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Tromboprofilassi in pazienti affetti da fibrillazione atriale nella reale pratica clinica

Thromboprophylaxis in patients with Atrial Fibrillation in the real practice

DOTTORANDA: Paola Deambrosis

SUPERVISORE: Chiar.mo Prof. Pietro Giusti

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ABSTRACT

Objectives

Oral anticoagulation is recommended in atrial fibrillation (AF) and atrial flutter to prevent strokes commonly associated with this pathology. Guidelines recommend anticoagulant therapy in AF patients at moderate or high risk of stroke, according to CHA2DS2-VASC scores. Despite the effectiveness in preventing strokes, this therapy remains broadly underused. The present study aimed to evaluate the influence of guidelines in the management of non-valvular AF (NVAF) patients in everyday clinical practice and the role of the oral anticoagulant treatments (OAT) in the prevention of stroke in a community setting, during the pre- and post- novel oral anticoagulants (NOACs) periods.

Methods

A retrospective observational study was performed on the databases of the Local Health Authority 9 of Treviso, Italy, in two different observational periods: pre-NOAC period form 2007 to2013 and post-NOACs period from 2013 to 2016. The NVAF population was extracted considering hospitalizations with diagnosis codes of AF; for each patient, the stroke risk scores, CHADS2 and CHA2DS2-VASC, were calculated. NVAF patients were further divided according to OAT. For VKA-treated patients, the Time in Therapeutic Range was calculated: therapeutic target was defined with a Time in Therapeutic Range (TTR) value ≥ 65%. For NOACs the adherence was also calculated. Multivariate analysis was performed to assess the stroke risk. Major bleeding risk and all cause-mortality were also evaluated in Cox regression model.

Results

6,138 (2007-2013) and 5,294 (2013-2015) participant with a diagnosis of NVAF were considered as eligible for the study: only 49% or 44% received a thromboprophylaxis (VKA, and VKA or NOACs, respectively). According to the CHA_2DS_2-VASc score, 83% and 81% of patients , despite a score ≥2, did not receive the therapy in the pre- and post-NOACs period respectively. On the contrary about a 2% of patients received a thromboprophylaxis although their score was 0, in both periods. Female sex, increasing age (age≥75), antiplatelet drugs and history of major bleeding negatively affected the possibility of receiving OAT. Furthermore, among patients treated with VKA, a range of 27.2% to 16.25% of patients reached the therapeutic target, as calculated by TTR. Adherence to treatment was found in the 62% of treated patients compared to the 37% of not adherent patients. Multivariate regression analysis clearly highlighted the correlation of stroke risk with therapeutic management. In particular, a major stroke risk was detected for patients with previous stroke/TIA.

Conclusions

Differently from the current guidelines, patients at high and low thromboembolic risk were undertreated and over-treated respectively. Moreover, many patients receiving VKA in everyday community care have poorly controlled anticoagulation treatment; additionally, the adherence is still problematic for NOACs therapy and may potentially lead to underestimation of bleeding risk and/or suboptimal stroke prevention. Also, what is evident in this real world study performed in a community setting is a persisting difficult of management of NVAF patients who are mostly elderly and with many comorbidities.

LIST OF ABBREVIATIONS

AF = Atrial fibrillation
aPTT = activated partial thromboplastin time
CAD = coronary artery disease
CKD = chronic kidney disease
DCC = direct current cardioversion
INR =International normal ratio
LAA = left atrial appendage
LHU = Local Health Units
LV = left ventricular
MEAs = managed entry agreements
NOACs = novel oral anticoagulants
NVAF = Non Valvular AF
OAT = oral anticoagulant treatment
PHT = Direct Distribution Formulary
SmPC = Summary of Product Characteristics
TP = Therapeutic Plan
TTR = time in therapeutic range
VKA = vitamin K antagonist

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major preventable cause of stroke and hospitalization [Ezekowitz MD. Ann Intern Med 1999; Go AS, JAMA 2001]. Its prevalence has increased over years [Miyasaka Y, Circulation 2006], and in Italy was found to be 1.85% [Zoni-Berisso M, Am J Cardiol. 2013; Bilato C, Am J Cardiol. 2009].

This arrhythmia confers, on average, a five-fold risk of stroke, doubles the risk of mortality, increases the risk of heart failure and is responsible for one-fifth of all strokes; in addition, strokes caused by AF tend to be more frequently fatal, disabling and recurring when compared to other causes of stroke [Wolf PA, 1987; Lin HJ, Stroke 1996; Dulli DA, Neuroepidemiology 2003; Lamassa M, Stroke 2001].

Current guidelines recommend oral anticoagulation therapy for AF patients at high risk of stroke [Camm AJ, European Heart Journal (2012); Raviele A, AIAC Guidelines on the management and treatment of atrial fibrillation. Update 2013. Associazione Italiana di Aritmologia e Cardiostimolazione. G Ital Cardiol (Rome). 2013], according to CHA2DS2-VASC scores of individual risk. However, even if oral anticoagulation is effective in preventing strokes due to AF [Singer DE, Chest 2004], there is extensive evidence suggesting that this therapy remains underused [Zoni-Berisso M, Am J Cardiol. 2013; Camm AJ, European Heart Journal 2012; Ogilvie IM, Am J Med. 2010; Connolly SJ, Circulation 2008 Nov 11; Hess PL, Am Heart J 2014]. Despite data from literature clearly showing that the efficacy of antiplatelet agents in thromboembolic prevention is significantly lower than that of oral anticoagulant therapy, antiplatelet agents are often used in substitution of the oral anticoagulant agents [Connolly SJ, Circulation 2008 Nov 11; Hess PL, Am Heart J 2014]. Also, among patients treated with vitamin K antagonist (VKA), the quality of anticoagulation control is often poor [Connolly SJ, Circulation 2008 Nov 11; Hess PL, Am Heart J 2014] and many discontinue treatment permanently [Zalesak M, Circ Cardiovasc Qual Outcomes 2013]. In Italy, strokes connected to the absence of treatment or related to an inadequate control of INR are estimated to be around 11,000 per year [Capizzi S, QIJPH 2013]. Given the recognized limitations of VKA, the availability of novel oral anticoagulants (NOAC) dabigatran, rivaroxaban and apixaban, could represent a valid alternative therapy to minimize stroke risk and to guarantee an appropriate management of AF.

This research focused in two periods: the pre-NOACs period from 2007 to 2013 and the post-NOACs period from 2013 to 2016. In the pre-NOACs period, since the recommended treatment to prevent strokes in AF was limited to the VKA therapy (2007-2013), we evaluated VKA treatment in patients with Non Valvular AF (NVAF) in everyday clinical practice in comparison with the guideline recommendations from 2007 to 2013.

In the post-NOACs period the research focused on comparing VKA and the non-VKA oral anticoagulants (NOAC) in everyday clinical practice, considering that NOACs dabigatran, rivaroxaban and apixaban have been shown to be non-inferior to VKA for stroke prevention in AF in different

clinical trials ([RE-LY_dabigatran, ROCKET-AF_rivaroxaban, ARISTOTELE_apixaban]. NOAC have some theoretical advantages over VKA such as the scarcity of interactions, predictable effects with fixed dosages and no need for monitoring. Nevertheless, they also have significant limitations, including the unavailability of tests for monitoring their anticoagulant effectiveness, the low availability of antidotes to reverse their effect, and renal clearance. Additionally, their cost far outweighs that of traditional anticoagulation.

NOAC are recommended as options for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

The decision about whether to start treatment with NOACs should be made after an informed discussion between the clinician and the person about the risks and benefits of NOACs compared with VKA. For people who are taking VKA, the potential risks and benefits of switching to one of the NOAC should be considered in light of their level of international normalised ratio (INR) control.

An important question is whether ease of NOAC use has translated into better treatment persistence and adherence. Unfortunately, information from large randomised controlled studies cannot provide a reliable indication of levels of persistence that might be anticipated in real world practice. Some studies, largely from pharmacy or health system administrative data and all limited to a single NOAC have attempted to estimate persistence and in some studies to determine whether that NOAC drug showed improved persistence compared with VKA [Ten Cate H. Thrombosis Journal 2013; Larock AS, Annals of Pharmacotherapy 2014; Martinez, Thromb Haemost 2016; Nelson WW, Curr Med Res Opin 2014].

2. Atrial fibrillation

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Furthermore, the number of patients with AF is predicted to rise steeply in the coming years [ESC 2016].

It is recognized as an increasing health-care burden, because of an ageing population and improved survival from disorders such as acute myocardial infarction. The lifetime risk for development of atrial fibrillation is about one in four for men and women aged 40 years and older, whereas for those without previous or concurrent congestive heart failure or myocardial infarction the lifetime risk is still about 16%.The presence of atrial fibrillation independently increases the risk of mortality and morbidity due to stroke and thromboembolism, congestive heart failure, and impaired quality of life, resulting in a high health-care cost and public health burden. [Freek W, Lancet 2015].

Atrial fibrillation is present in 3–6% of acute medical admissions, for which the most common comorbidities are coronary artery disease and congestive heart failure; in the community setting, hypertension is the most common causal risk factor. Atrial fibrillation is a common complication in the postoperative setting, especially after cardiothoracic surgery. However, it can also exist in isolation (known as lone atrial fibrillation), which is essentially a diagnosis of exclusion—ie, when there is a normal clinical examination, a normal chest radiograph and electrocardiogram (ECG) (apart from atrial fibrillation, with no evidence of previous myocardial infarction or left ventricular hypertrophy), a structurally normal heart on echocardiography, and no history of cardiovascular disease. Many patients are asymptomatic (silent atrial fibrillation) and a presentation with a complication associated with atrial fibrillation (eg, stroke) might be the first manifestation of the arrhythmia, when the disorder is first diagnosed. Even in patients with acute stroke, prolonged ECG monitoring would detect atrial fibrillation in one in 20 patients. Opportunistic screening—eg, palpitation of the pulse (for an irregular rhythm) when patients visit their family doctor—was shown to be more cost effective than was a systematic screening strategy for atrial fibrillation.

2.1. Epidemiology

2.1.1. Incidence and prevalence of atrial fibrillation

In 2010, the estimated numbers of men and women with AF worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries. One in four middle-aged adults in Europe and the US will develop AF. By 2030, 14–17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year. Estimates

suggest an AF prevalence of approximately 3% in adults aged 20 years or older, with greater prevalence in older persons and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease (CKD). The increase in AF prevalence can be attributed both to better detection of silent AF, alongside increasing age and conditions predisposing to AF. In Italy the estimate prevalence of AF was about 1.85% [Zoni-Berisso M, Am J Cardiol. 2013; Bilato C, Am J Cardiol. 2009].

2.1.2. Morbidity, mortality, and healthcare burden of atrial fibrillation

AF is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men. Death due to stroke can largely be mitigated by anticoagulation, while other cardiovascular deaths, for example due to heart failure and sudden death, remain common even in AF patients treated according to the current evidence base. AF is also associated with increased morbidity, such as heart failure and stroke. Contemporary studies show that 20–30% of patients with an ischemic stroke have AF diagnosed before, during, or after the initial event [Henriksson KM, Int J Stroke 2012; Grond M, Stroke 2013]. White matter lesions in the brain, cognitive impairment, decreased quality of life, and depressed mood are common in AF patients, and between 10–40% of AF patients are hospitalized each year. The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK, and between 6.0–26.0 billion US dollars in the US for 2008,36,37 driven by AF-related complications (e.g. stroke) and treatment costs (e.g. hospitalizations). These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner [ESC 2016].

In both developed and developing countries, the age-adjusted incidence and prevalence of AF are lower in women, while the risk of death in women with AF is similar to or higher than that in men with AF. Female AF patients who have additional stroke risk factors (particularly older age) are also at greater risk than men of having a stroke, even those anticoagulated with warfarin. Women with diagnosed AF can be more symptomatic than men and are typically older with more comorbidities. Bleeding risk on anticoagulation is similar in both sexes, but women appear less likely to receive specialist care and rhythm control therapy, while the outcomes of catheter ablation or AF surgery are comparable to those in men. These observations highlight the need to offer effective diagnostic tools and therapeutic management equally to women and men [ESC 2016].

2.2. Mechanisms leading to atrial fibrillation

2.2.1. Risk factors

Atrial fibrillation commonly coexists with cardiovascular risk factors and disorders, which in turn increase the risk of complications associated with the arrhythmia. Common predisposing factors for atrial fibrillation include both non-cardiovascular (eg, chest disease, infection) and cardiovascular (eg, hypertension, congestive heart failure, valvular heart disease, diabetes mellitus, and vascular disease) risk factors. Data from the Atherosclerosis Risk in Communities (ARIC) study [Huxley RR, 2012] have shown that about 5% of new-onset atrial fibrillation could be attributed to common cardiovascular risk factors, including hypertension, obesity, diabetes mellitus, and smoking. Although the precise mechanisms contributing to development of the disorder are unclear, several factors are likely, including activation of renin–angiotensin–aldosterone system, haemodynamic loading and structural changes in atria, focal triggers initiating paroxysmal atrial fibrillation, and atrial fibrosis promoting re-entry in persistent atrial fibrillation. The disorder can also be triggered by rapid atrial activation associated with other supraventricular tachycardias, such as atrial tachycardia or flutter, atrioventricular nodal re-entry tachycardia, or Wolff -Parkinson-White syndrome. The Framingham study published a risk score for development of atrial fibrillation that incorporated the presence of age, sex, body-mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, and congestive heart failure; additional incorporation of echocardiographic measurements only slightly improved the predictive ability of this risk schema. [H Lip, Atrial fibrillation. Lancet 2012; 379: 648–61; Schnabel RB, Lancet 2009].

2.2.2. Remodelling of atrial structure and ion channel Function

External stressors such as structural heart disease, hypertension, possibly diabetes, but also AF itself induce a slow but progressive process of structural remodelling in the atria. Activation of fibroblasts, enhanced connective tissue deposition, and fibrosis are the hallmarks of this process. In addition, atrial fatty infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis, and amyloidosis are found in AF patients with concomitant conditions predisposing to AF. Structural remodelling results in electrical dissociation between muscle bundles and local conduction heterogeneities, favouring re-entry and perpetuation of the arrhythmia. In many patients, the structural remodelling process occurs before the onset of AF. As some of the structural remodelling will be irreversible, early initiation of treatment seems desirable. In Table 1 an overview of the most relevant pathophysiological alterations in atrial tissue associated with AF, is provided and lists corresponding clinical conditions that can contribute to these changes. The functional and structural changes in atrial myocardium and stasis of blood,

especially in the left atrial appendage (LAA), generate a prothrombotic milieu. Furthermore, even short episodes of AF lead to atrial myocardial damage and the expression of prothrombotic factors on the atrial endothelial surface, alongside activation of platelets and inflammatory cells, and contribute to a generalized prothrombotic state. The atrial and systemic activation of the coagulation system can partially explain why short episodes of AF convey a long-term stroke risk [ESC 2016].

Table 1. Pathophisiological alteration in atrial tissue associated with atrial fibrillation and clinical conditions that could contribute to such alteration [ESC 2016].

Pathophysiological alteration	Clinical conditions contributing to the alteration	Pro-arrhythmic mechanism/ functional consequence
Changes of the extracellular matrix, fibroblast function and fat cells		
Interstitial and replacement fibrosis	AF (especially forms with a high AF burden), hypertension, heart failure, valvular heart disease (via pressure and volume overload).	Electrical dissociation, conduction block, enhanced AF complexity.
Inflammatory infiltration		Profibrotic responses, enhanced AF complexity.
Fatty infiltration	Obesity.	Profibrotic / proinflammatory responses, localized conduction block.
Amyloid deposition	Aging, heart failure, coronary artery disease (via atrial scarring), genetic factors.	Conduction disturbances.
Ion channel alterations		
Ion channel remodelling	AF (especially forms with a high AF burden), genetic predisposition to AF.	AF cycle shortening (if due to atrial tachycardia), AF cycle length prolongation (if due to heart failure), enhanced heterogeneity of atrial repolarization.
Ca^{2+} handling instability	AF (especially forms with a high AF burden), heart failure and hypertension (possibly through increased sympathetic activation).	Enhanced propensity to ectopy.
Gap-junction redistribution	AF	Conduction disturbances.
Myocyte alterations		
Apoptosis and necrosis	Coronary artery disease, heart failure (through cardiomyocyte death and atrial scarring).	May induce replacement fibrosis.
Myocyte hypertrophy	Atrial dilatation, AF.	Aggravates conduction disturbances.
Endothelial and vascular alterations		
Microvascular changes	Atherosclerosis, coronary and peripheral artery disease, possibly atrial fibrillation.	Aggravation of atrial ischaemia, heterogeneity of electrical function, structural remodelling.
Endocardial remodelling		Enhanced risk for thrombus formation.
Changes of the autonomic nervous system		
Sympathetic hyperinnervation	Heart failure, hypertension.	Enhanced propensity to ectopy.

2.2.3.Electrophysiological mechanisms of atrial fibrillation

AF provokes a shortening of the atrial refractory period and AF cycle length during the first days of the arrhythmia, largely due to downregulation of the Ca2+-inward current and upregulation of inward rectifier K+ currents.Structural heart disease, in contrast, tends to prolong the atrial refractory period,

illustrating the heterogeneous nature of mechanisms that cause AF in different patients. Hyperphosphorylation of various Ca2+-handling proteins may contribute to enhanced spontaneous Ca2+ release events and triggered activity, thus causing ectopy and promoting AF. Although the concept of Ca2+-handling instability has been challenged recently, it may mediate AF in structurally remodelled atria and explain how altered autonomic tone can generate AF. [ESC]

2.2.4. Classification of atrial fibrillation

Clinically, it is reasonable to distinguish five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF.

1_ Every patient who presents with AF for the first time is considered a patient with first diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.

2_ Paroxysmal AF is self-terminating, usually within 48 h. Although AF paroxysms may continue for up to 7 days, the 48 h time point is clinically important—after this the likelihood of spontaneous conversion is low and anticoagulation must be considered.

3_ Persistent AF is present when an AF episode either lasts longer than7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC).

4_ Long-standing persistent AF has lasted for ≥1 year when it is decided to adopt a rhythm control strategy.

5_ Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia is redesignated as ‘longstanding persistent AF.

This classification is useful for clinical management of AF patients, especially when AF-related symptoms are also considered. Many therapeutic decisions require careful consideration of additional individual factors and co-morbidities. Silent AF (asymptomatic) may manifest as an AF-related complication (ischaemic stroke or tachycardiomyopathy) or may be diagnosed by an opportunistic ECG. Silent AF may present as any of the temporal forms of AF [ESC 2010].

In many patients, AF progresses from short, infrequent episodes to longer and more frequent attacks. Over time, many patients will develop sustained forms of AF. In a small proportion of patients, AF will remain paroxysmal over several decades (2–3% of AF patients). The distribution of paroxysmal AF recurrences is not random, but clustered. AF may also regress from persistent to paroxysmal AF. Furthermore, asymptomatic recurrences of AF are common in patients with symptomatic AF.

The risk of developing AF is increased in a variety of physiological and disease states, and the historic term ‘lone AF’ is probably misleading and should be avoided. Although the pattern of AF may be the same, the mechanisms underpinning AF vary substantially between patients. This suggests that stratifying AF patients by underlying drivers of AF could inform management, for example, considering cardiac and systemic comorbidity (e.g. diabetes and obesity), lifestyle factors (e.g. activity level, smoking, alcohol intake), markers of cardiac structural remodelling (e.g. fibrosis – or electrocardiographic parameters of AF complexity), or genetic background. Systematic research defining the major drivers of AF is clearly needed to better define different types of AF.

2.2.5. Symptom burden in atrial fibrillation

Patients with AF have significantly poorer quality of life than healthy controls, experiencing a variety of symptoms including lethargy, palpitations, dyspnoea, chest tightness, sleeping difficulties, and psychosocial distress. Improved quality of life has been noted with both pharmacological and interventional therapies, but there are limited data to compare the benefit of different treatments. Assessment of quality of life is further constrained by a lack of cross-validation of the several AF-specific quality of life tools. With regard to symptom assessment, many scales are used to describe symptom severity in AF patients.: in Europe is used the EHRA symptom scale; a similar scale (the Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale) is used in Canada.

2.2.6. Detection and management of risk factors and concomitant cardiovascular diseases

Many cardiovascular diseases and concomitant conditions increase the risk of developing AF, recurrent AF, and AF-associated complications. The identification of such conditions, their prevention and treatment is an important leverage to prevent AF and its disease burden. Knowledge of these factors and their management is hence important for optimal management of AF patients.

2.2.7. Heart failure

Heart failure and AF coincide in many patients. They are linked by similar risk factors and share a common pathophysiology. Heart failure and AF can cause and exacerbate each other through mechanisms such as structural cardiac remodelling, activation of neurohormonal mechanisms, and rate-related impairment of left ventricular (LV) function. Patients with AF and concomitant heart failure, both with preserved ejection fraction [LV ejection fraction (LVEF) ≥50%] and reduced ejection fraction (LVEF, 40%), suffer from a worse prognosis, including increased mortality. Prevention of adverse

outcomes and maintenance of a good quality of life are the aims of management in all patients with AF and concomitant heart failure, regardless of LVEF. The general approach to AF management does not differ between heart failure patients and others, but a few considerations are worthwhile. Of note, the only therapy with proven prognostic value in these patients is anticoagulation, and appropriate oral anticoagulant treatment (OAT) should be prescribed in all patients at risk of stroke [ESC 2016].

2.2.8. Hypertension

Hypertension is a stroke risk factor in AF; uncontrolled high blood pressure enhances the risk of stroke and bleeding events and may lead to recurrent AF. Therefore, good blood pressure control should form an integral part of the management of AF patients. Inhibition of the renin–angiotensin–aldosterone system can prevent structural remodelling and recurrent AF. A recent analysis of the Danish healthcare database with long-term monitoring of the effect of different antihypertensive agents on the occurrence of overt AF suggests a beneficial effect of ACE inhibitors or angiotensin receptor blockers (ARBs) [ESC 2016].

2.2.9. Valvular heart disease

Valvular heart disease is independently associated with incident AF. Approximately 30% of patients with AF have some form of valvular heart disease, often detected only by echocardiogram. AF worsens prognosis in patients with severe valvular heart disease, including those undergoing surgery or transcatheter interventions for aortic or mitral valve disease. Valvular heart disease can be associated with an increased thrombo-embolic risk, which probably also adds to the stroke risk in AF patients. Similar to heart failure, valvular disease and AF interact with and sustain each other through volume and pressure overload, tachycardiomyopathy, and neurohumoral factors. When valve dysfunction is severe, AF can be regarded as a marker for progressive disease, thus favouring valve repair or replacement.

