR 0.54 (95% CI, 0.48-0.61, p<0.001) (Figure 2).

Discussion

Our study assessed effectiveness and safety of traditional antithrombotics used for stroke prevention in non-valvular AF under real-use conditions. We assessed 22,205 patients, initiated on VKA (40.8%), antiplatelets (33.4%) or untreated (25.8%) after AF diagnosis.

Untreated patients were generally younger and with lower stroke risk (61.2% had $CHADS_2$ index = 0-1) than those initiated on VKA or antiplatelets. Nevertheless, we found similar proportions of patients with low-moderate ($CHADS_2$= 0-1) and with

high risk of stroke ($CHADS_2 \geq 2$) in both antithrombotic groups, possibly indicating that antithrombotic prescription after AF diagnosis was not generally linked to the evaluation of potential stroke risk, though unknown factors might be also involved in the decision of the treatment prescription (frail patients, history of bleeding, frequent falls, living alone, etc.).

We found reduction of stroke risk with VKA and increase of stroke risk with antiplatelets therapy compared with untreated. No differences in the adjusted HR of cerebral bleeding were found, although we observed a positive association for VKA and cerebral haemorrhage. We found an increase in the risk of gastrointestinal bleeding with antiplatelets. Regarding all-cause mortality, incidence rates increased with age and were different between groups. Both VKA and antiplatelets evidenced lower rates than no treatment (Figure 2).

Similar benefits of anticoagulant therapy for stroke prevention were detected in other cohort studies. Forslund et al.[35] evaluated the benefits of warfarin, aspirin or no treatment in 41,810 AF patients from a database cohort. Those treated with aspirin showed increased stroke and bleeding risks. Warfarin patients had lower stroke rates, different according to CHA_2DS_2-VASc score, and lower mortality rates than aspirin or untreated patients. The higher stroke and mortality rates in the aspirin group might be pointing out a confounding by indication (not treating frail patients with OAC but with antiplatelets), rather than therapeutic effects of antiplatelets.

In another database study, Friberg et al.[13] assessed effectiveness and safety of warfarin versus no treatment in 182,678 AF subjects. Ischemic stroke rates increased with increasing CHA_2DS_2VASc scores from 0 to 12% annually in patients without warfarin and to 7% in patients with warfarin at baseline. Intracranial haemorrhage (ICH) occurred at an annual rate of 0.6% in warfarin-treated and untreated patients alike, whereas bleeding of any type occurred at an annual rate of 2.3%. So the risk of ischemic stroke without OAC is higher than the risk of ICH with OAC treatment. As in our study, VKA-treated had better effectiveness outcomes than untreated patients.

Singer et al.[16] assessed stroke and ICH rates in a cohort of 13,559 AF patients, 46.9% untreated (they could be on antiplatelets therapy) and 53.1% receiving warfarin. They described an overall unadjusted rate of stroke and thromboembolism of 1.27% (95% CI, 1.19-1.44) and an overall unadjusted rate of ICH of 0.58% (95% CI, 0.51-0.68). The adjusted net clinical benefit of warfarin over no-warfarin therapy was 0.68% per year, so despite the risk of ICH, anticoagulation reduced stroke risk.

Similar results to ours were found by Go et al.[14] They reported a 51% lower risk of thromboembolism with warfarin versus no warfarin (either no antithrombotic or aspirin). Warfarin was associated with a nearly 2-fold increased risk of ICH, so it was effective for preventing ischemic stroke while the absolute increase in ICH risk was small. It also reduced the risk of all-cause death in 31%.

Hylek et al.[15] assessed stroke rates in a cohort of 13,559 AF patients; 596 (4.4%) suffered a stroke during 20 months of follow-up, 32% were treated with warfarin, 27% with aspirin and 42% were untreated. Independent factors associated with stroke severity were being untreated, receiving warfarin and having an INR < 2.0, age and HF.

Therefore, our results showed VKA superiority in stroke prevention and mortality in comparison with no therapy, without significantly increasing bleeding risk, as shown in the previous studies.[13–16,35] There were no significant increases in cerebral haemorrhage risk, although there was a trend for VKA in increasing this risk, as previously seen in Forslund et al. or Friberg et al.[13,14] studies. Treatment with antiplatelets increased the risk of stroke and gastrointestinal haemorrhages, the latest being a very well-known side effect of this pharmacological group.[9,12,35,36]

Analysing the untreated cohort, we hypothesize it may include two different types of patients: better prognosis-patients, probably younger with low comorbidity and low risk of stroke, that might be in a status of sinus rhythm, so they do not need to be anticoagulated; and patients with worse prognosis, probably elderly with many comorbidities and high risk of stroke, who are not started on OAC because they are considered frail patients or present possible contraindications as dementia, bleeding history, frequent falls or particular social circumstances such as living alone.[8,35,37] In fact, all-cause mortality rates increased with age in all groups, and

they were higher in the antiplatelets group in comparison with VKA, and even higher in the untreated group when compared to antithrombotic groups.

This could be pointing out a selection bias produced by confounding by indication, meaning that patients with worse prognosis and high stroke risk are sometimes treated with antiplatelets or even untreated although OAC are indicated but they are not prescribed as patients are considered frail. These patients would have high mortality rates which could explain the high all-cause mortality associated with the whole group of untreated. A more detailed assessment of this cohort would help us to prove this hypothesis in the future.

Strengths and limitations

The strengths of our study are the large number of patients included, representativeness for the general population, complete socio-demographic and health records, long follow-up, and real clinical practice data. To our knowledge, this is the first population-based study in our setting which assesses the number of patients treated with traditional antithrombotics and the clinical results of their use in terms of stroke, haemorrhages and mortality rates, before assessing these clinical results including direct OAC.

Some weaknesses of observational studies conducted with electronic health records are missing or incomplete information, prescriptions not linked with diagnoses coded and possible confounders. To overcome the limitation of the lack of correlation between diagnoses and treatments, we took into account the

antithrombotic agents initiated during the time interval of ±3 months from the date of diagnosis. To minimize missing information and confounders' effects, we used missing imputation techniques and fitting Cox regression models adjusted for socio-demographical characteristics and for possible confounders and predictive factors, respectively, as described in the statistical analysis.

Conclusions

This study assesses the number of patients treated with the antithrombotics traditionally available for stroke prevention in non-valvular AF and the clinical results of their use in terms of stroke, bleeding and mortality rates through a population-based cohort study conducted with electronic health records in a PHC setting.

We found reduced stroke risk with VKA in patients with higher risk of stroke ($CHADS_2$ and CHA_2DS_2-VASc ≥2) in comparison with no antithrombotic treatment, with no significant increases in the risk of cerebral and digestive haemorrhages.

We observed increased risks of stroke and gastrointestinal haemorrhage with antiplatelets when compared with untreated.

Both VKA and antiplatelets showed lower rates of all-cause mortality.

We have found that anticoagulation is the best option for stroke prevention in non-valvular AF.

Other next steps in our research are to assess how the introduction of direct OAC dabigatran, rivaroxaban and apixaban in the management of non-valvular AF affects to effectiveness, safety and costs of stroke prevention with the antithrombotics already ascertained in the present work.

Conflict of Interest

All authors have completed the Conflict of Interest Disclosure Forms and declare no conflict of interests.

Ethical approval

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 PHC 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. Thus, it is not necessary to ask for informed consent to the participants.

For the linkage with CMBD-AH 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.

Supporting information

Baseline characteristics of the participants are shown in Tables S1, S2, S3, and S4.

Diagram for participants' inclusion and exclusion may be found at Figure S1.