Traditionally, patients with AF have been dichotomized into ‘valvular’ and ‘non-valvular’ AF [Molteni M. 2014]. Although slightly different definitions have been used, valvular AF mainly refers to AF patients that have either rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves. In fact, while AF implies an incremental risk for thromboembolism in patients with mitral valve stenosis, there is no clear evidence that other valvular diseases, including mitral regurgitation or aortic valve disease, need to be considered when choosing an anticoagulant or indeed to estimate stroke risk in AF [De Caterina R, Eur Heart J 2014].

2.2.10. Diabetes mellitus

Diabetes and AF frequently coexist because of associations with other risk factors. Diabetes is a risk factor for stroke and other complications in AF. In patients with AF, a longer duration of diabetes appears to confer a higher risk of thromboembolism, although without greater risk of OAT related bleeding. Unfortunately, intensive glycaemic control does not affect the rate of new-onset AF, while treatment with metformin seems to be associated with a decreased long-term risk of AF in diabetic patients [Chang S-H, Cardiovasc Diabetol 2014] and may even be associated with a lower long-term stroke risk. Diabetic retinopathy, a measure of disease severity, does not increase the risk of ocular bleeding in anticoagulated patients [ESC 2016].

2.2.11. Obesity and weight loss

Obesity increases the risk for AF with a progressive increase according to body mass index (BMI). Obese patients may have more LV diastolic dysfunction, increased sympathetic activity and inflammation, and increased fatty infiltration of the atria. Obesity may also be a risk factor for ischaemic stroke, thromboembolism, and death in AF patients.

2.2.12. Chronic obstructive pulmonary disease, sleep apnoea, and other respiratory diseases

AF has been associated with obstructive sleep apnoea. Multiple pathophysiological mechanisms can contribute to AF in obstructive sleep apnoea, including autonomic dysfunction, hypoxia, hypercapnia, and inflammation. Obstructive sleep apnoea exaggerates intrathoracic pressure changes, which in itself and via vagal activation can provoke shortening of the atrial action potential and induce AF. Risk factor reduction and continuous positive airway pressure ventilation can reduce AF recurrence. It seems reasonable to consider obstructive sleep apnoea screening in AF patients with risk factors. Obstructive sleep apnoea treatment should be optimized to improve AF treatment results in appropriate patients. Servo-controlled pressure support therapy should not be used in HFrEF patients with predominantly central sleep apnoea (of which 25% had concomitant AF). Patients with chronic obstructive pulmonary disease often suffer from atrial tachycardias, which need to be differentiated from AF by ECG. Agents used to relieve bronchospasm, notably theophyllines and beta-adrenergic agonists, may precipitate AF and make control of the ventricular response rate difficult. Non-selective beta-blockers, sotalol, propafenone, and adenosine should be used with caution in patients with significant bronchospasm, while they can safely be used in patients with chronic obstructive pulmonary disease. Beta-1 selective

blockers (e.g. bisoprolol, metoprolol, and nebivolol), diltiazem, and verapamil are often tolerated and effective.

2.2.13. Chronic kidney disease –CKD-

AF is present in 15–20% of patients with CKD [Hart RG Can J Cardiol 2013]. The definition of CKD in most AF trials is relatively strict. Although an estimated creatinine clearance (CrCl) rate of <60 mL/min is indicative of CKD, a number of trials in AF patients have used CrCl <50 mL/ min to adapt NOAC dosage, usually estimated using the Cockroft –Gault formula. CrCl in AF patients can deteriorate over time [Roldan V Am J Cardiol 2013].

2.3. Management of patients with atrial fibrillation

Most patients initially access the healthcare system through pharmacists, community health workers, or primary care physicians. As AF is often asymptomatic ("silent AF"), these healthcare professionals are important stakeholders to enable the adequate detection of AF and to ensure consistent management. The initial assessment should be performed at the point of first contact with the healthcare system, and is feasible in most healthcare settings (when an ECG is available). Possible domains to be considered in the initial assessment of patients presenting with newly diagnosed AF are:

(1) Haemodynamic instability or limiting, severe symptoms;

(2) Presence of precipitating factors (e.g. thyrotoxicosis, sepsis, or postoperative AF) and underlying cardiovascular conditions;

(3) Stroke risk and need for anticoagulation;

(4) Heart rate and need for rate control;

(5) Symptom assessment and decision for rhythm control.

An integrated, structured approach to AF care will facilitate consistent, guideline-adherent AF management for all patients [Berti D, Eur Heart J 2013], with the potential to improve outcomes [Lip GY, Eur Heart J 2014; Wagner EH, Milbank Q 1996; Nieuwlaat R, Am Heart J 2007]. Such approaches are consistent with the Innovative Care for Chronic Conditions Framework proposal put forward by the World Health Organization [Nuno R, Health Policy 2012]. Review by an AF service, or at least referral to a cardiologist, will usually be required after the initial assessment to fully evaluate the effect of AF on cardiovascular health. Integrated care of all patients with newly diagnosed AF should help to overcome the current shortcomings of AF management, such as underuse of anticoagulation, access to rate and rhythm control therapy, and inconsistent approaches to cardiovascular risk reduction. Integrated AF care requires the cooperation of primary care physicians, cardiologists, cardiac surgeons, AF specialists, stroke specialists, allied health practitioners, and patients, encompassing lifestyle interventions, treatment of underlying cardiovascular diseases, and AF-specific therapy.

2.3.1. Integrated atrial fibrillation care

Patients should have a central role in the care process. As treatment of AF requires patients to change their lifestyles and adhere to chronic therapy, at times without an immediately tangible benefit, they need to understand their responsibilities in the care process. Physicians and healthcare professionals are responsible for providing access to evidence-based therapy, but adherence to therapy is ultimately the responsibility of informed and autonomous patients.

Hence, information and the education of patients, and often of their partners and relatives, is indispensable to encourage a self-management role and to empower patients to participate in shared decision-making, and to support understanding of the disease and the suggested treatments [Lane DA. Europace 2015].

A multidisciplinary atrial fibrillation team including specialists, general physicians and physicians is a fundamental concept of integrated care models. A multidisciplinary AF team approach includes an efficient mix of interpersonal and communication skills, education, and expertise in AF management, as well as the use of dedicated technology. This approach underlines the importance of redesigning daily practice in a way that encourages non-specialists and allied professionals to have an important role in educating patients and co-ordinating care, while the specialist remains medically responsible. Cultural and regional differences will determine the composition of AF teams.

Some physicians in primary care have extensive expertise in stroke prevention and initial management of AF patients. Others may seek training to acquire such knowledge. Other components of AF management (e.g. assessment of concomitant cardiovascular conditions, antiarrhythmic drug therapy, or interventional treatment) often require specialist input. Integrated AF care structures should support treatment initiation by non-specialists where appropriate, and provide ready access to specialist knowledge to optimize AF care [Page K, Med J Aust 2014; Stock S, Health Aff 2014; Lundstrom H, Diabetologia 2014].

2.3.2. Recommended evaluation in all atrial fibrillation patients

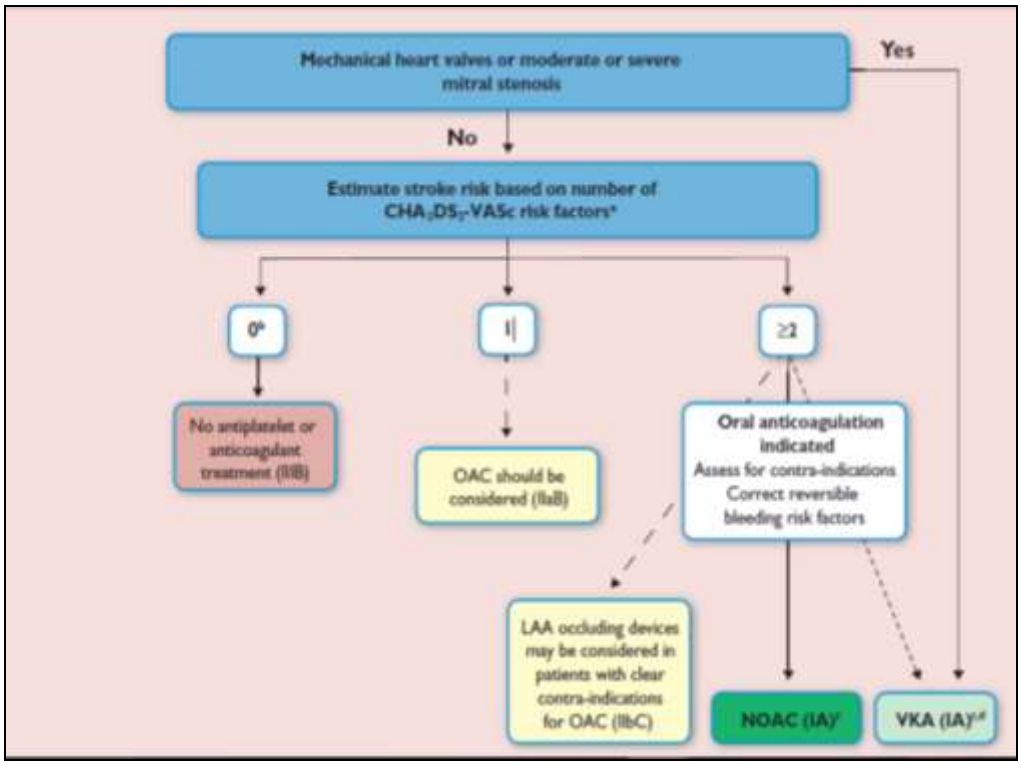
A complete medical history should be taken and all patients should undergo clinical evaluation that includes thorough assessment for concomitant conditions, establishing the AF pattern, estimation of stroke risk and AF-related symptoms, and assessment of arrhythmia-related complications such as thromboembolism or LV dysfunction. A 12-lead ECG is recommended to establish a suspected diagnosis of AF, to determine rate in AF, and to screen for conduction defects, ischaemia, and signs of structural heart disease.

Initial blood tests should evaluate thyroid and kidney function, as well as serum electrolytes and full blood count. Transthoracic echocardiography is recommended in all AF patients to guide treatment decisions. Transthoracic echocardiography should be used to identify structural disease (e.g. valvular disease) and assess LV size and function (systolic and diastolic), atrial size, and right heart function.
Ambulatory ECG monitoring in AF patients can assess the adequacy of rate control, relate symptoms with AF recurrences, and detect focal induction of bouts of paroxysmal AF. Transoesophageal echocardiography (TOE) is useful to further assess valvular heart disease and to exclude intracardiac thrombi, especially in the left atrial appendage, to facilitate early cardioversion or catheter ablation. Patients with symptoms or signs of myocardial ischaemia should undergo coronary angiography or stress testing as appropriate. In patients with AF and signs of cerebral ischaemia or stroke, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain is recommended to detect stroke and support decisions regarding acute management and long-term anticoagulation.
Most AF patients need regular follow-up to ensure continued optimal management. Follow-up may be undertaken in primary care, by specially trained nurses, by cardiologists, or by AF specialists. A specialist should co-ordinate care and follow-up. Follow-up should ensure implementation of the management plan, continued engagement of the patient, and therapy adaptation where needed.

2.3.3. Stroke prevention therapy in atrial fibrillation patients

OAT can prevent the majority of ischaemic strokes in AF patients and can prolong life. It is superior to no treatment or aspirin in patients with different profiles for stroke risk. The net clinical benefit is almost universal, with the exception of patients at very low stroke risk, and OAT should therefore be used in most patients with AF (**Figure 1).**

Figure 1. Stroke prevention in atrial fibrillation [ESC 2016]



Despite this evidence, underuse or premature termination of OAT is still common. Bleeding events, both severe and nuisance bleeds, a perceived 'high risk of bleeding' on anticoagulation, and the efforts required to monitor and dose-adjust VKA therapy are among the most common reasons for withholding or ending OAT [Frankel DS, Heart Rhythm 2015; Le Heuzey JY, Thromb Haemost 2014; O'Brien EC, Am Heart J 2014; Fang MC, Circ Cardiovasc Qual Outcomes 2010; Zalesak M, Circ Cardiovasc Qual Outcomes 2013]. However, the considerable stroke risk without OAT often exceeds the bleeding risk on OAT, even in the elderly, in patients with cognitive dysfunction, or in patients with frequent falls or frailty [Donze J, Am J Med 2012 Man-Son-Hing M; Arch Intern Med 1999]. The bleeding risk on aspirin is not different to the bleeding risk on VKA [Mant J, Lancet 2007] or NOAC [Diener HC, Lancet Neurol 2012] therapy, while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients.

2.3.4. Clinical risk scores for stroke and systemic embolism

The most widely employed scheme is the CHADS2 score [Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or TIA] (Table 2) [Lyp H. Lancet 2012]. Whilst well-validated, the limitations of the CHADS2 score have been debated, especially in the era of new oral anticoagulant

agents. Based on its original validation, it categorizes a score of 0 as ‘low risk’, 1-2 as ‘moderate/intermediate risk’ and ≥3 as ‘high risk’; thus a patient with previous stroke or TIA alone as a risk factor would be categorized as ‘moderate risk’ despite this type of patient having the highest risk for subsequent stroke or thromboembolism. One recent analysis using a nationwide cohort based on hospitalized AF patients found that those supposedly at low risk using the CHADS2 score (i.e., score=0) still had a rate of thromboembolism of 1.67 per 100 person years, whilst for those at "intermediate risk" using the CHADS2 score (score=1), this rate was 4.75 per 100 person years [Olesen JB, BMJ 2011]; these figures suggest that a CHADS2 score of 0-1 is not ‘truly low risk’.

Furthermore, other validation studies have shown a poor predictive value, evidenced by the c-statistic (c-statistic of 0.50 is no better than chance; closer c-statistic is to 1.0, better the predictive ability), for CHADS2 (and other) schema (c-statistics approximately 0.6) [Fang MC, J Am Coll Cardiol 2008; Baruch L, Stroke 2007; van Staa TP, et al. J Thromb Haemost 2011]. Furthermore, the CHADS2 score would categorise nearly 60-65% of various AF populations into the ‘moderate/intermediate risk’ category, where older management guidelines would recommend ‘warfarin or aspirin’ as suitable treatments [Fang MC, J Am Coll Cardiol 2008; Baruch L, Stroke 2007; van Staa TP, J Thromb Haemost 2011]. This would give some uncertainty as to what should one prescribe, with some clinicians prescribing aspirin rather than warfarin, as ‘the guidelines allow it’. Indeed, the limitations of the CHADS2 score have included its exclusion of common risk factors (eg, female gender, age 65-74, vascular disease, etc) associated with stroke or mortality (the two endpoints significantly reduced by OAT).

To complement the CHADS2 score, the ‘CHA2DS2-VASc’ score has been proposed [Lip GY, Chest 2010]. The CHA2DS2-VASc score places greater emphasis on what the ESC guidelines term ‘major risk factors’, that is, age ≥75 years and previous stroke/TIA, by allocating two points to each, with one point for the presence of each of the other ‘clinically relevant nonmajor’ risk factors, with total scores ranging from 0 to 9. The largest validation cohort study [Olesen JB, BMJ 2011] used Danish nationwide data on 73,538 hospitalized patients with AF between 1997-2006 who were not treated with warfarin. When patients were categorised into low, intermediate, and high risk strata, the predictive ability (evidenced by the c-statistic), of CHADS2 and CHA2DS2-VASc at 10-year follow-up was significantly better with CHA2DS2-VASc (0.888 vs. 0.812). Further, in this huge cohort, those with a CHADS2 score of 0-1 were not ‘low risk’ (stroke rate >1.67%/year), but those categorised as ‘low risk’ using CHA2DS2-VASc were ‘truly low risk’ for thromboembolism (stroke rate 0.78%/year). A more recent analysis again showed that the c-statistics of CHADS2 and CHA2DS2-VASc for predicting thromboembolism were 0.653 (0.50–0.81) and 0.898 (0.84– 0.96), respectively [Boriani G. Stroke 2011; Lyp H. Lancet 2012].

Table 2. CHA2DS2 and CHA2DS2-VASc scores

CHA2DS2 score

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A2	Age ≥75 years	1
D	Diabetes Mellitus	1
S2	Prior Stroke or TIA or thromboembolism	2

CHA2DS2-VASc scores

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A2	Age ≥75 years	2
D	Diabetes Mellitus	1
S2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

Other, less established risk factors for stroke include unstable international normalized ratio (INR) and low time in therapeutic range (TTR) in patients treated with VKAs; previous bleed or anaemia; alcohol excess and other markers for decreased therapy adherence; CKD; elevated high-sensitivity troponin; and elevated N-terminal pro-B-type natriuretic peptide [ESC 2016].

2.3.5. Clinical risk scores for bleeding

Several bleeding risk scores have been developed, mainly in patients on VKAs. These include HAS-BLED [hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)], ORBIT

(Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), and more recently, the ABC (age, biomarkers, clinical history) bleeding score, which also makes use of selected biomarkers. Stroke and bleeding risk factors overlap: for example, older age is one of the most important predictors of both ischaemic stroke and bleeding in AF patients. A high bleeding risk score should generally not result in withholding OAT. Rather, bleeding risk factors should be identified and treatable factors corrected [ESC 2016]

2.3.6. Recommended OAT for stroke prevention

2.3.6.1. Vitamin K antagonists

Warfarin and other VKAs were the first anticoagulants used in AF patients. VKA therapy reduces the risk of stroke by two-thirds and mortality by one-quarter compared with control (aspirin or no therapy) [Hart RG, Ann Intern Med 2007]. The use of VKAs is limited by the narrow therapeutic interval, necessitating frequent monitoring and dose adjustments, but VKAs, when delivered with adequate time in therapeutic range (TTR), are effective for stroke prevention in AF patients. VKAs are currently the only treatment with established safety in AF patients with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis.

Five large randomized trials published between 1989 and 1992 evaluated VKA mainly for the primary prevention of thromboembolism in patients with non-valvular AF. A sixth trial focused on secondary prevention among patients who had survived non-disabling stroke or TIA. In a meta-analysis, the RR reduction with VKA was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7%. When only ischaemic strokes were considered, adjusted-dose VKA use was associated with a 67% RR reduction. This reduction was similar for both primary and secondary prevention and for both disabling and non disabling strokes. Of note, many strokes occurring 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. Four of these trials were placebo controlled; of the two that were double blind with regard to anticoagulation, one was stopped early because of external evidence that OAT with VKA was superior to placebo, and the other included no female subjects. In three of the trials, VKA dosing was regulated according to the prothrombin time ratio, while two trials used INR target ranges of 2.5–4.0 and 2.0–3.0 [ESC 2010].

Direct comparison between the effects of VKA and aspirin has been undertaken in different studies, demonstrating that VKA were significantly superior, with an RR reduction of 39%. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that VKA (target INR 2–3) was

superior to aspirin 75 mg daily in reducing the primary endpoint of fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism by 52%, with no difference in the risk of major haemorrhage between warfarin and aspirin [Mant J, Lancet 2007].
This is consistent with the small Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trial, in which there were significantly more adverse events with aspirin (33%) than with warfarin (6%, P<0.002), including serious bleeding. When the trials conducted prior to BAFTA were considered, the risk for intracranial haemorrhage was doubled with adjusted dose warfarin compared with aspirin, although the absolute risk increase was small (0.2% per year) [Hart RG, Ann Intern Med 2007].

2.3.6.2. Non Vitamin K antagonists oral anticoagulant

The new oral anticoagulant drugs can be divided into two broad categories: the oral direct thrombin inhibitors and oral factor Xa inhibitors.
NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban, are suitable alternatives to VKAs for stroke prevention in AF. Their use in clinical practice is increasing rapidly. All NOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring. The phase III trials have been conducted with carefully selected doses of the NOACs, including clear rules for dose reduction that should be followed in clinical practice.

Dabigatran
In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study [Connolly SJ, N Engl J Med 2009] dabigatran 150 mg twice daily reduced stroke and systemic embolism by 35% compared with warfarin without a significant difference in major bleeding events. Dabigatran 110 mg twice daily was non-inferior to warfarin for prevention of stroke and systemic embolism, with 20% fewer major bleeding events. Both dabigatran doses significantly reduced haemorrhagic stroke and intracranial haemorrhage. Dabigatran 150 mg twice daily significantly reduced ischaemic stroke by 24% and vascular mortality by 12%, while gastrointestinal bleeding was significantly increased by 50%. There was a non-significant numerical increase in the rate of myocardial infarction with both dabigatran doses, which has not been replicated in large post-authorization analyses. These observational data have also replicated the benefit of dabigatran over VKA found in the RE-LY trial in patients who were mainly treated with the higher dabigatran dose (150 mg twice daily).

Rivaroxaban

In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial [Patel MR, N Engl J Med 2011], patients were randomized to rivaroxaban 20 mg once daily or VKA, with a dose adjustment to 15 mg daily for those with estimated CrCl 30–49 mL/min by the Cockroft–Gault formula. Rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment analysis achieved statistical superiority with a 21% reduction in stroke or systemic embolism compared with warfarin. Rivaroxaban did not reduce the rates of mortality, ischaemic stroke, or major bleeding events compared to VKA. There was an increase in gastrointestinal bleeding events, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage with rivaroxaban compared with warfarin. Comparable event rates have been reported in post-authorization analyses, which are part of the post-approval risk management process.

Apixaban

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation) trial [Granger CB, N Engl J Med 2011], apixaban 5 mg twice daily reduced stroke or systemic embolism by 21% compared with warfarin, combined with a 31% reduction in major bleeding and an 11% reduction in all-cause mortality (all statistically significant). Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on apixaban. Rates of gastrointestinal bleeding were similar between the two treatment arms. Apixaban is the only NOAC that has been compared with aspirin in AF patients; apixaban significantly reduced stroke or systemic embolism by 55% compared with aspirin, with no or only a small difference in rates of major bleeding or intracranial haemorrhage.