All this information can be found at:

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Bonaventura Bolíbar, Concepció Violán. **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**. *BMJ open* 2016;6:e010144. doi: 10.1136/bmjopen-2015-010144

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Table 1. Main baseline socio-demographic characteristics of patients included, n=22,205

	ALL PATIENTS INCLUDED, n=22205		
n (%)	**No antithrombotic 5724 (25.8)**	**Antiplatelets 7424 (33.4)**	**VKA 9057 (40.8)**
Sex (%)			
Women	46.9	50.3	48.3
Men	53.1	49.7	51.7
Age, years (mean, SD)	69.6 (16.4)	74.6 (12.9)	73.4 (10.3)
$CHADS_2$ [38] (%)			
0-1	61.2	52.5	47.3
≥2	38.8	47.5	52.7
CHA_2DS_2VASc [39] (%)			
0-1	34.5	22.3	17.8
2	16.5	19.2	19.5
3	21.4	23.8	26.6
≥4	27.6	34.7	36.0
HAS-BLED [40,41] (n, %)	2921, 51.0	4813, 64.8	6427, 71.0
0	475, 16.2	0, 0.0	426, 6.6
1-2	1856, 63.6	2048, 42.5	4432, 68.9
≥3	590, 20.2	2765, 57.4	1569, 24.4
Missing values	2803, 49.0	2611, 35.2	2630, 29.0

VKA, vitamin K antagonists; SD, standard deviation; $CHADS_2$, stroke-risk score which includes congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA/TE (2 points); TIA, transient ischemic attack; TE, thromboembolism. CHA_2DS_2VASc, stroke risk which includes congestive heart failure, hypertension, age ≥75 (2 points), diabetes mellitus, stroke/TIA/TE (2 points), vascular disease, age 65-74, female sex. HAS-BLED: hypertension (systolic blood pressure ≥160mmgHg), abnormal kidney and/or liver function, stroke, bleeding, labile INR, elderly, drugs (antiplatelets) and/or alcohol.

Table 2. Number and rates of strokes per 1000 person-years, overall and stratified by stroke risk index. N=22,205

Outcome	No antithrombotic	Antiplatelets	Vitamin K antagonists
Stroke			
Events	130	303	254
Event rate (95% CI)	13.3 (11.2-15.8)	20.8 (18.6-23.3)	12.9 (11.4-14.6)
Stroke in $CHADS_2$ <2			
Events	47	88	75
Event rate (95% CI)	6.8 (5.1-9.1)	10.7 (8.7-13.2)	7.8 (6.2-9.8)
Stroke in $CHADS_2$ ≥2			
Events	83	215	179
Event rate (95% CI)	28.5 (23.0-35.3)	34.1 (29.9-39.0)	17.7 (15.3-20.5)
Stroke in CHA_2DS_2-VASc <2			
Events	13	14	21
Event rate (95% CI)	2.9 (1.7-5.1)	3.7 (2.2-6.2)	5.8 (3.8-9.0)
Stroke in CHA_2DS_2-VASc ≥2			
Events	117	289	233
Event rate (95% CI)	21.7 (18.1-26.0)	27.0 (24.0-30.3)	14.5 (12.8-16.5)

CI, confidence interval; $CHADS_2$, stroke-risk score which includes congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA/TE (2 points); TIA, transient ischemic attack; TE, thromboembolism. CHA_2DS_2VASc, stroke risk which includes congestive heart failure, hypertension, age ≥75 (2 points), diabetes mellitus, stroke/TIA/TE (2 points), vascular disease, age 65-74, female sex.

Table 3. Number and rates of cerebral and gastrointestinal bleedings per 1000 person-years, stratified by bleeding risk. N=22,205

Outcome	No antithrombotic	Antiplatelets	Vitamin K antagonists
All bleeding events			
Events	134	325	539
Event rate (95% CI)	13.8 (11.6-16.3)	22.6 (20.3-25.2)	27.8 (25.5-30.2)
Cerebral bleeding			
Events	17	40	68
Event rate (95% CI)	1.7 (1.1-2.8)	2.7 (2.0-3.7)	3.4 (2.7-4.3)
Gastrointestinal bleeding			
Events	82	187	204
Event rate (95% CI)	8.4 (6.8-10.4)	12.8 (11.1-14.8)	10.3 (9.0-11.8)

CI, confidence interval

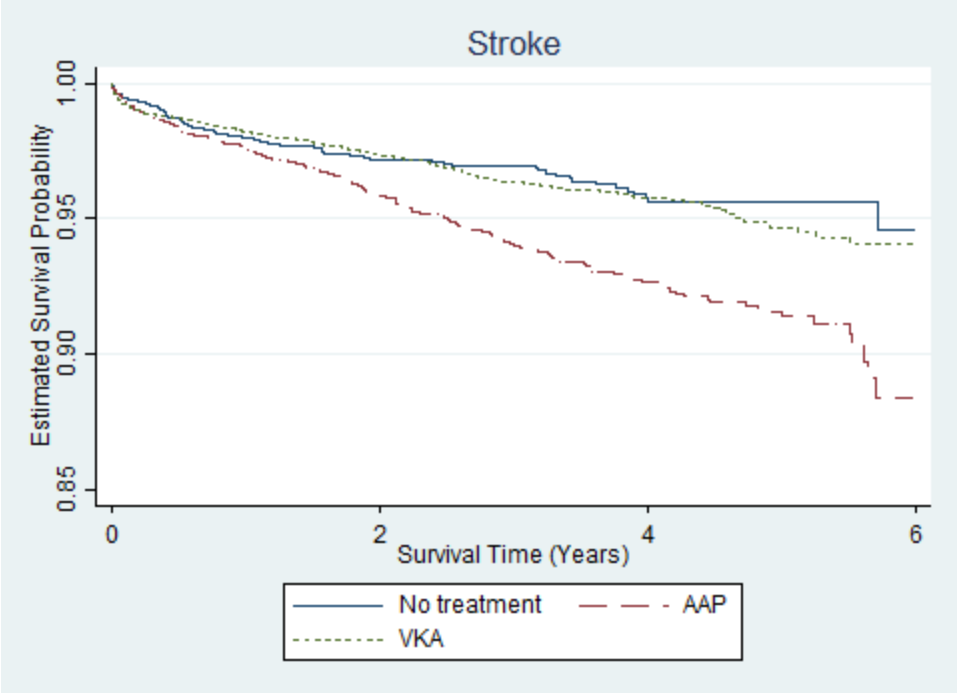
Table 4. Number and rates of all-cause mortality per 1000 person-years per age groups. N=22,205

Outcome	No antithrombotic	Antiplatelets	Vitamin K antagonists
Overall all-cause mortality			
Events	729	1129	622
Event rate (95% CI)	73.8 (68.6-79.3)	76.2 (71.9-80.8)	31.0 (28.7-33.6)
0-64 years-old			
Events	45	28	28
Event rate (95% CI)	10.5 (7.9-14.1)	8.1 (5.6-11.7)	8.5 (5.9-12.4)
65-74 years-old			
Events	72	68	64
Event rate (95% CI)	45.6 (36.2-57.5)	23.6 (18.6-29.9)	14.1 (11.0-18.0)
≥75 years-old			
Events	612	1033	530
Event rate (95% CI)	151.9 (140.4-164.5)	121.9 (114.7-129.6)	43.4 (39.9-47.3)

CI, confidence interval

Figure 1. Kaplan-Meier estimates of time to the event "Stroke" during follow-up, according to the antithrombotic medication status at baseline