Edoxaban

In the ENGAGE AF-TIMI (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial [Giugliano RP, N Engl J Med 2013], edoxaban 60 mg once daily and edoxaban 30 mg once daily (with dose reductions in certain patients, were compared with adjusted-dose warfarin. Edoxaban 60 mg once daily was non-inferior to warfarin. In an on-treatment analysis, edoxaban 60 mg once daily significantly reduced stroke or systemic embolism by 21% and significantly reduced major bleeding events by 20% compared with warfarin, while edoxaban 30 mg once daily was non-inferior to warfarin for prevention of stroke and systemic embolism but significantly reduced major bleeding events by 53%. Cardiovascular death was reduced in

patients randomized to edoxaban 60 mg once daily or edoxaban 30 mg once daily compared with warfarin. Only the higher dose regimen has been approved for stroke prevention in AF.

Since edoxaban was introduced in the Italian market starting from the second part of 2016, it was not included in the present study.

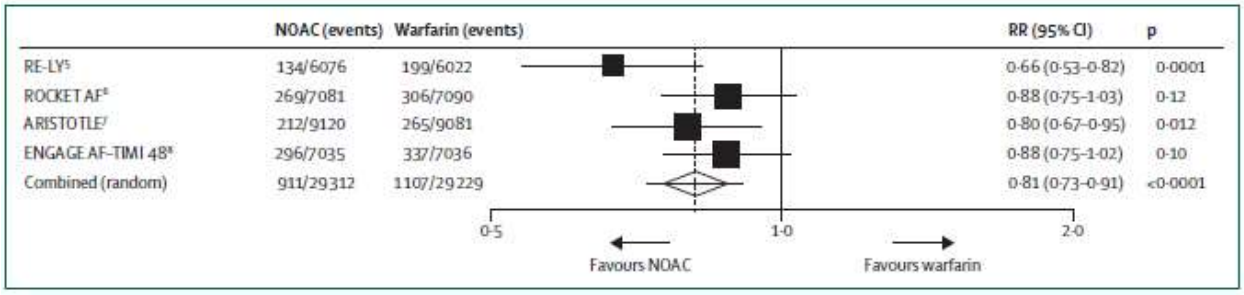
2.3.6.3. Non Vitamin K antagonists oral anticoagulant or vitamin K antagonist

Both VKAs and NOACs are effective for the prevention of stroke in AF. A meta-analysis [Ruff CT, Lancet 2014, Figure 2] based on the high-dose treatment groups of the pivotal studies of warfarin vs. NOACs included 42,411 patients receiving a NOAC and 29,272 receiving warfarin. NOACs in these dosages significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73–0.91; P<0.0001), mainly driven by a reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64; P< 0.0001). Mortality was 10% lower in patients randomized to NOAC therapy (RR 0.90; 95% CI 0.85 – 0.95; P = 0.0003) and intracranial haemorrhage was halved (RR 0.48; 95% CI 0.39 – 0.59; P< 0.0001), while gastrointestinal bleeding events were more frequent (RR 1.25; 95% CI 1.01 – 1.55; P=0.04).39 The stroke reduction with NOACs was consistent in all evaluated subgroups, while there was a suggestion of greater relative reduction in bleeding with NOACs at centers with poor INR control (interaction P =0.022). Notably, the substantial reduction in intracranial haemorrhage by NOACs compared with warfarin seems unrelated to the quality of INR control [Esc 2016].

Figure 2. Stroke or systemic embolism in the four trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin in patients with atrial fibrillation (RR=risk ratio).

	RE-LY[5]	ROCKET-AF[6]	ARISTOTLE[7]	ENGAGE-AF[8]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Renal clearance	~80%	~35%	~25%	~50%
Drug dosing	150 mg twice a day; 110 mg twice a day	20 mg once a day (15 mg for creatinine clearance <50 mL/min)	5 mg twice a day (2·5 mg when two of three following criteria are met: age ≥ 80 years, weight ≤60 kg, creatinine ≥1·5 mg/dL [133 μmol/L])	60 mg once a day (30 mg for creatinine clearance 30–50 mL/min, weight ≤ 60 kg, or strong P-glycoprotein inhibitor
Drug metabolism	P-glycoprotein	P-glycoprotein and CYP3A4	P-glycoprotein and CYP3A4	P-glycoprotein
Mean CHADS score	2·1	3·5	2·1	2·8
Design	Open label (dabigatran *vs* warfarin)	Blinded	Blinded	Blinded

Table 1: **The four large trials comparing non-vitamin K antagonist oral anticoagulants with warfarin for stroke prevention in atrial fibrillation**



2.3.6.4. Oral anticoagulation in atrial fibrillation patients with chronic kidney disease

CKD is associated with stroke and bleeding in large data sets. Anticoagulation can be safely used in AF patients with moderate or moderate-to-severe CKD [glomerular filtration rate (GFR) ≥15 mL/min]: the SPAF (Stroke Prevention in Atrial Fibrillation) III trial randomized 805/1936 participants with stage 3 CKD (estimated GFR ,59 mL/min/1.73 m2), and reported good outcomes on warfarin (INR 2–3). This finding is supported by a large Swedish database, in which stroke risk was lower in CKD patients with AF treated with warfarin (adjusted HR 0.76; 95% CI 0.72–0.80) [Friberg, Eur Heart J 2014] while bleeding was also slightly increased, especially during therapy initiation. In a meta-analysis of the major NOAC trials, patients with mild or moderate CKD suffered fewer strokes, systemic emboli, or major bleeding events on NOACs than on warfarin [Del-Carpio Munoz F, Am J Cardiol 2016; ESC 2016]. Kidney function should be regularly monitored in AF patients on OATs to allow dose adaptation for those on NOACs (Table 3, ESC 2016) and to refine risk estimation.

Table 3. Dose adjustment for NOACs from Phase III trials [Hart RG, Can J Cardiol 2013].

	Dabigatran (RE-LY) [318, 425]	Rivaroxaban (ROCKET-AF) [320, 426]	Apixaban (ARISTOTLE) [319, 427]	Edoxaban (ENGAGE AF-TIMI 48) [321]
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 mL/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl 30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 μmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

2.3.6.5. Management of bleeding

Although large clinical trials have provided clear evidence of the effects of NOACs versus warfarin in the atrial fibrillation population, there are several practical clinical issues that have not been fully addressed by those trials. To use the NOACs safely, there are special situations with which clinicians should be familiar. One of the advantages of the NOACs includes the lack of the need for anticoagulation monitoring. However, in case of serious or life-threatening bleeding the ability to assess anticoagulation status might be important. Yet, few accurate tests are commonly available. The activated partial thromboplastin time (aPTT) provides some information about the effect of dabigatran, such that a normal aPTT suggests relatively little dabigatran effect.

The prothrombin time is usually elevated, at least slightly, in patients treated with rivaroxaban. A modified thrombin time is commercially available to quantitate the effect of dabigatran, and anti-factor Xa assays are available that can establish the effects of the direct Xa inhibitors, although these assays are not widely available as tests with rapid turnaround times needed to guide emergent care. Since NOACs have a half-life of around 12 h, knowledge of when the last dose was taken allows an estimate of how much anticoagulation effect might be present. With dabigatran plasma drug level and clinical outcome are significantly correlated, with higher levels associated with lower risk of stroke and with higher rates of major bleeding. To treat serious bleeding, antithrombotic therapy should be stopped. Identification of bleeding source and local measures to control bleeding are the same as for any bleeding patient. If the patient took the NOAC within 2–4 h, oral activated charcoal will reduce absorption.

Reversal of other antithrombotics, such as aspirin with platelet transfusion, should be considered. Fluid resuscitation and blood transfusions might be indicated. Restoration of coagulation appears to be achieved, at least partly, by the administration of prothrombin complex concentrate or even activated factor VII, although no reliable clinical data exist to guide when and how to use the treatments [ESC 2015; Freek W A, Lancet 2015].

3. Pharmacology of oral anticoagulant treatments

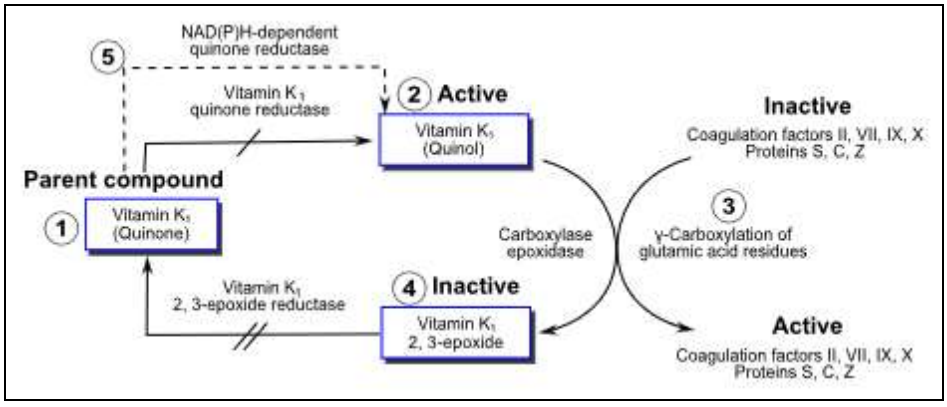
3.1. VKA

Vitamin K antagonists (VKA) are a group of substances that reduce blood clotting by reducing the action of vitamin K. These drugs deplete the active form of the vitamin by inhibiting the enzyme vitamin K epoxide reductase and thus the recycling of the inactive vitamin K epoxide back to the active reduced form of vitamin K. The drugs are structurally similar to vitamin K and act as competitive inhibitors of the enzyme. The term "vitamin K antagonist" is a misnomer, as the drugs do not directly antagonize the action of vitamin K in the pharmacological sense, but rather the recycling of vitamin K [Figure 3].

Vitamin K is required for the proper production of certain proteins involved in the blood clotting process. For example, it is needed to carboxylate specific glutamic acid residues on prothrombin. Without these residues carboxylated, the protein will not form the appropriate conformation of thrombin, which is needed to produce the fibrin monomers that are polymerized to form clots.

The action of this class of anticoagulants may be reversed by administering vitamin K for the duration of the anticoagulant's residence in the body, and the daily dose needed for reversal is the same for all drugs in the class. The vitamin K antagonists can cause birth defects (teratogens) [SPC].

Figure 3. Mechanism of actions of VKA.



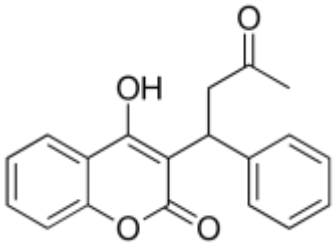
Coumarins (4-hydroxycoumarins) are the most commonly used VKAs. In medicine, the most commonly used VKA is warfarin. Warfarin was initially used as a rodenticide, but made the transition to pharmaceutical. Eventually some rodents developed resistance to it. The "second generation" VKAs for dedicated use as rodenticides are sometimes called "super warfarins." These VKAs are enhanced to kill warfarin-resistant rodents. The enhancement to the molecule takes the form of a larger lipophilic group to enhance the fat solubility of the poison and greatly increase the time it acts within the animal's body. However, as described above, the super-warfarins do not inhibit vitamin K and their effect is easily inhibited by vitamin K. Nevertheless, oral vitamin K may need to be given for times that may exceed a

month, in order to counter the effect of second-generation VKAs that have very long residence times in the fat of animals and humans.

Warfarin and acenocumarol are the only coumarins approved in Italy.

3.1.1. Warfarin

Active substance



Warfarin Sodium ($C_{19}H_{15}NaO_4$- 2H-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-, sodium salt) is an amorphous solid or a crystalline clathrate. The clathrate form consists principally of warfarin sodium and isopropyl alcohol, in a 2:1 molecular ratio; it contains not less than 8.0 percent and not more than 8.5 percent of isopropyl alcohol. Warfarin Sodium contains not less than 97.0 percent and not more than 102.0 percent of $C_{19}H_{15}NaO_4$, calculated on the anhydrous basis for the amorphous form or on the anhydrous and isopropyl alcohol-free basis for the crystalline form.

X-ray crystallographic studies of warfarin show that it exists in tautomeric form, as the cyclic hemiketal, which is formed from the 4-hydroxycoumarin and the ketone in the 3-position substituent. However, the existence of many 4-hydroxycoumadin anticoagulants (for example phenprocoumon) that possess no ketone group in the 3-substituent to form such a structure, suggests that the hemiketal must tautomerise to the 4-hydroxy form in order for warfarin to be active.

3.1.1.1. Pharmacodynamic properties

Mechanism of action

Warfarin is a synthetic anti-coagulant of the coumarin series and acts by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II-60 hours, VII-4-6 hours, IX-24 hours, and X-48-72 hours.

The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively.

Pharmacodynamic effects

The resultant in vivo effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

Clinical efficacy and safety

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of warfarin sodium may become more pronounced as effects of daily maintenance doses overlap.

Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

3.1.1.2. Pharmacokinetics properties

Warfarin is a racemic mixture of the R- and S-enantiomers with the S-enantiomer exhibiting 2-5 times greater anti-coagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption

Warfarin is essentially completely absorbed after oral administration with peak concentration generally reached within the first 4 hours.

Distribution

There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 12 hours is

distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in foetal plasma approach the maternal values, but warfarin has not been found in human milk. Approximately 99% of the drug is bound to plasma proteins.

Biotransformation

The elimination of warfarin is almost entirely by metabolism. Warfarin sodium is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine; and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4-, 6-, 7-, 8- and 10-hydroxywarfarin.

The Cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 1A2, and 34A. 2C9 is likely to be the principal form of human liver P-450 which modulates the in vivo anticoagulant activity of warfarin.

Elimination

The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-Warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-Warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

3.2. Novel oral anticoagulants –NOACs-

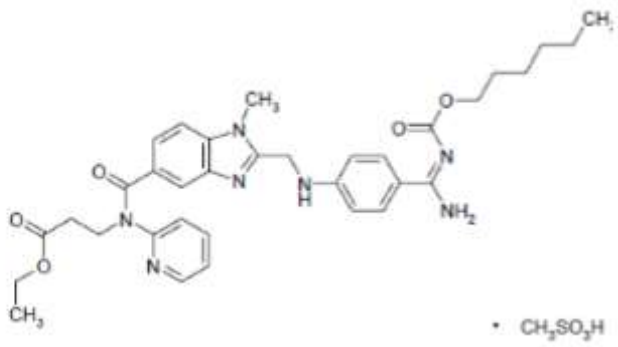
3.2.1. DABIGATRAN

Active Substance

Dabigatran etexilate (DE) is the oral pro-drug of the active moiety dabigatran. The dabigatran etexilate pro-drug was developed due to the limited oral availability of dabigatran, and it is converted into dabigatran (DAB) in vivo via esterases. The drug substance is the mesilate salt form of the pro-drug, called dabigatran etexilate mesilate (DEM).

The chemical name (IUPAC) of dabigatran etexilate mesilate is ethyl N-{[2-({[4-((E)-amino {[(hexyloxy) carbonyl] imino} methyl) phenyl] amino} methyl)-1-methyl-1H-benzimidazol-5-yl]

carbonyl}-Npyridin-2-yl-β-alaninate methanesulfonate corresponding to the molecular formula C34H41N7O5 x CH4O3S (C35H45N7O8S) and the structure shown below:



DEM exhibits polymorphism. Two forms, modification I and II are known. The drug substance is modification I in the anhydrous form, possibly mixed with modification II. A hydrated form with a stoichiomety close to a hemihydrate also exists.

3.2.1.1. Pharmacology

Dabigatran etexilate mesilate (DEM) is the oral pro-drug of the active moiety dabigatran. Dabigatran is a potent, synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. As a follow up on previous concerns the applicant provided experimental documentation for competitive inhibition of thrombin. Furthermore, Dabigatran is demonstrated to be equipotent for inhibiting free or clot bound thrombin.

Comprehensive experimental documentation for the off-target binding abilities of both DEM and Dabigatran showed that only DEM exhibits minor unspecific binding in this binding screen at concentrations 50-60-fold in excess of relevant concentrations in humans. A bleeding time study in rats treated with supratherapeutic doses showed that the activated factor VII or activated prothrombinase complex would be relevant unspecific antidotes in case of bleeding episodes in man.

3.2.1.2. Pharmacodynamic properties

Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors(SPAF).

Steady state geometric mean dabigatran peak plasma concentration, measured around 2hours after 150mg dabigatran etexilate administration twice daily, was 175ng/mL, with a range of 117-275ng/mL (25th-75th percentile range). The dabigatran geometric mean trough concentration, measured at trough in the morning, at the end of the dosing interval (i.e. 12hours after the 150mg dabigatran evening dose), was on average 91.0ng/mL, with a range of 61.0-143ng/mL (25th-75th percentile range).For patients with NVAF treated for prevention of stroke and SEE with 150mg dabigatran etexilate twice daily, • the 90th percentile of dabigatran plasma concentrations measured at trough (10-16hours after the previous dose) was about 200ng/mL, • an ECT at trough (10-16hours after the previous dose), elevated approximately 3-fold upper limit of normal refers to the observed 90th percentile of ECT prolongation of 103seconds, • an aPTT ratio greater than 2-fold upper limit of normal (aPTT prolongation of about 80seconds), at trough (10-16hours after the previous dose) reflects the 90th percentile of observations.

Clinical efficacy and safety

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomized Evaluation of Long–term anticoagulant therapy) a multicentre, multi-national, randomized parallel group study of two blinded doses of dabigatran etexilate (110mg and 150mg twice daily) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke and SEE. The primary objective in this study was to determine if dabigatran etexilate was non-inferior to warfarin in reducing the occurrence of the composite endpoint stroke and SEE. Statistical superiority was also analyzed.

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5years and a mean CHADS2 score of 2.1. The patient population was 64% male, 70% Caucasian and 16% Asian.

For patients randomized to warfarin, the mean percentage of time in therapeutic range (TTR) (INR2-3) was 64.4%(median TTR 67%).

The RE-LY study demonstrated that dabigatran etexilate, at a dose of 110mg twice daily, is non-inferior to warfarin in the prevention of stroke and SEE in subjects with atrial fibrillation, with a reduced risk of ICH, total bleeding and major bleeding. The dose of 150mg twice daily reduces significantly the risk of ischemic and haemorrhagic stroke, vascular death, ICH and total bleeding compared to warfarin. Major bleeding rates with this dose were comparable to warfarin. Myocardial infarction rates were slightly increased with dabigatran etexilate 110 mg twice daily and 150mgtwice daily compared to warfarin (hazard ratio 1.29; p=0.0929 and hazard ratio 1.27; p=0.1240, respectively). With improving monitoring of INR the observed benefits of dabigatran etexilate compared to warfarin diminish.

For the primary endpoint, stroke and SEE, no subgroups (i.e., age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin. For the primary safety

endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with dabigatran compared to warfarin increased with age. Relative risk was highest in patients ≥75years.The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with bothdabigatran etexilate and warfarin.There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.

RELY-ABLE (Long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial) The RE-LY extension study (RELY-ABLE) provided additional safety information for acohort of patients which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. Patients were eligible for the RELY-ABLE trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the same double-blind dabigatran etexilate dose randomly allocated in RE-LY, for up to 43months of follow up after RE-LY (total mean follow-up RE-LY + RELY-ABLE, 4.5years). There were 5897 patients enrolled, representing 49% of patients originally randomly assigned to receive dabigatran etexilate in RE-LY and 86% of RELY-ABLE–eligible patients. During the additional 2.5years of treatment in RELY-ABLE, with a maximum exposure of over 6years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses 110mgb.i.d. and 150mgb.i.d.. No new safety findings were observed. The rates of outcome events including, major bleed and other bleeding events were consistent with those seen in RE-LY.

3.2.1.3. Pharmacokinetics

Absorption

DEM was identified as a medium-affinity substrate for the efflux transporter P-glycoprotein in the human colon carcinoma derived cell line Caco-2. Moreover, DEM inhibited the apical-to-basolateral transport of the P-glycoprotein substrate digoxin in a concentration-dependent manner with an IC50 of 25 µM (50-fold clinical Cmax). A clinical study confirmed that no pharmacokinetic (PK) interactions occur when DEM is co-administered with digoxin. Following single administration, the oral bioavailability of [14C]-DEM was 16% in rat, 5% in rabbit, 8% in Rhesus monkey and 7% in man. The clearance was 4.5 to 6-fold higher in rat, rabbit and monkey when compared to man and consequently the half-life was lower in these species. Tmax was obtained 0.5 h following p.o. dosing in mouse and rat, at 1.3 h in rabbit and monkey and at 1.5 h in man. No gender differences were observed with respect to absorption following repeated dosing of mice, rats and monkeys. No consistent trend towards lower plasma exposure levels with repeated dosing was observed in the species tested.

Distribution

DEM related radioactivity distributed into most tissues 30 minutes following oral dosing in rats whereas only very limited levels of radioactivity were detected in the CNS. Besides the gastrointestinal tract, DEM related radioactivity was predominantly detected in liver, urinary tract, artery wall and adrenal medulla. Minor levels of radioactivity were detected in skin and bone marrow. 24 hours following oral dosing, traces of radioactivity were only detected in the liver. DEM and DAB displayed no affinity for melanin containing tissues. The distribution of [14C]-DAB from plasma into blood cells was negligible. Only very low levels of radioactivity were detected in foetal tissues following p.o. dosing to rats thus DEM exhibits low placental transfer. The plasma protein binding of [14C]-DAB was low in plasma of mice (22-26%), rat (29-33%), rabbits (32%), Rhesus monkeys (38 39%) and humans (29-30%).

Metabolism

The glucuronidation of dabigatran was investigated in vitro by using human liver or intestinal microsomes or expressed UDP-glucuronosyltransferases (UDP = Uridine-Diphosphate). This indicated a much lower capacity of the intestine compared to the liver for the glucuronidation of dabigatran. Incubation with a broad range of UGT enzymes indicated that UTG 2B15 exhibited the highest activity for the glucuronidation of dabigatran. Additional data on the specific glucuronidation of dabigatran was obtained through co-incubation with several non-specific inhibitors indicating the contribution to the glucuronidation of dabigatran by UGT1A9, UGT2B7 and UGT2B15. It was concluded that dabigatran was a non-specific, low-affinity substrate of UGT1A9, UGT2B7 and UGT2B15; the latter UGT was probably the major catalyst for the formation of the 1-O-acylglucuronide.