Log-rank test: p<0.001



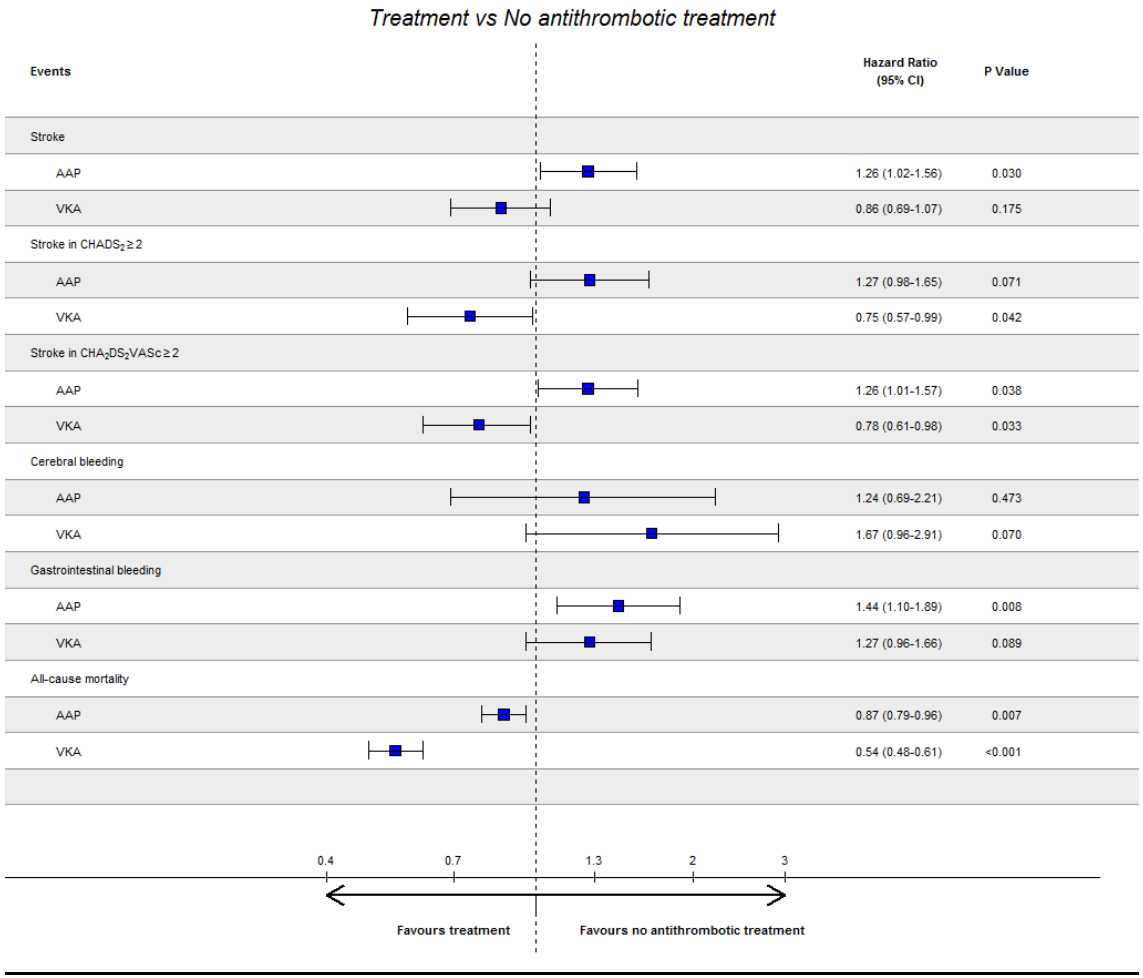
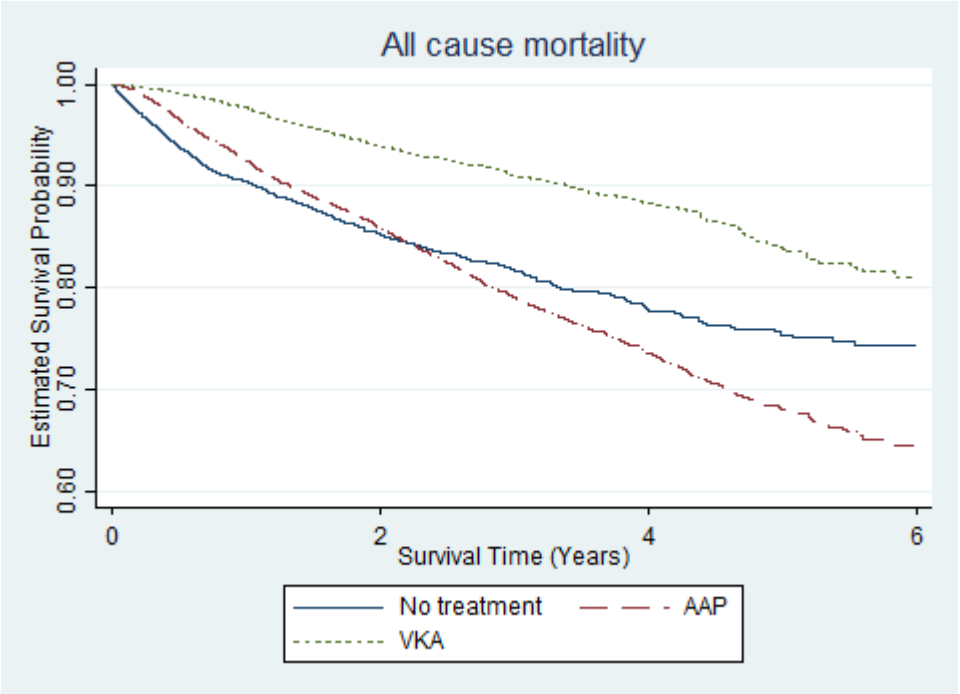