Pharmacokinetic drug interaction

In vitro studies in P-gp-expressing Lewis-lung cancer porcine kidney 1 cells indicated that dabigatran etexilate mesilate was a substrate of P-gp, and dabigatran was not a substrate of P-gp. DEM was considered to be a low-to-medium-affinity substrate of P-gp with an estimated Km value of above 10 µM. Different interaction/inhibition studies in P-gp-expressing cells, using digoxin, amiodarone, clarithromycin, itraconazole, quinidine and ritonavir as probe substrates showed that the potential of DEM and dabigatran to inhibit P-gp activity was minimal indicating that neither DEM nor dabigatran would influence the biliary excretion, urinary secretion or tissue distribution of co-administered drugs that are substrates of P-gp. Some inhibitory effects on DEM transport were observed and consequently, drug-drug interactions based on the inhibition of P-gp-mediated DEM could not be ruled out if the concentrations of these P-gp modulators at the interaction sites reach or exceed the IC50 values estimated in this study (0.5 to 75 µM). However, due to high intrinsic passive permeability DEM is

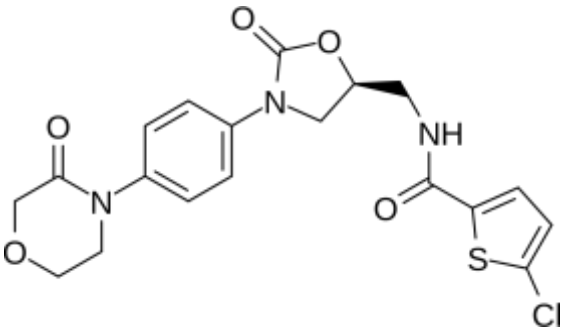
expected to be well absorbed in humans even during co administration of potent P-gp substrate inhibitors.

Other pharmacokinetic studies

A comparative PK study was conducted in male and female mice of two different strains (Crl:NMRI and CrllCR:CD1) following a single oral administration of DEM. The objectives of the study were to investigate possible differences between these two mouse strains concerning the PK behaviour of dabigatran and to examine the extent of circulating conjugates of dabigatran. Although a slight gender effect was observed in mice similar glucuronidation of dabigatran was recorded in NMRI and CD1 mice, in accordance with previous data on metabolite pattern in NMRI mice showing non-quantifiable traces of acyl-glucuronides of dabigatran. No significant gender related differences in pharmacokinetics were seen in rats and monkeys.

3.2.2.RIVAROXABAN

Active substance



The chemical name of Rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4morpholinyl)phenyl]-1,3-oxzolidin-5-yl}methyl)-2-thiophene-carboxamide. It is a white to yellowish powder with a molecular weight of 435.89. The empirical formula and the relative molecular mass of rivaroxaban have been confirmed by elementary analysis and mass spectrometry. The structure has been confirmed with spectral data: IR, UV-VIS, 1H-NMR, 13C-NMR, mass spectrometry and elementary analysis. The 1,3-oxazolidin ring system has in position 5 a chiral carbon-atom with (S) configuration. Single-crystal x-ray structural analysis confirms the S configuration of the molecule.

Rivaroxaban is only slightly soluble in organic solvents (e.g. acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media with pH 1 – 9 (pH-independent 5 - 7 mg/L are soluble at 25 °C). The partition coefficient in octanol / water (log Po/w) is 1.5.

Rivaroxaban has been tested for polymorphism and pseudo-polymorphism according to the ICH Q6A guideline (decision tree 4). Rivaroxaban crystallizes in three polymorphs. Polymorph I is the

thermodynamically stable one and has been used in all tablet formulations during clinical development and will be used in the commercial product. The identity of polymorph I is routinely controlled by Raman spectroscopy at release.

3.2.2.1. Pharmacodynamic properties

Mechanism of action Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC. The activated partial thomboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative antifactor-Xa tests.

Clinical efficacy and safety

The rivaroxaban clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of cardiovascular (CV) death, MI or stroke in subjects with a recent ACS (ST-elevation myocardial infarction [STEMI], non- ST-elevation myocardial infarction [NSTEMI] or unstable angina [UA]). In the pivotal double-blind ATLAS ACS 2 TIMI 51 trial, 15,526 patients were randomly assigned in a 1:1:1 fashion to one of three treatment groups: Xarelto 2.5 mg orally twice daily, 5 mg orally twice daily or to placebo twice daily co-administered with ASA alone or with ASA plus a thienopyridine

(clopidogrel or ticlopidine). Patients with an ACS under the age of 55 had to have either diabetes mellitus or a previous MI. The median time on treatment was 13 months and overall treatment duration was up to almost 3 years. 93.2 % of patients received ASA concomitantly plus thienopyridine treatment and 6.8 % ASA only. Among patients receiving dual anti-platelets therapy 98.8% received clopidogrel, 0.9 % received ticlopidine and 0.3 % received prasugrel. Patients received the first dose of Xarelto at a minimum of 24 hours and up to 7 days (mean 4.7 days) after admission to the hospital, but as soon as possible after stabilisation of the ACS event, including revascularisation procedures and when parenteral anticoagulation therapy would normally be discontinued.

Both the 2.5 mg twice daily and the 5 mg twice daily regimens of rivaroxaban were effective in further reducing the incidence of CV events on a background of standard antiplatelet care. The 2.5 mg twice daily regimen reduced mortality, and there is evidence that the lower dose had lower bleeding risks, therefore rivaroxaban 2.5 mg twice daily co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine is recommended for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers.

Relative to placebo, Xarelto significantly reduced the primary composite endpoint of CV death, MI or stroke. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period. Also the first secondary endpoint (all cause death, MI or stroke) was reduced significantly. An additional retrospective analysis showed a nominally significant reduction in the incidence rates of stent thrombosis compared with placebo. The incidence rates for the principal safety outcome (non-CABG TIMI major bleeding events) were higher in patients treated with Xarelto than in patients who received placebo. However the incidence rates were balanced between Xarelto and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding.

Patients with elevated biomarkers (troponin or CK-MB) and without a prior stroke/TIA constituted 80 % of the study population. The results of this patient population were also consistent with the overall efficacy and safety results.

3.2.2.2. Pharmacokinetics properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (Cmax) appearing 2 - 4 hours after tablet intake. Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100 %) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or Cmax at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10

mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %. Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and Cmax compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure. Bioavailability (AUC and Cmax) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion. Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on in vitro investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein). Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

Gender

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment. The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT. Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C.

Renal impairment

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min. Due to the high plasma protein binding rivaroxaban is

not expected to be dialysable. Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

3.2.2.2.1. Pharmacokinetic data in patients

In patients receiving rivaroxaban 2.5 mg twice daily for the prevention of atherothrombotic events in patients with ACS the geometric mean concentration (90 % prediction interval) 2 - 4 h and about 12 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 47 (13 - 123) and 9.2 (4.4 - 18) µg/l, respectively.

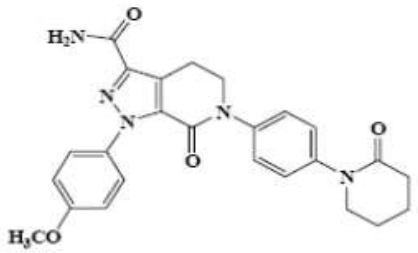
Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor-Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor-Xa activity was best described by an Emax model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

3.2.3.APIXABAN

Active Substance

The INN name of the active substance is apixaban and it chemical name is 1-(4-Methoxyphenyl)-7oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1Hpyrazolo[3,4-c]pyridine-3-carboxamide. The molecular formula of the active substance is C25H25N5O4, its relative molecular mass 459.50 and its structural formula is shown below.



Apixaban appears as a white to pale yellow, non hygroscopic crystalline powder, with an aqueous solubility of 0.028 mg/ml at 24°C. Apixaban is a non-ionizable compound and its partition coefficient at 24°C is 44.7 (log Po/w = 1.65) at pH 7.4 (n-Octanol / aqueous buffer). The molecule has no chiral centres, therefore, no stereoisomers exist. It shows polymorphism and a number of hydrates and solvates were identified. However, only one form is consistently produced by the proposed synthetic process.

3.2.3.1. Pharmacology

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

3.2.3.1.1. Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-FXa kits, however results differ across kits. Data from clinical trials are only available for the Rotachrom® Heparin chromogenic assay. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is approximately linear over a wide dose range of apixaban.

3.2.3.1.2. Pharmacokinetics

Absorption

In vitro data with excised segments of rat duodenum, jejunum, ileum and colon, showed that apixaban is absorbed throughout the rat intestinal tract. The permeability coefficient in the jejunum provided evidence for involvement of an intestinal efflux transport mechanism. A range of in vitro studies in monolayers of Caco-2 cells expressing a number of efflux transporters including P-gp and BCRP, porcine kidney-derived cells (LLC-PK1) transfected with P-gp transporters, canine kidney-derived (MDCKII) cells transfected with BCRP transporters, indicated that apixaban is a substrate for both P-gp and BCRP, and it is not transported by MRP or OAT1, OAT3, OATP1B1, OATP1B3 and OATP2B1 transporters. These active transport mechanisms may play a role in the limited bioavailability after oral administration of apixaban. In addition, evidence was found for paracellular transport. Absorption may also be limited by dissolution rate (at high doses).

Single dose pharmacokinetics

In a comparative study elimination half-life in rats (2-3 hrs) was shorter than in dogs (5-6 hrs) and chimpanzees (5-7 hrs). Distribution volume is relatively low in rats (0.31 L/kg), dogs (0.30 L/kg) and chimpanzees (0.17 L/kg). Clearance (rat 4.3 ml/min/kg, dog 0.87 ml/min/kg, chimpanzee 0.30 ml/min/kg) is low (10, 2 and 1% respectively) compared to hepatic blood flow. The toxicokinetic data show that exposure increases less than dose-proportional. In particular at high doses and in the dietary

studies exposure hardly increased with increasing dose. There is no evidence of sex-related differences. In some studies exposure increases somewhat with prolonged administration, but this is not consistently found in all studies.

Distribution

Plasma to blood ratios of about one in dog and human blood indicate uniform distribution between plasma and red blood cells and thus no specific distribution to red blood cells.

Protein binding differs between the species. The unbound fraction at concentrations of 1-10 µM is about 13% in human vs about 4% in rats and 8% in dogs. At the tested concentrations there was no effect of concentration or gender. In mice protein binding is much lower, with 44-67 % unbound, dependent on the tested concentration (range 100 – 2000 ng apixaban/ml). These differences between the species used in the toxicological studies and humans should be taken into account in interpreting the toxicology studies.

Two single dose radiolabel distribution studies were provided in rats. The data show a wide distribution, with the highest values in excretory organs (liver, kidney, urinary bladder (and contents), bile) and intestinal tract (and contents). After a dose of 20 mg/kg in male Long-Evans rats also relatively high Cmax and AUC were found in adrenals, lungs, thyroid gland, but after a dose of 5 mg/kg in Sprague Dawley rats (both sexes) these organs showed Cmax similar to most other organs and tissues. There was no qualitative difference in distribution between male and female rats, but the female rats showed higher Cmax values in the intestinal tract.

Distribution in pregnant rats/fetuses: Cmax in amnion was high. Significant concentrations were found in placenta and fetal blood, kidney and liver. Toxicokinetic data collected in the reproductive and developmental toxicity studies in rats, mice and rabbits showed that generally fetal plasma concentrations of apixaban were lower than those in the dams. Distribution to rat milk: Pregnant rats showed a high Cmax in mammary gland. Concentrations of apixaban in rat milk exceed those in blood and plasma. The high concentration in milk vs plasma (at the plasma Tmax (0.5 hr) 8.5 fold, AUC in milk was about 30 fold plasma AUC) suggests involvement of active transport (possibly BCRP transporter). Elimination half life from rat milk, blood and plasma was similar.

Metabolism

Apixaban is mainly metabolized by CYP3A4/5 with conjugation via SULT1A1, but several other CYP and SULT isozymes are also involved. No apixaban metabolites were found to have pharmacological activity and there were no unique human metabolites.

Excretion

After single oral administration of radiolabelled apixaban to intact male mice, male rats, female rabbits or male dogs, most of the dose was excreted in faeces (in mice about 70% in the first 12 hrs, in rats and dogs about 70% in the first 48 hrs, and in female rabbits about 55 % in the first 48 hrs) and most of the remainder of the dose in urine (mice about 14% in the first 12 hrs, rats 11-13% in 48 hrs, dogs about 8.5% in 48 hrs, and female rabbits much less > 2% in 48hrs). Bile-duct cannulated rats showed that part of the dose was eliminated by the biliary route (about 3% over a 48 hr period after oral gavage). After intravenous infusion intact male rats or female rabbits excreted a larger part into urine (male rats 21% and female rabbits 23% in 24 hrs). Intravenously treated bile-duct cannulated rats excreted even more into urine (47% in 24 hrs) and also a large part into bile (23% in 24 hrs). Most of the faecally and urinary eliminated material consists of parent compound. A large part of the faecally cleared material is probably unabsorbed apixaban. Furthermore, there is evidence for secretion of apixaban and metabolites into the intestine which is mostly likely caused by excretion via Pglycoprotein. The rabbit data showed a much larger extent of biotransformation (larger role of metabolic clearance) in this species compared to the other species.

3.2.3.1.2.1. Pharmacokinetics interactions

Apixaban is not an inhibitor or inducer of CYP; inhibition was only observed at concentrations 25 times the maximal observed human plasma concentrations. In addition, apixaban does not affect the absorption of drugs that are P-glycoprotein substrates. Since apixaban is a substrate for CYP3A4/5, BCRP, and P-glycoprotein, co-administration of drugs that modulate their activities could affect the absorption and disposition of apixaban. However, the relatively low dependence of apixaban on metabolic clearance for its elimination and the multiple pathways available for apixaban elimination (renal and biliary clearance and, possibly, intestinal secretion) suggests that any such effects are likely to be of relatively low magnitude. Since apixaban is a substrate for the P-glycoprotein transporter, its absorption may be affected by P-glycoprotein inhibitors. The SmPC advises caution when coadministering pixaban with strong inhibitors and inducers of both CYP3A4 and P-glycoprotein.

Other pharmacokinetics studies

In fasted beagle dogs, bioavailability of apixaban was reduced (up to 50%) by active charcoal treatment, given 0.25 – 3 hrs after the oral apixaban dose. The highest reduction was found when activated charcoal was administered 3 hrs after the apixaban dose (1 hour before Tmax).

3.3. Comparative pharmacology of approved anticoagulants

The NOACs have been shown collectively to be safer (for avoiding intracerebral hemorrhage) and more effective than warfarin, leading some guidelines to recommend them preferentially [ESC 2016]. However, these drugs have much shorter time to onset and offset compared with warfarin, and each exhibits some level of renal clearance (table 4) [Benjamin A Steinberg, BMJ. 2014].

Table 4. Pharmacologic properties of oral anticoagulants

	Drug			
Property	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Mechanism	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Dosing†	Variable (dose adjusted on the basis of international normalised ratio)	150 mg; 110 mg bid (Europe only); 75 mg bid for creatinine clearance‡ 15-30 (US only), not recommended if <15	20 mg daily; 15 mg daily for creatinine clearance‡ 15-50, not recommended if <15	5 mg bid; 2.5 mg bid for patients with >2 of the following: creatinine ≥133 µmol/L, age ≥80 years, or weight ≤60 kg; creatinine clearance‡ <15: no data available
Oral bioavailability	100%	3-7%	60%	58%
Time to effect (h)	72-96	1-2	2-4	3-4
Half life (h)	~40	12-17	5-9	8-15
Notable drug interactions	Numerous	Strong P-glycoprotein inducers		
		Strong P-glycoprotein inhibitors with concomitant kidney dysfunction	Strong P-glycoprotein inhibitors; strong cytochrome P450 inducers and inhibitors	

3.3.1. Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants

Treatment with VKAs requires careful consideration of multiple food and drug interactions. Despite high expectations of less interactions with the NOAC drugs, physicians will have to consider pharmacokinetic (PK) effects of accompanying drugs and of comorbidities when prescribing NOACs. The uptake, metabolism, and elimination of the different NOACs are summarized in the table 5 as reported from the Esc 2015 guideline [ESC 2015].

Table 5. Absorption and metabolism of NOACs [ESC 2015].

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	66% without food. Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

An important interaction mechanism for all NOACs consists of significant re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut.

Moreover, the P-gp transporter may also be involved in renal clearance: competitive inhibition of this pathway therefore will result in increased plasma levels. Many drugs used in AF patients are P-gp inhibitors (e.g. verapamil, dronedarone, amiodarone, and quinidine). CYP3A4-type cytochrome P450-dependent elimination is involved in rivaroxaban and apixaban hepatic clearance. Strong CYP3A4 inhibition or induction may affect plasma concentrations and effect, and should be evaluated in context. Non-renal clearance of apixaban is diverse (metabolism, biliary excretion, and direct excretion into the intestine), with at most a minor contribution of CYP3A4, which makes CYP3A4 interactions of less importance for this drug. The apixaban SmPC indicates that it is not recommended in combination with strong inhibitors of both CYP3A4 and P-gp. Conversely, strong inducers of P-gp and CYP3A4 (such as rifampicin, carbamazepine, etc.) will strongly reduce the NOAC plasma levels, and therefore such combination should also be used with caution. The bioavailability of dabigatran is markedly lower than that of the other drugs. This means that slight fluctuations in absorption may have a greater impact on the plasma levels than with other drugs.

There is good rationale for reducing the dose of NOACs in patients with a high bleeding risk and/or when a higher plasma level of the drug can be anticipated. Data from RE-LY and ENGAGE-AF have shown a relationship between dose, patient characteristics, plasma concentration, and outcomes, with similar data on file for the other NOACs. A post hoc analysis of RE-LY data has shown that similar

dose adjustments for dabigatran as per the EU label (i.e. 110 mg BID if age ≥80 years or concomitant use of verapamil) would have further improved its overall net clinical benefit over the randomized use of 110 or 150 mg BID as per the design of the RE-LY trial [Connolly SJ, N Engl J Med 2009; Dabigatran SmPC; ESC 2015]

3.3.2. Interactions with food and commonly prescribed drugs in atrial fibrillation

Unlike with warfarin, with which variable amounts of vitamin K in food contributes to instability of effect, there are no dietary restrictions with NOACs. The only important issue with respect to food is that rivaroxaban has 40% more gastrointestinal absorption when taken with a high calorie meal than with a low calorie meal, thus it is generally recommended to be taken with dinner as the most consistent meal. Many patients with atrial fibrillation are on several drugs, and a substantial proportion of these interact with metabolic pathways of NOACs. CYP3A4 and P-glycoprotein inhibitors are the most important drugs that increase plasma concentrations of NOACs, although drug interactions are much less of an issue than with VKA. For example, even though amiodarone has some inhibition of P-glycoprotein pathway and effect on NOAC metabolism, the benefits of NOACs appear to be at least as great in this subgroup of patients, perhaps because the interactions are even greater with warfarin. In the NGAGE trial the dose of edoxaban was reduced by 50% for patients on verapamil or quinidine, strong inhibitors of the P-glycoprotein pathway. The doses of NOACs in the other trials were not reduced for patients taking these drugs, although this could be taken into account, especially for patients on the border of dose reduction based on other criteria such as renal function. [SmPC; Freek W Lancet 2015].

3.3.3. Pharmacodynamic interactions

Apart from the PK interactions, it is clear that association of NOACs with other anticoagulants, platelet inhibitors (aspirin, clopidogrel, ticlodipine, prasugrel, ticagrelor, and others), and non-steroidal anti-inflammatory drugs increases the bleeding risk. There are data indicating that the bleeding risk in association with antiplatelet agents' increases by at least 60% (similar as in association with VKAs). Therefore, such associations should be carefully balanced against the potential benefit in each clinical situation. Association of NOACs with dual antiplatelet drugs requires active measures to reduce time on triple therapy [SmPC; ESC 2015].

Advantages and disadvantages of oral anticoagulants are summarised in Figure 4.

Figure 4: Advantages and disadvantages of oral anticoagulants [ESC 2015].

	Warfarin	Direct oral anticoagulants*
Dosing	Once daily dosing may be more convenient	May require more frequent dosing
Dietary restrictions	Need to ensure relatively constant level of vitamin K intake	None; rivaroxaban should be taken with food when used for atrial fibrillation thromboprophylaxis
Monitoring therapy	PT/INR monitoring is required, which entails periodic visits to a facility for most patients (point of care devices may be an option for some)	Not required; however, non-compliance will not be as readily apparent
Drug interactions	Many	Rivaroxaban interacts with CYP-3A4 and P-glycoprotein inhibitors; dabigatran may be affected by P-glycoprotein inducers or inhibitors
Time in therapeutic range	Approximately 65 percent based on clinical trials	Expected to be superior to warfarin, although therapeutic ranges have not been established
Reversal agent (s)	Several available (eg, vitamin K, FFP, PCC, rFVIIa)	Idarucizumab is available to reverse dabigatran. Specific reversal agents are not available for direct factor Xa inhibitors but several are in development. Activated charcoal; antifibrinolytic agents; PCC may be used for life-threatening bleeding. Hemodialysis could be used in severe cases for dabigatran (but not rivaroxaban or apixaban).
Monitoring reversal	PT/INR can be used	TT can be used for dabigatran; anti-factor Xa can be used for apixaban
Effect of comorbid conditions		Renal function affects pharmacokinetics; dosing unclear in those with obesity

dabigatran, rivaroxaban, apixaban

3.4. The importance of adherence

The anticoagulant effect of NOACs fades rapidly 12–24 h after the last intake. Therefore, strict adherence to medication intake is crucial. Even if appropriate new anticoagulation tests would be used to gauge NOAC plasma levels, they cannot be considered as tools to monitor adherence since their interpretation is highly dependent on the timing of testing in respect to the last intake of the drug. In contrast to INR measurements in VKA-treated patients, NOAC plasma determination does not indicate anything about adherence before the last intake.

The absence of a need for routine plasma level monitoring means that NOAC patients are less likely to be seen as frequently during follow-up compared with VKA patients. Physicians should develop ways to optimize adherence, since this is known to be ≤80% for most drugs in daily practice. Such low adherence rate would severely diminish the benefit of treatment. There are limited data yet on the actual adherence to NOAC therapy, nor studies on how it can best be optimized. Initial real world data do suggest variable adherence to NOAC intake (mainly studied for dabigatran, the first available NOAC) [Gorst-Rasmussen A, J Thromb Haemost 2015; Cutler TW, J Manag Care Spec Pharm 2014]. Interestingly, patients with higher morbidity, including patients with a higher risk of stroke or bleeding, exhibited better adherence to dabigatran [Gorst-Rasmussen A, J Thromb Haemost 2015]. There is also evidence for significantly lower discontinuation rates in NOAC patients than in VKA patients ('persistence') [Martinez C, Thromb Haemost 2015].

Some practical considerations

(i) Patient education on the relevance of strict adherence is of utmost importance. Many simultaneous approaches should be employed in this regard: leaflets and instructions at initiation of therapy; a patient anticoagulation card; group sessions; re-education at every prescription renewal. Several organizations also offer online patient support websites, including EHRA, the AF Association in the UK, Anticoagulation Europe, and AFNET;

(ii) Family members should be involved in this education, so that they can understand the importance of adherence, and help the patient in this regard.

(iii) There should be a pre specified follow-up schedule for the NOAC patient, known to and shared by general practitioners, pharmacists, nurses, anticoagulation clinics, and other professionals providing care. Each of those actors has responsibility to reinforce adherence.

(iv) Some countries have a highly networked pharmacy database, which can help track the number of NOAC prescriptions that individual patients claim. In such countries, pharmacists could be involved in adherence monitoring, and this information should be used to cross-check appropriate prescription and dosing.

(v) Many technological aids are being explored to enhance adherence: the format of the blisters; medication boxes (conventional or with electronic verification of intake); smartphone

applications with reminders and/or SMS messages to alert the patient about the next intake some even requiring confirmation that the dose has been taken. Again, the long term effects of such tools are unknown and one tool may not suit all patients. The prescribing physician, however, should consider individualization of these aids.

(vi) An OD dosing regimen was related to greater adherence vs. BID regimens in cardiovascular patients, and in AF patients (for diabetes and hypertension drugs). It is likely that also for NOACs an OD dosing regimen is best from a total pill count perspective, but it is unknown whether any regimen is superior in guaranteeing the clinical thromboembolic preventive effects and safety profile as seen in the clinical trials. There is modelling data suggesting that there is potentially a larger decrease in anticoagulant activity occurring when a single pill is omitted from an OD dosing regimen compared with when a single or even two pills are omitted from a BID regimen. The clinical relevance of these fluctuations is unknown and until proven clinically it is essential to ensure that drugs are taken according to the prescribed regimen to obtain the results observed in the clinical trials. FDA-compiled registry data with dabigatran have confirmed the risk/benefit profile of dabigatran compared with VKA as seen in RE-LY. Similar registry data will be important for all NOACs since they may shed light on the performance of all NOACs in daily life, where adherence may be less optimal than in the trials.

(vii) Some patients may explicitly prefer INR monitoring to no monitoring or NOAC over VKA therapy. Patient education needs to discuss these preferences before starting/converting to NOAC therapy and management decisions have to take these preferences into account to optimize health outcomes.

(viii) In NOAC patients in whom low adherence is suspected despite proper education and additional tools, conversion to VKAs could be considered [ESC 2015].

4. European medicine authorisations

Since NOACs were considered new active substances, the marketing authorizations were granted through the centralized procedures, according to Regulation (EC) No 726/2004. The European Medicines Agency –EMA- is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. Once granted by the European Commission, the centralised marketing authorisation is valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein.

Regarding the marketing authorisation, the most important directive and regulation in EU are the Directive 2001/83/EC, as amended, on the Community code relating to medicinal products for human use and the Regulation (EC) No 726/2004, as amended, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Difference among Regulation and Directive in EU are reported in the Box 1 below:

Box 1: Regulation and Directive in EU

Regulations

"Regulation" is a term used for the European Union which refers to the legislative act of the E.U. Regulations immediately become laws in all member states at the same time or simultaneously. They are addressed to all members and are always applied in full. Regulations are directly applicable in all member states without the need for legislation in the nation.

The legal effect of regulation is that they do not need to be made into national laws through implementing measures. When regulations are drafted and formulated, a great deal of care is taken because they are one of the most important and powerful forms of E.U. laws.
A regulation can override any and all national laws which deal with a certain subject matter. In the case of a regulation, the national legislation is made consistent with the regulation. They cannot be prohibited by any member state.

Directives

Directives are also legislative acts of the E.U. but they are not self-executing. The member states are left with leeway to decide which rules are to be adopted. Directives are usually adopted through a number of legislative procedures depending upon the different subject matters. Directives, unlike regulations, need to be transposed into national laws before adoption in principle. They are addressed to all state members but are objectives which need to be achieved by the members by a given date.

4.1. Directive 2001/83/EC

The Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 is the the Community code relating to medicinal products for human use. This Directive did apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process (Article 2).

The provisions of the Directive did not affect:
-the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions;
-the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission. -Article 4 (3)-.

Within the Directive 2001/83/EC, no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (2) and Regulation (EC) No 1394/2007.

When a medicinal product has been granted an initial marketing authorisation in accordance with the above mentioned articles, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).

In Italy the Directive 2001/83/EC had come into force with the Decree Law 219/2006.

4.2. Regulation (EC) No 726/2004

The purpose of the Regulation (EC) No 726/2004 was to lay down Community procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human and veterinary use, and to establish a European Medicines Agency (EMA) (art.1). The provisions of the Regulation did not

affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions.

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Union (an Union authorisation). The marketing authorisation holder must be established within the EEA.

A marketing authorisation lays down the terms under which the marketing of a medicinal product is authorised in the EU. A marketing authorisation is composed of: (i) a decision granting the marketing authorisation issued by the relevant authority; and (ii) a technical dossier with the data submitted by the applicant in accordance with Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007.

All human medicines derived from biotechnology and other high-tech processes must be evaluated by the Agency via the centralised procedure. The same applies to all advanced therapy medicines and medicinal products containing new active substances intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases -Art.3, (2).

For medicines that do not fall under any of the above-mentioned categories, companies can submit an application to the Agency, provided the medicine is a new active substance, constitutes a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patients at EU level -Art.3, (2). Also, generics of centrally authorised products and applications for certain medicinal products for paediatric use may be authorised in this way. Therefore, the Agency does not evaluate all medicines currently in use across Europe. For medicines falling outside the scope of the centralised procedure, the decentralised procedure, mutual-recognition procedure or purely national authorisation procedures should be used, depending on the number of countries in which authorisation is sought.

4.3. Type of National authorisations (Directive 2001/83/EC)

The competent authorities of the Member States are responsible for granting marketing authorisations for medicinal products which are placed on their markets, except for medicinal products which are authorised under Regulation (EC) No 726/2004.

In cases where national authorisations are requested for the same medicinal product in more than one Member State and the marketing authorisation holder has received a marketing authorisation in a Member State, the applicant/marketing authorisation holder must submit an application in the Member States concerned using the procedure of mutual recognition. The Member States concerned should then recognise the marketing authorisation already granted by the reference Member State and authorise the marketing of the product on their national territory.

If no marketing authorisation has been granted in the Union, the applicant may make use of a decentralised procedure and submit an application in all the Member States where it intends to obtain a marketing authorisation at the same time, and choose one of them as reference Member State. Based on the assessment report prepared by the reference Member State and any comments made by the concerned Member State, marketing authorisation should be granted in accordance with the decision taken by the reference Member State and concerned Member State in this decentralised procedure.

Both the decentralised and the mutual recognition procedures are based on the recognition by national competent authorities of an assessment performed by the authorities of one Member State.

4.3.1. Decentralised procedure

For medicinal products not falling within the mandatory scope of the centralised procedure, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, summary of product characteristics (SmPC), labelling and package leaflet as proposed by the chosen reference Member State. An application is submitted to the competent authorities of the reference Member State and the concerned Member State(s), together with the information and particulars referred to in Articles 8, 10, 10a, 10b, 10c, and 11 of Directive 2001/83/EC. The applicant must give an assurance that the dossier, including the proposed SmPC, labelling and package leaflet, is identical as submitted in all Member States concerned (reference Member State and concerned Member State). Differences in proposed prescription status and names of the medicinal product are acceptable, in line with national rules in force.

At the end of the decentralised procedure with a positive agreement, a national marketing authorisation will be issued in the reference Member State and the concerned Member State. The harmonisation is maintained through the procedures of Regulation (EC) No 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions.

4.3.2. Mutual recognition procedure

This procedure is based on the mutual recognition by concerned Member State(s) of a national marketing authorisation granted by the reference Member State. The concerned Member State refers to the reference Member State that issued the national marketing authorisation on which the mutual recognition procedure is based.

At the end of the mutual recognition procedure, a national marketing authorisation will be issued in the concerned Member State(s). The harmonisation is maintained through the procedures of Regulation (EC) No 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions and renewals.

4.3.3. Product and prescribing Information

In accordance with Article 8.3 (j), Article 11 and Title V of Directive 2001/83/EC applicants/marketing authorisation holders must include proposals for Summary of Product Characteristics (SmPC), labelling and package leaflet in their application.

SmPCs are a key part of the marketing authorisation of all medicines authorised in the European Union and the basis of information for healthcare professionals on how to use a medicine safely and effectively. They are kept updated throughout the lifecycle of a medicine as new efficacy or safety data emerge. SmPCs are also the basis for the preparation of package leaflets, so are important documents in enabling information on medicines to reach patients.

All information included in the SmPC through centralised procedure must be the same in all Member State. According to the Article 14 of Regulation (EC) No 726/2004, when adopting its opinion, EMA includes a proposal concerning the criteria for the prescription or use of the medicinal products in accordance with Article 70(1) of Directive 2001/83/EC.
The Article 70 says "*When a marketing authorization is granted, the competent authorities shall specify the classification of the medicinal product into:*
- a medicinal product subject to medical prescription,
- a medicinal product not subject to medical prescription.
The competent authorities may fix subcategories for medicinal products which are available on medical prescription only. In that case, they shall refer to the following classification:
(a) medicinal products on medical prescription for renewable or non-renewable delivery;
(b) medicinal products subject to special medical prescription;

(c) medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas."

This means that prescribing information should be the same throughout the Member States.

4.4. From European to National level

According to Regulation (EC) No 726/2004, the Italian Regulatory Agency –AIFA- granted automatically a market authorisation for medicines. However, specific submissions to AIFA were requested to set the prices of medicinal products in order to be reimbursed by the Italian National Health System (NHS). Indeed, in accordance with Law n. 326 of November 24, 2003 and Interministerial Committee for Economic Planning (Comitato Interministeriale per la Programmazione Economia – CIPE) Resolution of February 1st 2001, AIFA applies a price regulation only to reimbursed medicines. For non-reimbursed medicines price is free and is monitored by the Agency and the Ministry of Health.

The prices of pharmaceuticals reimbursement by the NHS is set through negotiation between AIFA and the Pharmaceutical Companies. The procedure of negotiation with manufacturers is administered by the AIFA Pricing and Reimbursement Unit assisted by the Pricing and Reimbursement Committee (Commissione Prezzi e Rimborso or CPR), which is chaired by the AIFA Executive Director and composed of 12 members. The pricing procedure is strictly interlinked to the reimbursement decisions as both decisions are taken in the same procedure by the same regulatory body. The process of negotiation takes place after the evaluation and opinion on reimbursement classification expressed by the AIFA Technical Scientific Committee (Commissione Tecnico Scientifica or CTS). The negotiation procedure includes four stages:

• Manufacturer applies for reimbursement and pricing, submitting a dossier.

• CTS provides its opinion on reimbursement by an evaluation of the clinical-therapeutic value.

• CPR evaluates manufacturer's dossier and hears the company for negotiation.

• The negotiation outcome is submitted to the CTS for its final opinion and then to the AIFA Management Board for approval.

• The results of the negotiation procedure are published in the Official Journal of the Italian Republic.

If there is no agreement on the price, the medicine is classified as not-reimbursable. The negotiation procedure is conducted according to the following criteria: therapeutic value, pharmacovigilance data, price in other EU countries, price of similar products within the same pharmacotherapeutic group, internal market forecasts, number of potential patients and therapeutic innovation.

The prices are negotiated at ex-factory level and are, normally, established for 24 months. After that, the applicant can submit a second application to confirm the price or to re-negotiate price and conditions, when applicable.

Prices of non-reimbursable medicines are free since 1995 but are monitored by AIFA in order to keep them at reasonable levels. The prices assigned by manufacturer are maximum price at national level.

Prices reductions by manufacturers are allowed at any time, whilst price increasing is endorsed on January of odd years.

4.4.1. Italian National Health Service

The Italian National Health Service (NHS) was founded in 1978 and it is based on the Beveridge model, providing uniform and comprehensive care, free of charge, to the entire population. The Italian NHS is organised into three levels: the Central Government; 21 Regional Governments (Regions); 195 Local Health Units (LHU). A network of 147 Independent Hospitals (HIs) and University Hospitals (UHs) complete the organisation of the system. Currently, following a 2001 amendment to the Constitution [Constitutional Law n. 3/2001 Amendment to the Title V of the Italian Constitution], the health care system is decentralized: the Central Government has exclusive power to set the framework of basic principles including the ‘‘essential levels of care’’ (Livelli Essenziali di Assistenza or LEAs) [Definition of the essential level of care Act 2017], which must be assured homogenously to citizens throughout the country. Regions have power to legislate within the framework established by the central government and have responsibility for the management, organisation and delivery of health-care services in their jurisdictions. LHU are responsible for the health of their population, providing services directly or reimbursing the HIs and UHs and/or accredited private providers for care delivered to their residents. Public expenditure on healthcare (PHE) is mostly funded through general taxation (97%), at both national and regional level, and by patient co-payment. The amount of public money to be spent on health care is established in the annual Budget Law, proposed every year by the central government and then amended and approved by the Parliament within the 31st December of every year.

The health budget is annually assigned to the Regions in order to provide the LEAs. Each Region allocates the funds to its LHU mainly, on an age-adjusted capitation basis. Assigned funds are used by LHU for the direct provision of both in-patient and out-patient care, for general practitioners’ remuneration and for the costs reimbursement of healthcare services afforded by His and UHs and/or accredited private providers.

<u>Pharmaceutical reimbursement system</u>

The Italian pharmaceutical reimbursement system covers all relevant diseases and the whole country providing universal pharmaceutical coverage to the whole population, including legal residents. The pharmaceutical reimbursement system in Italy covers both prescription medicines for primary care and medicines for in-patient care. The current reimbursement classification categorises medicines into two reimbursement classes, according to a combination of criteria in terms of effectiveness and cost:

(a) **Class A** comprises essential medicines and medicines for serious and chronic diseases. Medicines of this class are fully reimbursed by NHS. The class also includes the subgroup H, consisting of medicines requiring specialist supervision and eligible for reimbursement only when used for in-patient care (hospital use only or HOM).

(b) **Class C** includes medicines for disease of slight importance and for minor disorders, medicines whose use is discouraged since the clinical evidence are lacking and medicines not requiring a medical prescription. Pharmaceutical products included in the class C are not reimbursed by the NHS.

In Italy the reference price system (RPS) was implemented since 2001. Under the RPS the NHS reimburses the lowest price among the prices of off-patent pharmaceuticals with equal composition in active ingredients, with the same pharmaceutical form, same method of administration, same number of units and same unit dosage. When patients refuse the substitution of a medicine within the system for generic substitution and/or if the doctor prescribes a pharmaceutical product with a price higher than the reference price, the difference is paid by patients.

The out-of-pocket payments (OOP) include fixed prescription fees named ‘‘ticket’’ corresponding to a fixed amount per prescription and/or per package and the co-payment (at regional and national level) deriving from the RPS and the substitution mechanism. Limited to some Regions, specific types of exemption on medicines are applied for particular categories of people: chronically ill patients and people with rare diseases, disabled people and pregnant women.

4.4.1.1. Cost containment policies

AIFA has also responsibilities for monitoring and managing the pharmaceutical expenditure. A structural reform of the pharmaceutical sector has been implemented in 2008 in order to assure sustainability and promote innovation in a context promoting synergy between stakeholders.

The system until 2007

The main price and expenditure control mechanisms used until 2007 were dictated by the Law n. 405/2001 [Law n. 405/2001], that introduced pharmaceutical expenditure ceilings, both for primary care and hospital care, and corrective measures in case of exceeding ceilings.

The pharmaceutical primary care expenditure was not allowed to exceed 13% of the overall health expenditure both at national and regional level. Furthermore, the amount of the overall pharmaceutical expenditure, including pharmaceutical in-patient expenditure, could not exceed 16% of the total health

expenditure. In case of overspending the following corrective measures were foreseen by the Law: (a) updating and delisting in the positive list of reimbursable medicines (PFN) and/or (b) reducing the PRPs of medicines or (c) reducing the producers' earning margin at ex-factory level. In the latter case producers paid 60% of breakings in the expenditure ceiling, while the 40% was responsibility of Regions, which adopted specific restraint actions in order to meet the planned pharmaceutical expenditure.

Direct distribution

According to the Law n. 405/2001 [Law n. 405/2001], among the different measures implemented by Regions in order to keep pharmaceutical expenditure under the assigned threshold and to guarantee a balance in drug distribution and cost containment, the pharmaceutical direct distribution of medicines listed in the Direct Distribution Formulary (PHT) has been commonly adopted.

The direct distribution is realised by two different channels:

(a) Direct distribution by hospital and other health care structures of reimbursable medicines to the patients (e.g. first cycle of therapy at patient's discharge or specialised outpatient visits).

(b) Distribution by community pharmacies (Distribuzione Per Conto -DPC) of medicines directly bought by the NHS through agreements stipulated with wholesalers and pharmacies associations.

Selective or generalized price reduction were also included among the corrective measures. In January 2006 a price cut of 4.4% was applied to all reimbursed SSN medicines, then increased to 5%, and in September 2006 a further reduction of 5% was established with prolongation to financial year 2007.

As an alternative to price cuts the 2007 Budget Law introduced the option for pharmaceutical manufacturers to use a pay-back mechanism, consisting in a payment to Regions equivalent to the estimated amount deriving from the price cut.

The new system introduced from 2008

A general reform of the pharmaceutical sector is in force since 1st January 2008. This reform is the result of the Coordination Group on Pharmaceuticals, established by the Ministry of Health and including representatives of the Italian Medicines Agency (AIFA), the Ministry of Economy and Finance, the Ministry of industry and the Regions.

The new system included all the companies holding a marketing authorisation for pharmaceutical products (patented and non-patented) reimbursed by the NHS. Products not reimbursed are excluded by the specific system. The main innovative elements and pivotal principles of the system for the

governance of pharmaceutical expenditure and the regulation and development of the pharmaceutical sector can be summarised as: • New ceiling expenditure level, for primary care and for in-patient pharmaceutical expense. • Programmed incremental resources, defined by the Budget Law. • Promotion of innovation, specific fund for reimbursement of innovative products. • Assignation of a budget for each company, which represents the basis for pay-back calculation in case of overspending.

The new legislation (Law n. 222/2007) established that the primary care budget—including patient co-payments and direct distribution—cannot exceed the 14.0% ceiling of the overall public health expenditure both at national and regional level. In case of over expenditure at national level the re-balancing will be exclusively set up through a pay-back mechanism. In case of over-expenditure Regions are obliged to introduce re-balancing measures for 30% of the over expenditure as a condition to have access to the 3.0% fund of the National Health Fund (NHF). This prevents the risk of a reduced degree of accountability and control by the Regions as a result of the pay-back mechanism. The refund is not necessary if the overall annual regional budget is positive or neutral. • The hospital (in-patient) budget for pharmaceuticals expenditure cannot exceed a 2.40% ceiling of the overall public health expenditure. Regions are directly responsible for the respect of this ceiling and any overspending must be refunded by the Region through a reduction in hospital spending or in health care or any other reduction in the regional budget.

From 2008 the pharmaceutical expenditure ceiling decreased progressively until the 11.35% for primary care (including a specific ceiling for direct distribution medicines of 6.89%, starting from 2017) but increased up to 3.5 % for hospital care.

Additionally, the last annual Budget Law 2017 established a specific fund for innovative oncologic medicines, besides the innovative medicine fund.

Budget for an individual company and pay-back mechanism

An estimated budget—the amount of money that NHS is available to spend—is calculated every year for every company and this represents the basis for payback calculation in case of overspending. The budget is calculated according to the three following principles: • Volumes and pricing data during the last 12 months will be increased by a factor, identical for every individual company, and calculated every year as a function of the increase in NHS funds and the resources made available by patent expirations. • The individual budget is reduced, for the product whose patent will expire in the year, by an amount corresponding to these new off-patent products. • The individual budget is reduced by the amount paid back in the last year because of overspending, if any.

Every company may increase without limits its own budget provided, this increase happens, within any specific therapeutic class, at charge of other companies (market competition). The competitiveness

between companies and competition in the market is fostered through the guarantee fund equivalent to 20% of the increased resources which is not allocated in order to promote competition. Furthermore, the allocation to each pharmaceutical company can be increased without any ceiling, thus allowing companies to gain market shares within the available resources and according to the strictest principles of competition. In case of overspending at a national level a pay-back mechanism is set up. Companies have to pay directly to the Regions with an overspending, according to the calculation performed by AIFA but if at national level the ceiling is respected no amount has to be paid back, stimulating Regions to control at the best their own expenditure [P. Folino-Gallo, Eur J Health Econ 2008].

4.4.2. AIFA registries

The negotiation procedure did not set only the price for NHS reimbursed medicine, but usually adopted pricing and reimbursement schemes in order to manage that uncertainty after a coverage decision. The negotiation is made broadly through one of two approaches: (1) financial-based (cost or economic-driven) schemes that largely rely on usage data from providers; and (2) outcomes-based (healthcare or clinic-driven schemes) in which the level of reimbursement is linked to evidence generated on the technology's effectiveness, which rely more on primary data from randomized controlled trials and registries.

These reimbursement mechanisms used in Italy are summarised as follows: risk sharing scheme and payment for outcomes. In particular, AIFA adopted the outcome-based scheme classified as managed entry agreements (MEAs) "an agreement between a pharmaceutical company and payer/provider that enables access to (coverage/ reimbursement of) a health technology subject to specified conditions".

In order to collect outcome information, AIFA established in 2005 the Registry system which represent an example of a national application of a computerized workflow handling the personalized drug distribution in hospitals and local public pharmaceutical services, with the intent of improving the efficiency of both regulatory and reimbursement related activities, including real world outcome analyses. Only specialist and physicians in hospitals and local public pharmaceutical services are allowed to fill in the registries.