Figure 2. Forest plot of adjusted hazard ratios on treatment regimen of various outcomes during follow-up, n= 22,205

Figure 3. Kaplan-Meier estimates of survival during follow-up, according to the antithrombotic medication status at baseline

Log-rank test: p<0.001



11. Annex 2: summary tables of evidence on antithrombotics use for stroke prevention in non-valvular atrial fibrillation

Table A1. Randomized clinical trials comparing vitamin K antagonists with antiplatelets

Study and reference	Design and objectives	Patients included	Treatments	Primary endpoints	Results
BAFTA study **Mant J et al.** *Lancet.* 2007 Aug 11;370(9586):493–503.	Randomized clinical trial	N= 973 (>75 y-o) UK 56.7% men 81.5 y-o CHADS2 1-2: 71.7%, 3-6: 28.3%	Warfarin (50.2%) or aspirin (49.8%)	Stroke and ICH	Stroke: RR yearly 0.46 (CI95% 0.26-0.79) warf vs aspirin. ICH: RR 1.92 (CI95% 0.10-113.3)
ACTIVE-W study **Connolly S et al.** *Lancet* 2006;367(9526):1903–	Randomized clinical trial	N= 6 706 Canada 66.1% men	OAC (50.3%) or clopidogrel + aspirin (49.7%)	Stroke, non-central nervous system systemic embolus, MI or vascular death	Composite endpoint RR 1.44 (95% CI 1-18-1.76). Study stopped early for clear superiority of

12.		70.2 y-o			OAC.
Van Walraven C et al. *JAMA* 2002;288(19):2441–8.	Meta-analyisis of randomized clinical trials	N= 4 052	OAC (47.9%) or OAC + aspirin (52.1%)	Stroke, ishcaemic stroke, cardiovascular events, major bleeding	Ischaemic stroke: HR 0.71 (95% CI 0.37-0.63) OAC vs OAC+aspirin. Bleeding: HR 1.71 (95% CI 1.21-2.41)

Table A2. Observational studies comparing vitamin K antagonists with antiplatelets and/or no antithrombotic treatment

Study and reference	Design and objectives	Patients included	Treatments	Primary endpoints	Results
Nielsen PB et al. *Circulation* 2015;132(6):517–25.	Cohort study, electronic database. To assess risk of recurrent stroke and mortality in AF patients who had an ICH.	N= 1 752 (had an ICH) Denmark 62% men 78 y-o CHA_2DS_2-VASc 0: 2%, 1: 7%, ≥2: 91%	OAC (VKA or DOAC), OAC + antiplatelets or no antithrombotic	Composite of ischaemic stroke or systemic embolism and all-cause mortality	HR 0.55 (CI95% 0.39-0.78) OAC vs untreated HR 0.87 (0.67-1.14) OAC vs antiplatelets Only mortality: HR 0.55 (0.37-0.82) OAC vs untreated
Lip GYH et al. *J Am Coll Cardiol.* 2015;65(14)	Cohort study, electronic database. To assess impact of OAC in patients with CHA_2DS_2-VASc 0-1.	N= 39 400 Denmark 37.8% women	Warfarin (27%), antiplatelets (13%) or no antithrombotic (60%)	Ischaemic stroke or systemic embolism, bleeding (ICH, major, GI bleeding, traumatic ICH), death	Ischaemic stroke: HR 1.85 (1.11-3.07) warf vs untreated, 1.05 (0.55-2.02) warf vs aspirin.

		59 y-o CHA_2DS_2-VASc = 0 (men) or 1 (women)			ICH: HR 1.09 (0.39-3-04) and 1.71 (0.33-8.97). Death: HR 0.61 (0.47-0.80) and 0.72 (0.51-1.02). With one risk factor-increase, at one year stroke increased 3.01-fold, and death 3.12-fold
Forslund T et al. *Eur J Clin Pharmacol*. 2014;70(12):1477–85	Cohort study, electronic database. To describe patients profile and to assess effectiveness and safety	N= 41 810 Sweden. 44.6% women 73.2 y-o Mean CHA_2DS_2-VASc =3.78 (37.3% had scores 5-9)	Warfarin (37.5%), aspirin (34%) or no antithrombotic (23.8%) [4.7% clopidogrel excluded]	Ischaemic stroke, ICH, other major bleeding and all-cause mortality. Composite stroke + death	Stroke: HR 0.55 (0.37-0.81) warf vs untreated, HR 0.87 (0.65-1.17) aspirin vs untreated. ICH: HR 0.79 (0.52-1.19), HR 0.56 (0.37-0.84). Bleeding: HR 0.90 (0.44-1.81), HR 1.31 (0.73-1.76). Death: HR 0.56 (0.44-0.71), HR

					0.87 (0.72-1.04).
Friberg L et al. *Circulation* 2012;125(19):2298–307.	Cohort study, discharge register. To determine net clinical benefit of OAC.	N= 170 292 Sweden 53% men 76.2 y-o	Warfarin at baseline (53.3%) of never warfarin (40.1%) (6.6% used warfarin at different times)	Stroke and ICH	Stroke rate: 0 → 12% annually in non-warfarin, 0 → 7% in warfarin ICH: 0 → 0.6% in all patients. Positive net clinical benefit of warfarin.
Singer DE et al. *Ann Intern Med* 2009;151(5):297–305.	Cohort study (from ATRIA study[39]). To quantify net clinical benefit of warfarin	N= 13 559 USA 42.7% women 73 y-o	Warfarin (53.1%) and non-warfarin (might receive antiplatelets) (46.9%)	Stroke and ICH	Stroke (rate per 100 p-y): 1.27% (1.19-1.44) ICH: 0.58% (0.51-0.68). Net benefit 0.68% per year
Go AS et al. *JAMA.* 2003;290(20):2685–92.	Cohort study (from ATRIA study[39]). To evaluate effect of warfarin on risk of TE, haemorrhage and death.	N= 11 526 USA 43% women 71 y-o	Warfarin (54.8%) or non-warfarin (might receive aspirin) (44.2%) (1% unknown treatment at baseline)	TE, ICH and all-cause mortality	TE: HR 0.49 (95% CI 0.40-0.61) ICH: HR 1.97 (1.24-3.13) Death: HR 0.69 (0.61-0.77)