Two different type of registries are defined:

(c) Registry equals to a web-based prescription: applicable if the medicine could be used only in a hospital setting (Class H); the prescription usually covers 30 days of therapy;

(d) Registry used as Therapeutic Plan (TP): applicable if medicine has not the above mentioned restriction (i.e. classified in Class A or Class A inserted in the Direct Distribution Formulary – PHT); the TP covers usually 3, 6 or 12 months of therapy. During 3, 6 or 12 months, as long as

the validity of the TP, the general practitioner is authorised to prescribe the treatment instead of the specialist.

In 2012, AIFA registries officially became part of the NHS Information Technology system. These web tools are positioned in the early phases after marketing authorisation, in some cases, for the "authorized" off-label use with the clear purpose to verify the drug appropriateness, and additionally to measure real world safety and effectiveness, apply the MEAs themselves, and monitor their financial effects (Law n. 135/2012). For those medicines for which AIFA established a registry, data collection is mandatory under national legislation. Therefore, the data collected are owned by AIFA and the maintenance costs are shared with the Marketing Authorization Holders. At the end of 2015, 76 medicines were being monitored through the system, for use in more than 55 different diseases; more than 797,000 individual treatments have been recorded, covering a population of _714,000 patients [AIFA].

Real world data collected by registries (i.e., baseline characteristics and a longitudinal view of patient treatment, including route of administration, dose, duration of use, and reason for treatment discontinuation/interruption) together with pharmacovigilance and economic information, allow reassessment of a pharmaceuticals' value and related decisions. Within its HTA pathway, AIFA performs the re-evaluation of cost-effectiveness profile (usually taking 24–36 months), after which the pricing and reimbursement agreement is reassessed, also comparing efficacy and safety results expected at the moment of the decision, with real practice outcomes (effectiveness). This activity eventually determines a reconsideration of the original reimbursement and pricing decision, and a new negotiation with the Marketing Authorization Holders is conducted [SD Faulkner, 2016].

AIFA registries are also tool to guide the proper prescription into the NHS reimbursed medicines: contrarily from the therapeutic indications approved through different procedures (centralised or national authorisations), AIFA could decide to partially reimburse one or more indications or to reimburse the indication/s in a specific group of patients. In that cases, AIFA registries apply only for reimbursed indication/s/ subgroups of patients.

4.5. NOACs in ITALY

Dabigatran was the first NOAC introduced on the Italian market in June 2013 (as published on the Official Journal of Italy), followed by rivaroxaban in August 2013 and apixaban in December 2013.

They were classified in the Class A/ PHT which involved a pharmaceutical direct distribution. Most Regions decided to use the Distribution by community pharmacies (DPC) in order to facilitate patients to get the medicines.

As part of the pricing and reimbursement scheme, for NOACs, AIFA introduced an annual maximum estimated volume for each company, which represents the basis for pay-back calculation in case of overspending, together with AIFA registries to verify the drug appropriateness and to apply the MEAs themselves. However, from 2016 the annual ceiling for each company is no longer applicable, after an updated pricing and reimbursement agreement.

The NOACs registries are considered therapeutic plans since they cover 12 months of treatment.

4.6. From National level to Regional level

Considering the responsibility for the management, organisation and delivery of health-care services in their jurisdictions and the need to guarantee the respect of the ceiling within the regional health budget (i.e. in 2017, 11.35% and 3.5 % of the NHF for primary care and for hospital care respectively), the Regions have adopted specific actions, so far, including direct distribution.

Since this research has been conducted in the LHU n.2, Region of Veneto, District of Treviso (Italy), the organisation of this region is described in detail, as below.

With the Regional Deliberation no. 952/ 2013 (DGR 952/2013), as amended, the Veneto Region changed the functions of Pharmaceutical Committees in order to balance the regional need to manage health problems consistently with local need and related specificity of LHU. With the same deliberation the new Regional Technical Drugs Committee were nominated.

According to the new organisation the Pharmaceutical Committees were organized on two levels: a regional level, represented by the Regional Technical Drugs Committee and a local level, represented by the LHU Therapeutic Committee, which were in charge to develop coordinated actions to manage all healthcare settings.

The Regional Technical Drugs Committee is responsible for:

- expressing opinions or recommendations on individual drugs or therapeutic categories;

- preparing scientific guidelines to help physician and GPs using medicines correctly;

- monitoring the appropriateness, safety and expenditure of medicinal products both for primary care and for hospital care;

- identifying and proposing to the Health Secretariat the objectives of improving prescriptive appropriateness and expenditure control as well as advice on the updating and revision of centers authorized to prescribe medicines with therapeutic plan / AIFA or specialist knowledge;

- undertaking actions to improve the appropriateness and safe use of pharmacological therapies considering pharmacovigilance and pharmacoepidemiology reports;

- applying the provisions of national and regional law (Dgrv 1307/2007) on scientific information on medicines;

- expressing opinions on medicine distribution (direct distribution).

All provisions adopted at regional level are mandatory for all Units working within the NHS.

4.6.1.NOACs in Veneto Region

Insight this framework, after the definition of the price and the conditions for the marketing authorisation with the publication of the Italian Official Journal, fixed by AIFA, the Veneto region determined the following actions:

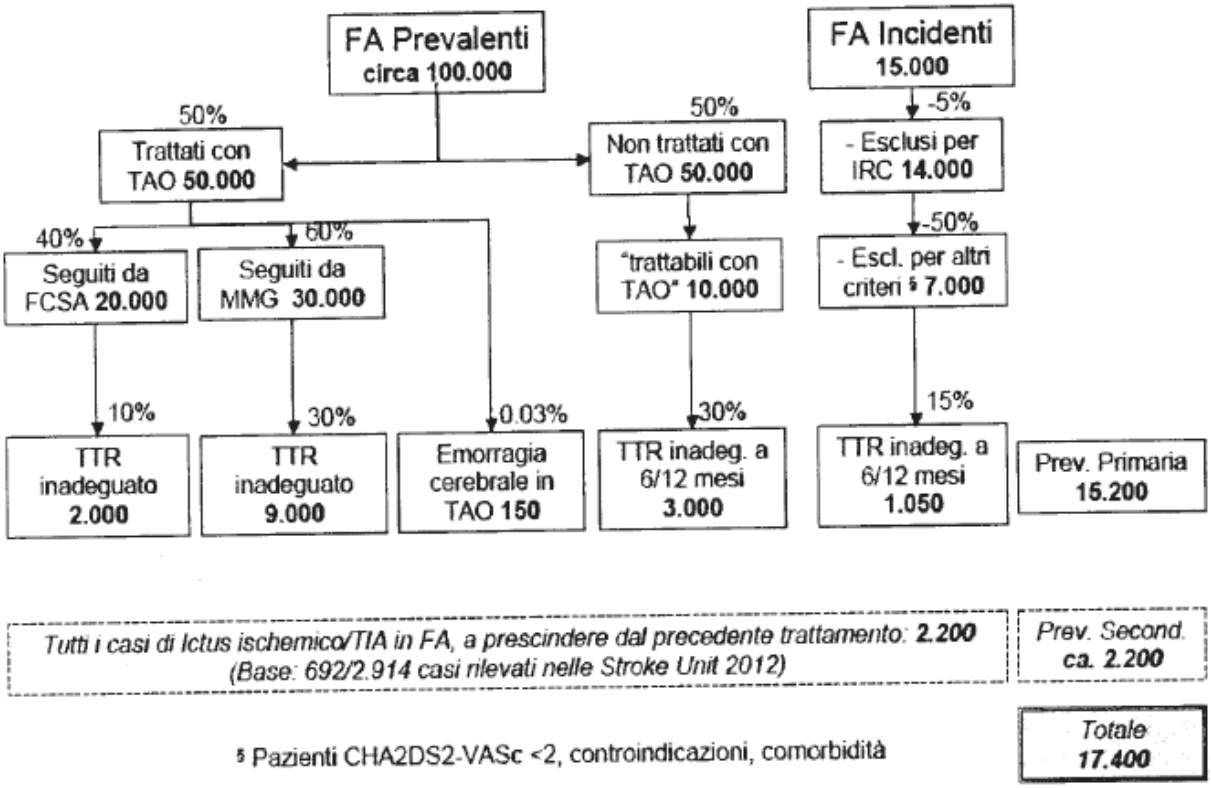
(a) To defined which Hospital Unit and/or specialist were allowed to prescribe NOACs, within the NHS.

At first, Units of Cardiology, Neurology and Geriatric in public hospitals were listed in the decree no.75/2013. The list was kept updated including new therapeutic indications and new Units so far (decree no.66/2017).

(b) To prepare guideline on the use of oral anticoagulants in patients with non-valvular atrial fibrillation (decree no.75/2013, as amended in 2014 and in 2017);

The guideline firstly compared data from clinical trials and tried to define the place in therapy of NOACs, considering the VKA therapy as standard treatment. Starting from the epidemiology, the estimated prevalent number of patients with AF were about 115.000 in the Veneto Region, in 2012 (Figure 5). Applying the criteria listed in the decree no.75/2013, in order to maximize the clinical benefits from NOACs therapy, no. 17.400 were considered as eligible patients for NOACs (Figure 5).

Figure 5. Possible number of eligible patients to NOACs in 2012



(c) Every LHU and hospital should have established a multidisciplinary atrial fibrillation team (decree no.75/2013);

A multidisciplinary atrial fibrillation team including specialists working in the Hospital Units which were allowed to prescribe NOACs, general physicians, hospital pharmacists and physicians were considered a fundamental concept of integrated care models.

The multidisciplinary AF team is responsible for:

- Monitoring the no. of treated patients with regard to the regional guideline;
- Analysing patients who stopped treatment;
- Defining an internal procedure to manage bleeding complications;
- Educational training to improve an integrate care between hospital care and primary care;
- Monitoring the NOACs expenditure.

(d) Direct distribution was activated in the regional area.

5. From efficacy to effectiveness: the reason for observational studies

Randomized controlled trials (RCTs) provide the ideal study design for demonstrating causality between the use of a specific medicine and intended and unintended effects under ideal conditions. In conventional RCTs conducted during phase III drug development, patients are based on stringent inclusion and exclusion criteria and subsequently randomized to different treatment arms to counteract the influence for known and unknown confounders [Schwartz D, J Clin Epidemiol 2009; Freemantle N., J Clin Epidemiol 2010]. In addition, monitoring and follow- up procedures for trial subjects are often highly controlled.

The highly selective populations examined within the setting of RCTs are often not comparable with the more heterogeneous populations in clinical practice in which medicines are administered to patients with genetic variability, who present with different comorbidities or already receive different medications for other morbidities. Consequently, experimental medicines being presented for marketing authorization are accompanied by data that provide efficacy as well as safety data with very high internal validity but whose results may not be easily generalizable to a broader, more heterogeneous population [Freemantle N., J Clin Epidemiol 2010]. This disparity of findings on the therapeutic efficacy of medicines from tightly controlled RCT settings and the effectiveness of medicines in the real world has been previously defined by Eichleretal. [Eichler HG. Nat Rev Drug Discov 2011] as the "efficacy-effectiveness gap.

Regulatory agencies are thus faced with the issue of making decisions on the basis of data with inherent uncertainties on the aspects of real-world effectiveness. Similarly, health technology assessment (HTA) agencies and health care payers conventionally exploit RCT-generated evidence available at the time of initial reimbursement decisions to assess the relative effectiveness of new products. As a result, many stakeholders such as the pharmaceutical industry, regulatory agencies, HTA agencies, and payers have begun exploring options for the use of real-world data as a complementary source to RCT data for establishing a more robust evidence base on the effectiveness of medicines, as well as the relative effectiveness compared with existing products in clinical practice [Berger ML, Value Health 2015].

Real-world data can include electronic medical records originating from health care providers, data used to coordinate and pay for care, and pharmacy data used to fill prescriptions. Data may also be collected inpatient registries or pragmatic clinical trials. Real-world data become "big data" when multiple data sets are combined.

5.1. Interventional and non-interventional trial

In classical, experimental clinical trials, there are fundamental interventions, which include applying strict criteria for inclusion and exclusion of the subjects, allocating treatment a priori (e.g. by randomisation), and enforcing study requirements according to a protocol. Observational, pharmacoepidemiological studies are fundamentally different in these respects. Treatment of the subject is not determined or assigned by study procedures, but instead non-interventional research involves its observation and monitoring and recording what is happening or has happened in the clinical setting.
A 'non-interventional trial' is defined in Article 2(c) of Directive 2001/20/EC as follows:
"*a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data*."

5.1.1. Interventional trials

Randomized controlled trial -RCT

A randomized controlled trial is a type of interventional trial which aims to reduce bias when testing a new treatment. The people participating in the trial are randomly allocated to either the group receiving the treatment under investigation or to a group receiving standard treatment (or placebo treatment) as the control. Randomization minimises selection bias and the different comparison groups allow the researchers to determine any effects of the treatment when compared with the no treatment (control) group, while other variables are kept constant. The RCT is often considered the gold standard for a clinical trial. RCTs are often used to test the efficacy of various types of medical intervention and may provide information about adverse effects, such as drug reactions. Random assignment of intervention is done after subjects have been assessed for eligibility and recruited, but before the intervention to be studied begins.

After randomization, the two (or more) groups of subjects are followed in exactly the same way and the only differences between them is the care they receive. For example, in terms of procedures, tests, outpatient visits, and follow-up calls, should be those intrinsic to the treatments being compared. The most important advantage of proper randomization is that it minimizes allocation bias, balancing both known and unknown prognostic factors, in the assignment of treatments.

Clinical trials of experimental drug, treatment, may proceed through four phases:

- Phase I clinical trials test a new biomedical intervention in a small group of people for the first time to evaluate safety (e.g., to determine a safe dosage range, and to identify side effects).
- Phase II clinical trials study the intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- Phase III studies investigate the efficacy of the intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Crossover studies

Another modification of the randomised controlled trial is the crossover design. This is particularly useful when outcome is measured by reports of subjective symptoms, but it can only be applied when the effects of treatment are short lived (for example, pain relief from an analgesic).

In a crossover study, eligible patients who have consented to participate receive each treatment sequentially, often with a "wash out" period between treatments to eliminate any carry over effects. However, the order in which treatments are given is randomised so that different patients receive them in different sequence. Outcome is monitored during each period of treatment, and in this way each patient can serve as his own control

Experimental study of populations

Most experimental studies allocate and compare treatments between individual subjects, but it is also possible to carry out experimental interventions at the level of populations. As in studies of individuals, interventions in populations can be randomly allocated. However, if the number of populations under comparison is small then randomisation may not be of much value. Instead, it may be better to assign interventions in a deliberately planned way to ensure maximum comparability between different intervention groups. Control of residual confounding can be strengthened by comparing study and control populations before and after the intervention is introduced.

Like longitudinal studies, experimental investigations tend to be time consuming and expensive. They should not, therefore, be undertaken without good reason. However, if well designed and conducted, they do provide the most compelling evidence of cause and effect.

5.1.2.Non interventional studies

Longitudinal study

In a longitudinal study subjects are followed over time with continuous or repeated monitoring of risk factors or health outcomes, or both. Such investigations vary enormously in their size and complexity. At one extreme a large population may be studied over decades. At the other extreme, some longitudinal studies follow up relatively small groups for a few days or weeks.

Most longitudinal studies examine associations between exposure to known or suspected causes of disease and subsequent morbidity or mortality. In the simplest design a sample or cohort of subjects exposed to a risk factor is identified along with a sample of unexposed controls. The two groups are then followed up prospectively, and the incidence of disease in each is measured. By comparing the incidence rates, attributable and relative risks can be estimated. Allowance can be made for suspected confounding factors either by matching the controls to the exposed subjects so that they have a similar pattern of exposure to the confounder, or by measuring exposure to the confounder in each group and adjusting for any difference in the statistical analysis.

A problem when the cohort method is applied to the study of chronic diseases such as cancer, coronary heart disease, or diabetes is that large numbers of people must be followed up for long periods before sufficient cases accrue to give statistically meaningful results. The difficulty is further increased when, as for example with most carcinogens, there is a long induction period between first exposure to a hazard and the eventual manifestation of disease.

One approach that can help to counter this problem is to carry out the follow up retrospectively. Obviously, such a study is only feasible when the health outcome of interest can be measured retrospectively. Mortality and cancer incidence can usually be ascertained reliably, but disorders such as asthma may be harder to assess in retrospect. A further requirement is that the selection of exposed people for study should not be influenced by factors related to their subsequent morbidity.

Another modification of the method is to use the recorded disease rates in the national or regional population for control purposes, rather than following up a specially selected control group. This technique is legitimate when exposure to the hazard in the general population is negligible.

Retrospective cohort study

Retrospective studies are by definition ‘non-interventional’ and can classified as follow:

• Purely observational database review and/or research

• Retrospective review of records where all the events of interest have already happened – e.g. case-control, cross-sectional, and purely retrospective cohort studies
• Studies in which the prescriber later becomes an investigator but prescribing has already occurred – e.g. retrospective data collection from individual medical records at the site of the investigator.

A retrospective cohort study, is a longitudinal cohort study used in medical research. A cohort of individuals that share a common exposure factor is compared to another group of equivalent individuals not exposed to that factor, to determine the factor's influence on the incidence of a condition such as disease or death.

The retrospective cohort study compares groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and ones who do not smoke) in terms of a particular outcome (such as lung cancer). Data on the relevant events for each individual (the form and time of exposure to a factor, the latent period, and the time of any subsequent occurrence of the outcome) are collected from existing records and can immediately be analysed to determine the relative risk of the cohort compared to the control group. This is expressed as a risk ratio or odds ratio.
The first objective of a retrospective cohort study is to establish two groups - exposed versus non-exposed - which are then assessed retrospectively to establish the most likely temporal sequence of events leading to the current disease state in both the exposed and unexposed groups. Retrospective cohort studies require particular caution because errors due to confounding and bias are more common than in prospective studies.
Retrospective studies have disadvantages, especially if compared with prospective studies, that some key statistics cannot be measured, and significant biases may affect the selection of controls. The retrospective aspect may introduce selection bias and misclassification or information bias. With retrospective studies, the temporal relationship is frequently difficult to assess. Also, retrospective studies may need very large sample sizes for rare outcomes.

Case-control studies

One of the drawbacks of using a longitudinal approach to investigate the causes of disease with low incidence is that large and lengthy studies may be required to give adequate statistical power. An alternative which avoids this difficulty is the case-control or case-referent design. In a case-control study patient who have developed a disease are identified and their past exposure to suspected aetiological factors is compared with that of controls or referents who do not have the disease. This permits estimation of odds ratios (but not of attributable risks). Allowance is made for potential confounding factors by measuring them and making appropriate adjustments in the analysis. This

statistical adjustment may be rendered more efficient by matching cases and controls for exposure to confounders, either on an individual basis (for example by pairing each case with a control of the same age and sex) or in groups (for example, choosing a control group with an overall age and sex distribution similar to that of the cases). Unlike in a cohort study, however, matching does not on its own eliminate confounding. Statistical adjustment is still required.

Selection of cases

The starting point of most case-control studies is the identification of cases. In addition, care is needed that bias does not arise from the way in which cases are selected. In general, it is better to use incident rather than prevalent cases: prevalence is influenced not only by the risk of developing disease but also by factors that determine the duration of illness. Furthermore, if disease has been present for a long time then premorbid exposure to risk factors may be harder to ascertain, especially if assessment depends on people's memories.

Selection of controls

Usually it is not too difficult to obtain a suitable source of cases, but selecting controls tends to be more problematic. Ideally, controls would satisfy two requirements. Within the constraints of any matching criteria, their exposure to risk factors and confounders should be representative of that in the population "at risk" of becoming cases - that is, people who do not have the disease under investigation, but who would be included in the study as cases if they had. Also, the exposures of controls should be measurable with similar accuracy to those of the cases. Often it proves impossible to satisfy both of these aims.

Two sources of controls are commonly used. Controls selected from the general population (for example, from general practice age-sex registers) have the advantage that their exposures are likely to be representative of those at risk of becoming cases. However, assessment of their exposure may not be comparable with that of cases, especially if the assessment is achieved by personal recall. Cases are keen to find out what caused their illness and are therefore better motivated to remember details of their past than controls with no special interest in the study question.

Measurement of exposure can be made more comparable by using patients with other diseases as controls, especially if subjects are not told the exact focus of the investigation. However, their exposures may be unrepresentative.

Sometimes interpretation is helped by having two sets of controls with different possible sources of bias. When cases and controls are both freely available then selecting equal numbers will make a study most efficient. However, the number of cases that can be studied is often limited by the rarity of the disease under investigation. In this circumstance statistical confidence can be increased by taking more than one control per case. There is, however, a law of diminishing returns, and it is usually not worth going beyond a ratio of four or five controls to one case.

Cross sectional studies

A cross sectional study measures the prevalence of health outcomes or determinants of health, or both, in a population at a point in time or over a short period. Such information can be used to explore aetiology - for example, the relation between cataract and vitamin status has been examined in cross sectional surveys. However, associations must be interpreted with caution. Bias may arise because of selection into or out of the study population. A cross sectional survey of asthma in an occupational group of animal handlers would underestimate risk if the development of respiratory symptoms led people to seek alternative employment and therefore to be excluded from the study. A cross sectional design may also make it difficult to establish what is cause and what is effect. Because of these difficulties, cross sectional studies of aetiology are best suited to diseases that produce little disability and to the presymptomatic phases of more serious disorders.

6. Objectives of the study:

The aims of this retrospective observational study were

- to evaluate oral anticoagulant treatment in patients with Non Valvular AF (NVAF) in everyday clinical practice in comparison with current guideline recommendations;
- to assess the effectiveness of NOACs *vs* VKA in terms of preventing strokes due to AF and preventing deaths;
- to describe the patterns of prescription of oral anticoagulants (VKA and NOAC) as a starting treatment in naïve and prevalent patients with non valvular atrial fibrillation, and to study factors associated with treatment initiation with NOACs

in the LHU n.2, Region of Veneto, District of Treviso (Italy).

Since the first NOAC (dabigatran) was available in Italy from July 2013, we aimed to compare anticoagulation practice during the pre- and post- new oral anticoagulant periods, including patients with a hospital admission for NVAF from 2007 to 2013, when the oral anticoagulant therapy option was limited to VKA. Then, we identified a second cohort of patient with a hospital admission or an emergency ward admission for NVAF from 2013 to 2016.

7. MATERIALS AND METHODS

7.1. Consulted administrative databases

A retrospective cohort study was performed on the population affected by AF and treated in the LHU n.2, Region of Veneto, District of Treviso (Italy). All information was collected from national databases of the Health Care Authority, which contain information related to age, sex, prescriptions and pathologies. Additionally, local databases with information on international normalized ratio (INR) monitoring and hospital admissions were used.

Data collected from administrative databases included:

i) demographic data on NHS beneficiaries;
ii) pharmaceutical prescriptions of drugs reimbursed by the NHS and delivered either by territorial or hospital pharmacies;
iii) AIFA national registers, i.e. registries created by the Italian Regulatory Agency of Medicines (AIFA) and filled in at time of drug prescription and drug delivery for the monitoring of the use of specific drugs;
iv) hospital discharge records, with any diagnosis fields coded through ICD9-CM codes reported in;
v) blood laboratory tests with their relative result;
vi) medical exemption databases, which contains information on patients with certain medical conditions which allow to get free NHS related prescriptions.

Record linkage among databases was performed using the individual identification code (Regional Health Code-RHC) univocally attributed to each beneficiary. The Local Ethic Committee gave the necessary permissions to get access to information related to patients included in the administrative databases.
In addition, in respect with the Italian rules on privacy, the original RHC was replaced by an anonymous univocal identification code.

7.2. Identification of the cohort: inclusion and exclusion criteria

Taking into account the introduction of NOACs on the Italian market (i.e. from July 2013), we slepted up the analysis in two observational periods: pre-NOACs period from January 1st 2007 to December 31st 2013 where VKA therapy was the only indicated oral anticoagulant treatment for AF patients, and

post-NOACs period from January 1st 2013 to December 31st 2016 where VKA or NOACs were alternatively prescribed to AF patients. In order to have comparable population, all analysis was limited to patients with Non Valvular Atrial Fibrillation, since it is the approved indication of NOACs.

The eligible population included all participants hospitalized with a diagnosis of atrial fibrillation (detected using the 9th Revision diagnosis code ICD-9 CM 427) during a hospital admission (considered as the index date, ID) resident in the LHA of Treviso. For each patient hospitalized, 5 diagnosis codes were usually available: the first one was the diagnosis which caused the hospitalization; the other diagnosis codes represented comorbidities. All patients with a diagnosis of AF detected among the 5 diagnosis codes, were considered in the analysis. Starting from 2013, the cohort of patients affected by AF was also identified considering patients with an admission to the emergency ward (i.e. do not involve a subsequent hospital admission) with a diagnosis of AF, detected among the 5 diagnosis codes.

Exclusion criteria were:

-patients with a hospital admission for valvular AF, defined according to the current guidelines [January CT, J Am Coll Cardiol 2014], as detected at any time during the observational periods among the 5 diagnosis codes and/or surgical, diagnostic, and therapeutic procedures codes carried in the hospital admission database (rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair, corresponding to the ICD-9 diagnosis code: 350* or 351* or 352* or 359 or 3596 or 3599; and/or surgical, diagnostic, and therapeutic procedures codes: 3941 or 3942 or 3950 or 3951 or 3952 or 396* or 99602 or V422 or V433, not 3969);

-patients who died within 7 days from the diagnosis;

-patients who received the AVK therapy occasionally (= number of prescriptions which covered less than 6 months continuatively) and not having one INR control per month according to guidelines [January CT, J Am Coll Cardiol 2014]; and patients who received the NOACs therapy occasionally (= number of prescriptions which covered less than 6 months continuatively).

Participants who met the inclusion and exclusion criteria were included in the study cohorts. For the pre-NOACs period cohort, the follow-up period was defined as the time between the ID and 31 December 2013 or death date, whichever occurred first; differently, for the post-NOACs period, the second cohort' follow-up period was defined as the time between the ID and 31 December 2016 or death date, whichever occurred first.

The above mentioned two cohorts are summarised in the table 6.

Table 6. Comprehensive table of cohorts enrolled in the observational periods

	Enrolled period	Follow up period
1ST cohort (hospital admission for AF)	1.1.2007 to 31.07.2013	ID to 31.12.2013 or death date
2ND cohort (hospital admission + admission to the emergency ward for AF)	1.1.2013 to 31.12.2015	ID to 31.12.2016 or death date

7.3. Characterization of the cohort

All patients were characterized based on demographic information:

i) sex;
ii) age at diagnosis;

Patients were characterized also by the presence of comorbidities at baseline: previous heart failure, hypertension, diabetes mellitus, stroke/TIA, myocardial infarction, previous bleeding, previous or concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs use and corticosteroids use. Data concerning comorbidities were captured from either:

i) hospitalizations occurred at any time before NVAF diagnosis;
ii) medical exemption when available;
iii) continuative therapies used at time of diagnosis, captured from the databases of either territorial or hospital drug deliveries.

7.4. Populations defined according to therapeutic categories and risk of stroke

According to treatment (VKA or NOACs) three different populations with non valvular atrial fibrillation were defined to answer the study objectives.

1- N- group: participants who did not receive any treatment.
2- VKA group: participants who received at least 6 months of VKA treatment.
3- NOAC group: participants who received 6 months of NOAC treatment.

Patients were assigned to the VKA group or to the NOACs group if they had received the treatments for at least 6 months, regardless the first treatment used after the ID. Patients who received less than 6 months' prescriptions were excluded. The achievement of responses was arbitrarily attributed to the

assigned treatment group, although eventual treatment switches among VKA or among NOACs had occurred in the meanwhile. Each patient were possibly assigned to only one of the above mentioned group (leading to counting patient one time in estimation of risks).

CHADS2 and CHA2DS2-VASC scores

The individual stroke risk for each patient was defined according to CHADS2 and CHA2DS2-VASC scores. The CHADS2 score was the sum of points obtained after addition of one point each for heart failure, hypertension, age ≥ 75, and diabetes and two points for previous stroke/transient ischemic attack (TIA). The CHA2DS2-VASC score was the sum of points after addition of one point each for heart failure, hypertension, diabetes, vascular disease, age 65-74 years, and female sex and two points each for previous stroke/TIA, previous systemic embolism, and age ≥ 75 years. Given the observational periods, both scores have been considered. According to guidelines [ESC 2011], the CHADS2 score was used until 2011, replaced by the CHA2DS2-VASC score from 2012[Olesen JB, BMJ 2011].

	Condition	**Points**
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A2	Age ≥75 years	2
D	Diabetes Mellitus	1
S2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

In order to define the pre-existing medical condition included in the $CHADS_2$ and CHA_2DS_2-VASc scores, different databases were analysed and linked together. Hence the $CHADS_2$ and CHA_2DS_2-VASc scores were calculated as the sum of points obtained from the detected clinical conditions at the time of the ID.

Clinical conditions were identified mixing hospital admissions (considering diagnosis and/or surgical, diagnostic, and therapeutic procedures codes), exemption codes and prescriptions of related medicines, used as a proxy of the comorbidities. Methods are specified and described as follows:

Congestive heart failure/left ventricular dysfunction: NVAF patients with at least an hospital admission with a diagnosis of heart failure (ICD-9 diagnosis code: 402*1- or 428* or 404*1" Or "404*3" Or "78550" Or "78551" Or "5184) from 2006 to 2013 were included. But, considering that not all patients with heart failure had a hospital admission, we included also NVAF patients with the heart failure medical exemption code 021.

Hypertension: NVAF patients with the medical exemption code 031 or A31, which identified the hypertension condition, from 2006 to 2013.

Diabetes mellitus: NVAF patients with the medical exemption code 013 from 2006 to 2013. However, many patients with diabetes for several reasons don't apply for a medical exemption certificate, so we added patients who received prescriptions of antidiabetic drugs (ATC code: A10*) in the same period, using the prescriptions databases.

Previous stroke/transient ischemic attack: NVAF patients with at least an hospital admission with a diagnosis of stroke and/or transient ischemic attack (ICD-9 diagnosis code: 430 Or "431" Or Like "432*" Or Like "433*" Or Like "434*" Or Like "435*" Or "436" Or Like "437*" Or "438"; and/or surgical, diagnostic, and therapeutic procedures codes: 3811 Or "3812" Or "3831" Or "3832" Or "3841" Or "3842") from 2006 to 2013 were included.

Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque): NVAF patients with at least an hospital admission with a diagnosis of stroke and/or transient ischemic attack (ICD-9 diagnosis code: Like "2507*" Or Like "440*" Or Like "442* Or Like "443*" Or Like "444*" Or Like "447*" Or Like "459*" Or "7854" Or Like "895*" Or Like "896*" Or Like "897*" and/or surgical, diagnostic, and therapeutic procedures codes: V434 Or "3813" Or "3814" Or "3815" Or "3816" Or "3818" Or "3925" Or "3929" Or "8410" Or "8411" Or "8412" Or "8413" Or "8414" Or "8415" Or "8416" Or "8417" Or "8418" Or "8419" Or "8622) from 2006 to 2013 were included.

Quality of the above mentioned databases were good since they were used as administrative databases from 2002 in the LHU of Treviso, but an underestimation of such clinical conditions cannot be excluded.

The HAS-BLED score has also been calculated limited to the pre-NOACs period [ie, risk stratification scheme to estimate baseline risk of major hemorrhage based on the presence of hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition, age > 65 years, antiplatelet or nonsteroidal anti-inflammatory drug use and alcoholism] in order to measure the baseline bleeding risk. However medical conditions such abnormal renal function, abnormal liver function and alcoholism were not obtainable using the available administrative databases. So we decided to not include this result in the study, given that high bleeding risk should generally not result in withholding OAT. We instead considered patients who had hospital admission with a diagnosis code for major bleeding, both pre- (as a pre-existing medical condition) and post-ID (to calculate the bleeding risk).

All drugs were identified through the international Anatomical Therapeutic Chemical classification system, ATC code.

Vitamin K antagonist users were identified through the prescription of warfarin or acenocumarol (ATC B01AA); in addition, the INR controls were collected and reported as the Time in Therapeutic Range (TTR), calculated according to the Rosendal method [Rosendaal FR, Thrombosis and Haemostasis 1993]. To calculate the TTR, each patient should have a sufficient number of INR controls, i.e. one INR control per month according to guidelines [January CT, J Am Coll Cardiol 2014]. For few patients, the INR controls were not detected in the administrative databases of the LHU of Treviso, since they were performed in different area. This patients were then excluded.

Limited to the second part of this research, the TTR was also calculated at baseline for patients on VKA therapy, who had a pre-existing hospital admission for AF.

NOACS prescriptions where identified through the ATC code B01AE01, B01AF01, B01AF02.

7.5. Therapy Adherence with NOACs

Adherence to NOAC treatment was defined as the ratio between the amount of the days which were actually covered by the drug prescriptions and the days covered considering the amount of the drug that should have been prescribed, i. e. the proportion of days covered by repeat prescriptions after the NOAC commencement. The duration of a single NOAC prescription was calculated as the number prescribed capsules divided by the recommended daily dose (two capsules per day for apixaban and dabigatran and one per day for rivaroxaban).

According to the proportion of days covered, two classes were defined:

- Non-adherence: < 80%
- Adherence: ≥ 80%

7.6. Evaluation of major bleeding as adverse effect

Occurrence of major bleedings were evaluated at any time following treatment beginning, based on acute events leading to hospitalizations; the first major bleeding recorded after the ID was considered. Major bleeding were identified using the following ICD-9 diagnosis code: 4560 or 45620 or 00804 or 0786 or 2463 or 2851 or 2865 or 287* or 430* or 432* or 5307 or 5302 or 5304 or 5310* or 5312* or 5314* or 5316* or 5320* or 5322* or 5324* or 5326* or 5330* or 5332* or 5334* or 5336* or 5340* or 5342* or 5344* or 5346* or 535*1 or 53783 or 56202 or 56203 or 56212 or 56213 or 5693 or 56985 or 578* or 6021 or 7827 or 7848 or 99702.

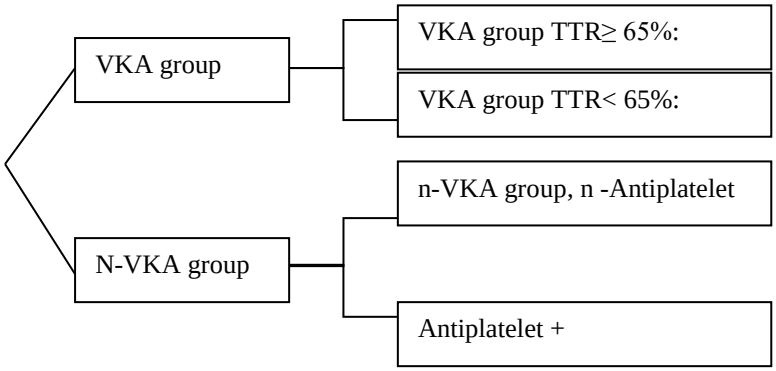
7.7. Statistical analysis

The baseline characteristics of the populations were reported by means or medians and standard deviations (SDs) for quantitative information and with frequencies and percentages for qualitative characteristics. Statistical differences were identified with a t-test or chi-square analysis.

To determine the influence of risk factors and treatments on occurrence of stroke, death and major bleeding, a multivariate regression analysis (Cox analysis) were performed, with regard to age, sex, previous heart failure, hypertension, diabetes mellitus, stroke/TIA, myocardial infarction, previous major bleeding; additionally, the contribution of CHADS2-VASC or CHADS2 scores was evaluated.
The first stroke recorded after the ID, defined as the first hospital admission with diagnosis of stroke or major bleeding, was considered.

Limited to the first part of this study, previous or concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs use and corticosteroids use are considered risk factors as well.
Also, according to treatments, four subcategories were therefore identified (figure 6) and included in the regression analysis.

Figure 6: Flow chart of subcategories identified by treatment



1- Group VKA, TTR ≥ 65%: participants who received at least 6 months of VKA treatment and reached the target, calculated as the Time in Therapeutic Range (TTR ≥ 65%) [Connolly SJ, Circulation 2008].
2- Group VKA, TTR < 65%: participants who received at least 6 months of VKA treatment and did not reach the target (TTR < 65%) [Connolly SJ, Circulation 2008].
3- N-VKA group: participants who did not receive any VKA treatment.
4- antiplatelet +: participant who received only antiplatelets drugs, for at least 6 months.

Regarding the second part of this research, the contribution of pre-existing hospital admission with a diagnosis of AF, previous use of VKA treatment and the related TTR value, are considered risk factors as well. Hence, comparing to the first part observational period, different subcategories of patients were identified and included in the regression analysis according to treatments. They are summarized below:

1- N- group: participants who did not receive any treatment (nor VKA, nor NOAC)
2- Group VKA, TTR < 65%: participants who received at least 6 months of VKA treatment and did not reach the target (TTR < 65%).
3- Group VKA, TTR ≥ 65%: participants who received at least 6 months of VKA treatment and reached the target, calculated as the Time in Therapeutic Range (TTR ≥ 65%).
4- Group NOAC, non- adherent: participants who received at least 6 months of NOAC treatment but considered not adherent to therapy according to the definition as above.
5- Group NOAC, adherent: participants who received at least 6 months of NOAC treatment and adherent to therapy according to the definition as above.

Statistical analysis was performed using the software STATA version 11. Statistical significance was considered with p-values <0.05.

8. RESULTS

Years 2007-2013

8.1. AF Population identification and characteristic

The cohort of patients firstly identified consisted of 8640 patients with a hospital admission for AF from 2007 to 2013 with an estimated prevalence of 2.1% considering 419,728 inhabitants. Among 8,640 patients, the 52% is male with a mean age of 74.7 ±11.5 years.

The incidence rate is reported in Table 7, stratified by sex. Starting from 2008 the incidence rate trend is increasing, except in 2011. Of note, the incidence rate in 2012 is 0.43 which is approximately twofold compared to other years. This large increase in the diagnosis of AF in 2012 is difficult to explain with the administrative database, but clinicians suggested that in 2012 were set a different method in diagnosis recording in hospital setting. The female data are constantly lower than the male rate over years, except for 2011 where the incidence rate is the same.

Table 7. Incidence rate over years

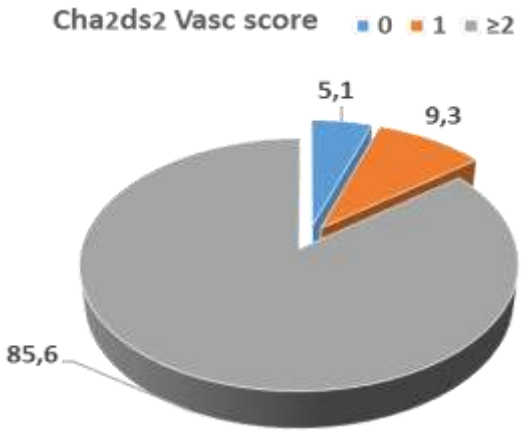
Year of incidence	Incidence rate (%)	Male (%)	Female (%)
2007	0.30	0.31	0.28
2008	0.26	0.28	0.24
2009	0.27	0.28	0.26
2010	0.28	0.30	0.26
2011	0.24	0.24	0.24
2012	0.43	0.45	0.40
2013	0.28	0.30	0.26

Focusing on patients with a diagnosis of Non Valvular Atrial Fibrillation, 8,006 patients out of 8640 were identified. Again the 52% is male with a mean age of 74.9 ± 11.5 years (mean ± SD), slightly greater comparing to the AF population.

8.2. CHA_2DS_2-VASC and $CHADS_2$ score for NVAF patients

The CHA_2DS_2-VASc and $CHADS_2$ score was calculate for NVAF patients (n.8,006). According to the CHA2DS2-VASc score, 5.11%, 9.33% and 85.56% patients were classified in the low-risk, intermediated-risk and high-risk categories, respectively (mean CHA_2DS_2-VASc score 3.5 ± 1.8 SD) (Figure 7). According to the $CHADS_2$ score, the distribution of patients in the low-risk, intermediated-risk and high-risk categories was as follows: 15,33%, 24.88% and 61.04% (mean $CHADS_2$ score 2.9 ± 1.0)

Figure 7. CHA_2DS_2-VASc score for NVAF patients



Patients with a CHA2DS2-VASc ≥2 were additionally stratified according to their risk score in table 8. The scores 2,3 and 4 are the most represented (i.e. 18, 25 and 24%).

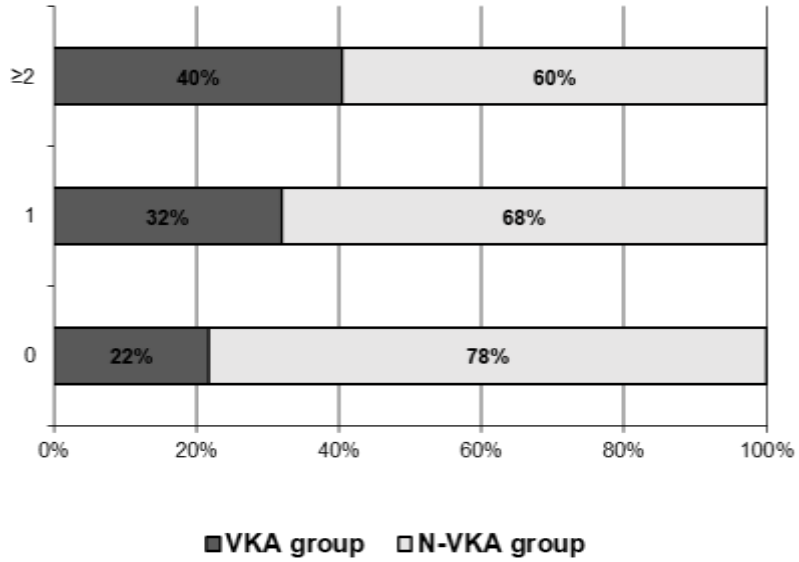
Table 8. CHA2DS2-VASC score for high-risk patients

CHA2DS2-VASC score	n. of patients	%
2	1235	18
3	1700	25
4	1670	24
5	1177	17
6	665	10
7	290	4
≥8	113	2

8.3. VKA treatment after the NVAF diagnosis

We collected all prescriptions of VKA after the diagnosis of NVAF and divided patients who received or not received a first prescription of VKA after the diagnosis during the entire observational period (VKA group *vs* N-VKA group). We observed that 53% of the 6,850 patients with a CHA2DS2-VASc ≥2 received a first prescription of VKA therapy; in addition, 52% of the 747 patients with a CHA2DS2-VASc =1 and 40% of the 409 patients with a CHA2DS2-VASc =0 received a first prescription of VKA therapy. Taking into account the elevate probability of discontinuation of therapy with VKA, we presented the results limited to NVAF patients who received VKA treatment for at least 6 months (Figure 8).

Figure 8. Percentage of NVAF patients receiving VKA treatment (VKA group) for at least 6 months or not receiving VKA treatment (N-VKA group), according to their CHA2DS2-VASc score.



We observed that 40% of the 6,850 patients with a CHA2DS2-VASc ≥2, 32% of the 747 patients with a CHA2DS2-VASc =1 and about 22% of the 409 patients with a CHA2DS2-VASc =0 received a continuous VKA therapy.

Among patients not receiving VKA treatment, we found that 27%, 48% and 72% of patients received at least one prescription of antiplatelet agents, according to CHA2DS2-VASc score 0, 1, ≥2, respectively.

8.4. Baseline characteristics of the cohort

Overall 8,006 patients with NVAF were identified from 1 January 2007 to 31 December 2013 (figure 9); applying the inclusion and exclusion criteria, 6138 participants were considered as eligible for the study. The baseline characteristics of the NVAF population are reported in Table 9.