Hylek EM et al. *NEJM* 2003;349(11):1019–26.	Cohort study (from ATRIA study[39]). To assess the effect of the intensity of anticoagulation on the severity of stroke and 30-day mortality	N= 596 (had a stroke) USA 55% women 78 y-o	Warfarin (32%), aspirin (27%) and untreated (42%).	Stroke severity and 30-day mortality	Independent factors associated with stroke severity: untreated, receiving warfarin and an INR < 2.0, age and HF.

GI: gastrointestinal, TE: thromboembolism, HF: heart failure

Table A3. Drug utilization studies of antithrombotics for stroke prevention

Study and reference	Design and objectives	Patients included	Treatments	Results
PREFER study. **Kirchhof P et al.** *Europace* 2014 Jan;16(1):6–14	Descriptive observational study. Description of characteristics of AF patients: socio-demographics, risk factors, comorbidities, treatments...	N= 7 243 7 European countries 60.1% men 71.5 y-o	Antithrombotics prescribed after AF diagnosis	VKA 66.3%, VKA + antiplatelet 11.2%, dabigatran 6.1%, antiplatelets 11.2% and no antithrombotic 17.7%
GARFIELD study. **Kakkar AK, et al.** *PLoS One* 2013;8(5):e63479.	Observational study. To describe antithrombotic patterns in patients newly diagnosed with non-valvular AF and to understand the burden of thromboembolic and bleeding complications in this population.	N= 10 614 19 countries 43.2% women 70.2 y-o CHA_2DS_2-VASc 0: 2.9%, 1: 12.7%, ≥2: 84.4%	Antithrombotics prescribed after AF diagnosis	VKA frequently not used according to stroke risk, overuse in patients at low risk and underuse in high risk (52.8% patients with $CHADS_2$ = 0-1 and 61.9% with $CHADS_2$ = 2-6 were receiving VKA).

Scowcroft ACE et al. *Heart* 2013 Jan;99(2):127–32	Retrospective cohort study. To examine OAC treatment of elderly patients (>80 y-o) compared with younger patients (60–69 y, 70–79 y) and to determine the extent to which any differences in treatment prescribing among different age groups might be explained by bleeding risk.	N= 81 381 UK, GPRD 52% women 21% 60-69 y, 37% 70-79 y, 42% >80y.	Warfarin and non-warfarin	Warfarin underuse in >80 and in women compared with men with the same stroke risk factors, not explained by increased comorbidity or increased bleeding risk

12. Annex 3: conference papers

- **Oral communication, XXVII Congreso de la Sociedad Española de Farmacología Clínica, 2014**

Giner-Soriano M, Morros Pedrós R, Vedia Urgell C, Roso-Llorach A, Casajuana M, Castells X, Capellà D. Effectiveness, safety and costs of stroke prevention in non-valvular atrial fibrillation patients (ESC-FA study). Description of cohorts and baseline characteristics of patients. XXVII Congreso de la Sociedad Española de Farmacología Clínica. Sevilla, 2nd-4th October 2014. *Basic & Clinical Pharmacology & Toxicology*, 115 (Suppl 3), 12-19.

- **Oral communication, 12th Congress of the European Association of Clinical Pharmacology and Therapeutics, 2015**

Giner-Soriano M, Morros Pedrós R, Vedia Urgell C, Roso-Llorach A, Castells X, Capellà D. Effectiveness and safety of antithrombotic drugs used in non-valvular atrial fibrillation (ESC-FA study). 12th Congress of the European Association for Clinical Pharmacology and Therapeutics. Madrid, 27th-30th June 2015. Best Communications Awards. Monday June 29th. *Clinical Therapeutics,* Vol. 37, Issue 8, e 12.