Figure 9: flow chart of patients with NVAF (years 2007-2013)

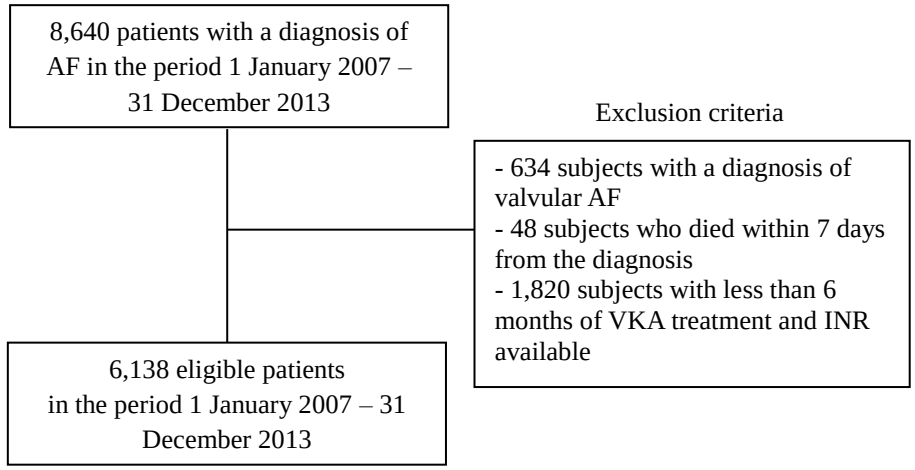


Table 9. Baseline characteristics, VKA group *vs* N-VKA group

	total population (n = 6,138)	**VKA group (n = 3,024)**	**N-VKA group (n = 3,114)**	**p value**
Age, yrs (mean ± SD)	75.59±11.51	75.09 ±8.90	76.08 ±13.67	p<0.001
Sex				
Male n. (%)	3053 (49.74)	1594 (52.71)	1459 (46.85)	p<0.001
Female n. (%)	3085 (50.26)	1430 (47.29)	1655 (53.15)	p<0.001
Follow up (death or study end date i.e. 31/12/2013) (mean month ± min-max)	37.70 (0-85.17)	48.73 (6.70 - 85.17)	23.47 (6-85.13)	
Thromboembolic risk factors				
Prior heart failure	1726 (28.12)	951 (31.45)	775 (24.89)	p<0.001
Prior hypertension	4045 (65.90)	2177 (72.00)	1868 (60.00)	p<0.001
Age ≥75 yrs	3651 (59.48)	1810 (59.85)	2058 (66.09)	p<0.001
Prior diabetes	1272 (20.72)	676 (22.35)	596 (19.14)	p<0.001
Prior stroke/TIA	1089 (17.74)	519 (17.16)	570 (18.30)	ns
Prior peripheral artery disease (including myocardial infarction)	868 (14.14)	413 (13.66)	455 (14.61)	ns
CHA_2DS_2-VASC				
0	297 (4.84)	67 (2.31)	230 (7.39)	p<0.001
1	504 (8.21)	197 (6.51)	307 (9.86)	p<0.001
≥2	5337 (86.95)	2760 (91.27)	2577 (82.75)	p<0.001
CHA2DS2				
0	815 (13.28)	252 (8.34)	563 (18.08)	p<0.001
1	1435 (23.38)	762 (25.20)	673 (21.61)	p<0.001
≥2	3888(63.34)	2010 (66.47)	1878 (60.31)	p<0.001
Antiplatelet agents at baseline	2504 (40.79)	1146 (37.90)	1358 (43.61)	p<0.001
Antiplatelet agents after AF diagnosis	1742 (28.38)	340 (11.24)	1402 (45.02)	p<0.001
NSAID/ corticosteroids at baseline	2111 (34.39)	1064 (35.18)	1047 (33.62)	ns
History of major bleeding	279 (4.55)	80 (2.62)	199 (6.39)	p<0.001

VKA group= patients on vitamin K antagonist therapy

N-VKA group = patients no treated with vitamin K antagonist therapy

Values are mean ±SD, median or n (%).

Statistical differences were found between groups for the most part of the considered baseline characteristics, except for the following: prior stoke/TIA, peripheral artery disease and NSAID/corticosteroids drugs use ($p>0.05$). These differences reflected the clinical judgement on deciding whether patient should be treated or not, i.e. if the risk-benefit profile of the treatment was positive. Female sex, increasing age (age≥75), antiplatelet drugs and history of major bleeding negatively affected the possibility of receiving VKA therapy. Comparing the antiplatelet at baseline and the antiplatelet prescribed after the diagnosis, we observed a discontinuation rate of around 70% in the VKA-group. Otherwise the antiplatelet treatment in N-VKA group increased up to 45.02%. Additionally, among the N-VKA group, we found that 1.8%, 5,4% and 92.7% of patients received antiplatelet agents instead of OAC therapy, according to the CHA_2DS_2-VASc score 0, 1, ≥2 respectively.

Of note, the median follow-up period was very different between groups: 48.73 and 23.47 months for the VKA and N-VKA groups, respectively ($p<0.001$). No specific reason was detected to justify this difference.

According to CHA2DS2-VASC and $CHADS_2$ respectively, 82.75% and 60.31% in the N-VKA group did not receive the therapy, despite a score ≥2, indicating a major stroke risk. On the other hand, 2.31% of patients in the VKA group received a thromboprophylaxis although their score was 0. The most common risk factor contributing to the scores across groups was hypertension (65.90 %) followed by age >75 years (59.48%).

The TTR was calculated for the 3,024 patients in the VKA group: overall the mean TTR was 55.76 (±14.83) and only 27.22% of patients reached the target (TTR ≥65%); the percentage of patients who reached the target increased over the years from 24.55% in 2007 to 37.23% in 2013.

8.5. Stroke risk

In the Table 10, the occurrence of clinical outcome, i.e. stroke events, was reported in a multivariate regression analysis.

Table 10. Hazard ratio (HR) for stroke risk evaluation (Cox regression model)

Hazard ratio for stroke risk (Cox regression model) has been evaluated by sex, age, previous stroke-TIA, CHA_2DS_2-VASC and CHA_2DS_2 scores, previous bleeding, use of antiplatelet agents at baseline, and by therapeutic treatment; Hazard ratio by combination of these covariates has been evaluated as well, excluding CHA_2DS_2-VASC and CHA_2DS_2 indexes. CHA_2D_2 is not reported in the following table, although it statistically correlates with stroke risk.

Information on corticosteroid therapy, renal and hepatic disease were not statistically associated with stroke risk and have been excluded from the analysis.

	Univariate analysis				Multivariate analysis			
	Hazard Ratio	**Sd. Err.**	**P>|z|**	**[95% Conf. Interval]**	**Hazard Ratio**	**Std. Err.**	**P>|z|**	**[95% Conf. Interval]**
Anamnestic information								
Sex								
Female	1,194	0,092	0,021	1,027-,388	0,913	0,076	0,273	0,814 – 1,119
Age class								
65-74	1,772	0,328	0,002	1,233 - 2,546	1,824	0,362	0,002	1,237 – 2,690
75-84	3,423	0,588	0,000	2,444 - 4,798	2,971	0,558	0,000	2,056 – 4,294
≥85	6,585	1,167	0,000	4,653 - 9,320	4,475	0,886	0,000	3,036 – 6,595
Stroke/ TIA	3,832	0,304	0,000	3,280 - 4,476	2,986	0,249	0,000	2,535– 3,517
Previous bleeding events	1,621	0,199	0,000	1,275 - 2,060	1,598	0,203	0,000	1,246 – 2,049
Antiplatelet agents at baseline	1,826	0,140	0,000	1,571-2,122	1,460	0,123	0,000	1,238 – 1,721
CHA_2DS_2-VASC								
2 - 3	2,893	0,703	0,000	1,798 - 4,657				
4 - 5	5,749	1,372	0,000	3,644 - 9,216				
≥6	12,243	2,937	0,000	7,651 - 9,591				
Therapeutic management								
VKA-; Antiplatelet +	1,188	0,134	0,126	0,953 - 1,481	0,916	0,114	0,483	0,717 – 1,170
VKA +; TTR<65%	0,700	0,072	0,001	0,572 - 0,857	0,786	0,089	0,034	0,629 – 0,982
VKA+; TTR≥65%	0,513	0,074	0,000	0,386 – 0,682	0,594	0,094	0,001	0,435 – 0,810

Increasing age was a major risk factor for stroke (HR =1.82, 2.97 and 4.48 for patients aged 65-74, 75-84 and ≥85, respectively, $p<0.001$). With regard to comorbidities previous stroke/TIA (HR = 2.99, $p<0.001$) and previous bleeding events (HR= 1.60, $p<0.001$) were significantly associated with the risk of stroke.

Similarly, the use of antiplatelet agents at baseline significantly increased stroke risk (HR= 1.46, $p<0.001$). On the other hand, sex was no significantly associated with stroke risk (HR = 0.91, $p>0.05$).

According to treatments, N-VKA; N-antiplatelet group was considered the group with the highest stroke risk. The addition of antiplatelet drug (N-VKA, antiplatelet+ group) did not allow a significant decrease in such a risk (HR= 0.92, $p>0.05$). VKA treatment significantly reduced the stroke risk: VKA group TTR≥ 65% group had an HR= 0.79 ($p<0.05$). Such a risk further decreased to 0.59 ($p<0.01$) for VKA-group TTR ≥65%.

Years 2013-2016

8.6. AF Population identification and characteristic

The cohort of patients identified consisted of 5,597 patients with a diagnosis of Non Valvular Atrial Fibrillation out of 6,063 patients with a hospital admission or an admission to the emergency ward (i.e. do not involve a subsequent hospital admission) for AF (ICD9-CM 4273**)** from 2013 to 2015 with an estimated prevalence of 1.3 considering 426,228 inhabitants. Among 5,597 patients, the 50.2% is male with a mean age of 76.4 ±11.9 years.

8.7. Baseline characteristics of the cohort

Applying the inclusion and exclusion criteria, 5,249 out of 5,597 participants with NVAF were considered as eligible for the study (figure 10). The baseline characteristics of the NVAF population are reported in Table 11. In order to have at least 1- year follow up period for each patient, the cohort was observed until 31 December 2016.

Figure 10: flow chart of patients with NVAF (years 2013-2015)

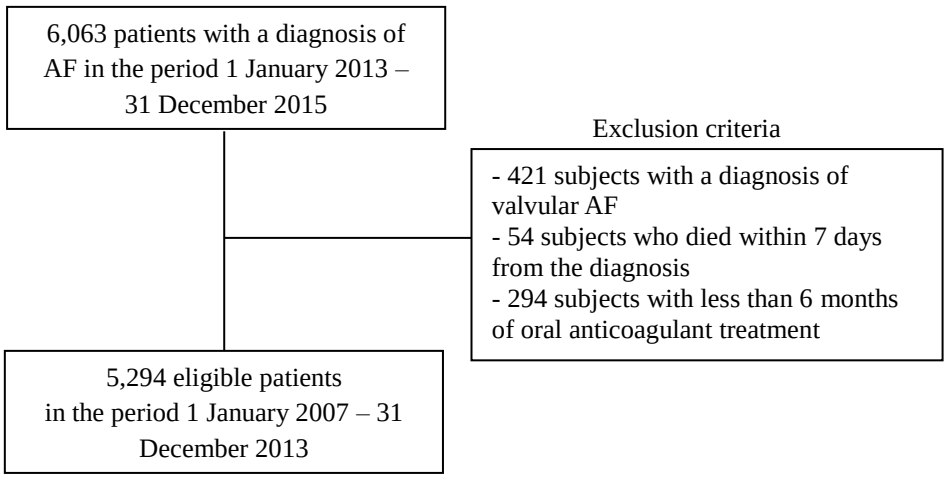


Table 11. Baseline characteristics

	N-group (N=2,303)	VKA-group (N=2,172)	NOAC-group (N=774)	p value
Age, yrs (mean ± SE)	77.05 ± 0.30	76.15 ± 0.20	76.13 ± 0.34	0.025
Sex				
Male n. (%)	1,049 (45.55)	1,202 (55.34)	354 (45.74)	<0.001
Female n. (%)	1,254 (54.45)	970 (44.66)	420 (54.26)	<0.001
Follow up (median month ± SE)	25.97 ± 0.27	30.83 ± 0.24	27.11 ± 0.38	<0.001
Thromboembolic risk factors at baseline				
Major Bleeding	138 (5.99)	68 (3.13)	35 (4.52)	<0.001
Heart failure	835 (36.26)	931 (42.86)	225 (29.07)	<0.001
Hypertension	1,188 (51.58)	1,274 (58.66)	482 (62.27)	<0.001
Pre-existing NVAF	510 (22.15)	753 (34.67)	239 (30.88)	<0.001
Age ≥75 yrs	1,454 (63.14)	1,344 (61.88)	473 (61.11)	0.519
Diabetes	436 (18.93)	586 (26.98)	142 (18.35)	<0.001
Prior stroke/TIA	89 (3.86)	57 (2.62)	62 (8.01)	<0.001
Vascular disease	398 (17.28)	451 (20.76)	123 (15.89)	0.001
Duration of disease, days (mean ± SE)	779.08 ± 8.12	925.04 ± 7.28	813.26 ± 11.41	<0.001
TTR at baseline	156	473	102	
<65	142 (91.03)	385 (81.40)	88 (86.27)	0.014
≥65	14 (8.97)	88 (18.60)	14 (13.73)	
CHA2DS2-VASC				
0	179 (7.77)	62 (2.85)	24 (3.10)	<0.001
1	256 (11.12)	204 (9.39)	58 (7.49)	<0.001
≥2	1,868 (81.11)	1,906 (87.75)	692 (89.41)	<0.001
TTR post ID				
<65	-	1,819 (83.75)	-	-
≥65	-	353 (16.25)	-	
Adherence to treatment				
No	-	-	294 (37.98)	-
Yes	-	-	480 (62.02)	

Statistical differences were found between groups for mostly all the considered baseline characteristics, except for age. These differences strongly reflected the clinical judgement on deciding whether patient should be treated or not; and with which therapy options the patients should start.

Again, female sex, increasing age and history of major bleeding negatively affected the possibility of receiving a thromboprophylaxis.

According to CHA2DS2-VASC score, 81.11% in the N-group did not receive the therapy, despite a score ≥2, indicating a major stroke risk. On the other hand, 2.85% of patients in the VKA group and 3.10% of patients in the NOACs group received a thromboprophylaxis although their score was 0. The most common risk factor contributing to the scores across groups was age >75 years (62.31%), followed by hypertension (56.09 %).
Comparing the VKA group and the NOACs group, the initiation of therapy with NOAC was positively associated with female sex, history of major bleeding and prior stroke or TIA. On the contrary patients with heart failure, diabetes, pre-existing hospital admission for AF and vascular disease were less likely to initiate with NOAC.

We found n.1,502 (28.61%) out of 5,249 patients with a pre-existing hospital admission with a diagnosis of AF before the years 2013-2015. Only the 48.67% received a VKA therapy and very few patients reached the target (overall n. 116 out of 731).
All patients with pre-existing AF, had a second hospital admission or an emergency ward admission in the years 2013-2015, which induced to stop the VKA treatment (21.35%), to continue the VKA therapy (64.70%), or to switch to NOACSs (13.95%). Of note, among patients on VKA therapy at baseline who stop the treatment, the 91.03% had a TTR<65.
The TTR post ID <65, as calculated in the VKA-group, was still dramatically high and occurred in the 83.75% of patients.
Adherence to NOACs treatment were found in the 62.02% of treated patients compared to the 37.98% of patients not adherent to therapy.

8.8. Stroke risk

In the Table 12, the occurrence of clinical outcome related to the cohort with NVAF enrolled in the years 2013-2015, i.e. stroke events, collected at any time after the ID until 31 December 2016, was reported in a multivariate regression analysis. The number of stroke detected after the ID was 374.

Table 12. Hazard ratio (HR) for stroke risk evaluation (Cox regression model)
HR for stroke risk was evaluated with regard to sex, age, previous stroke-TIA, previous bleeding, CHA2DS2-VASC score, and to therapeutic treatment. HR by combination of these covariates has been evaluated as well. The baseline characteristics not statistically correlated with the risk of stroke in the Univariate analysis have been excluded from the multivariate analysis.

	Univariate analysis			Multivariate analysis		
	HR ± SE	**95%CI**	**p-value**	**HR ± SE**	**95%CI**	**p-value**
Age, yrs						
<65	1			1		
65-74	2.23 ± 0.61	1.30 – 3.82	0.004	1.12 ± 0.36	0.60 – 2.10	0.730
75-84	3.79 ± 0.98	2.29 – 6.28	<0.001	1.53 ± 049	0.82 – 2.86	0.177
≥85	8.14 ± 2.08	4.94 – 13.42	<0.001	3.29 ± 1.04	1.76 – 6.13	<0.001
Sex						
Male	1			1		
Female	1.28 ± 013	1.05 – 1.57	0.017	0.86 ± 0.09	0.70 – 1.07	0.176
Thromboembolic risk factors at baseline						
Bleeding	1.41 ± 0.30	0.93 – 2.13	NS 0.103			
Heart failure	1.65 ± 0.17	1.35 – 2.02	<0.001	1.12 ± 0.13	0.89 – 1.39	0.329
Hypertension	1.13 ± 0.12	0.92 – 1.38	NS 0.263			
Pre-existing NVAF	0.72 ± 0.08	0.57 – 0.90	0.005	0.77 ± 0.09	0.61 – 0.98	0.031
Diabetes	1.65 ± 0.19	1.33 – 2.06	<0.001	1.52 ± 0.18	1.21 – 1.91	<0.001
Prior stroke/TIA	19.80 ± 2.51	15.44 - 25.38	<0.001	15.58 ± 2.09	11.99 – 20.26	<0.001
Vascular disease	1.68 ± 0.20	1.34 – 2.12	<0.001	1.39 ± 0.17	1.10 – 1.77	0.007
CHA_2DS_2-VASC						
0	1			1		
1	2.37 ± 1.85	0.51– 10.95	NS 0.271	2.38 ± 1.88	0.50 – 11.19	0.274
≥2	13.07 ± 9.27	3.26 – 52.47	<0.001	5.03 ± 3.90	1.10 - 22.95	0.037
Type of treatment						
No treatment	**1**			**1**		

VKA; TTR<65	**0.90 ± 0.11**	**0.72 – 1.14**	**0.400**	**0.88 ± 0.11**	**0.69 – 1.13**	**0.322**
VKA; TTR ≥65	**0.38 ± 0.11**	**0.21 – 0.66**	**0.001**	**0.53 ± 0.16**	**0.30 – 0.94**	**0.031**
NOACs; not adherent	**1.22 ± 0.29**	**0.76 – 1.94**	**0.414**	**1.28 ± 0.32**	**0.79 – 2.08**	**0.315**
NOACs; adherent	**1.80 ± 0.28**	**1.32 – 2.44**	**<0.001**	**1.67 ± 0.28**	**1.21 – 2.30**	**0.002**

Overall increasing age was a risk factor for stroke, but only age ≥85 was significantly associated with the risk of stroke (HR=3.29, p<0.001).

With regard to comorbidities, diabetes, previous stroke/TIA and vascular disease were significantly associated with the risk of stroke. In particular, previous stroke/TIA represents a major stroke risk factor, with a HR= 15.58 (p<0.001). On the contrary, pre-existing NVAF significantly reduced the stroke risk (HR= 0.77, p<0.05). On the other hand, sex was no significantly associated with stroke risk (HR = 0.86, p>0.05).

According to treatments, NOAC-adherent group was considered the group with the highest stroke risk (HR= 1.67, p=0.002). Such a risk decreased to no significant HR=1.28 (p>0.05) for NOAC-not adherent group. VKA treatment had a preventive effect on the stroke risk, even if the stroke risk was significantly reduced only in the VKA group with TTR≥ 65% (HR= 0.53, p<0.05).

However results might be partially explained by the small numbers effect. For instance, the number of stroke event according to treatments was 146 in the no treatment-group, 151 in the VKA group (with TTR≥65 no.14), 77 in the NOACs group (adherent no. 58).

8.8.1. Stroke risk for patients with prior stroke or TIA

Considering the prior stroke/TIA as a major risk factor for having a second stroke event, we performed a specific multivariate analysis on this subgroup of patients. But since the limited number of observations (n. 119) we decided to considered only VKA *vs* NOACs groups (Table 13).

Table 13. Hazard ratio (HR) for stroke risk evaluation (Cox regression model)

HR by combination of the following covariates: stroke risk was evaluated with regard to sex, age, thromboembolic risk factors and to therapeutic treatments.

	Multivariate		
	HR ± SE	**95%CI**	**p-value**
Age, yrs			
<65	1		
65-74	1.88 ± 1.50	0.39 - 9.03	0.430
75-84	2.35 ± 1.82	0.51 - 10.70	0.270
≥85	3.69 ± 2.84	0.82 - 16.64	0.089
Sex			
Male	1		
Female	0.99 ± 0.26	0.59 - 1.66	0.978
Thromboembolic risk factors at baseline			
Heart failure	1.29 ± 0.30	0.80 - 2.06	0.293
Pre-existing NVAF	0.65 ± 0.20	0.35 - 1.21	0.176
Diabetes	1.40 ± 0.37	0.83 - 2.36	0.207
Vascular disease	0.92 ± 0.29	0.49 - 1.73	0.804
Type of treatment			
No treatment	1		
VKA-group	0.45 ± 0.14	0.24 - 0.85	0.014
NOACs -group	0.56 ± 0.18	0.29 - 1.07	0.082

The increasing age, heart failure and diabetes were associated with an increased stroke risk (but not statistically significative). Comparing no treated patients and treated patients a decreasing risk was connected to VKA and to NOACs treatment with HR=0.45, $p<0.05$ and HR = 0.56 p=0.082, respectively. However given the small event number, clinical significance cannot be drawn.

8.9. Risk of death

Table 14 reported in a multivariate regression analysis the occurrence of death collected at any time after the ID until 31 December 2016. 674 death were detected after the ID.

Table 14. Hazard ratio (HR) for death risk evaluation (Cox regression model)
HR for death risk was evaluated with regard to sex, age, comorbidities and to therapeutic treatment. HR by combination of these covariates has been evaluated as well.

	Univariate analysis			**Multivariate analysis**		
	HR ± SE	**95%CI**	**p-value**	**HR ± SE**	**95%CI**	**p-value**
Age, yrs						
<65	1					
65-74	4.27 ± 1.45	2.20-8.31	0.000	3.23 ± 1.32	1.45-7.19	0.004
75-84	10.12 ± 3.27	5.37-19.07	0.000	6.16 ± 2.54	2.75-13.81	0.000
≥85	23.61 ± 7.57	12.60 - 44.26	0.000	9.20 ± 3.78	4.11 - 20.61	0.000
Sex						
Male	1					
Female	1.26 ± 0.09	1.09 - 1.47	0.002	0.82 ± 0.07	0.70 - 0.96	0.015
Thromboembolic risk factors at baseline						
Bleeding	1.99 ± 0.27	1.52 - 2.61	0.000	1.20 ± 0.17	0.91 - 1.58	0.183
Heart failure	3.59 ± 0.29	3.06 - 4.22	0.000	2.21 ± 0.191	1.86-2.62	0.000
Hypertension	1.01 ± 0.07	0.87-1.18	0.887 N.S.			
Pre-existing NVAF	1.03 ± 0.09	0.88 - 1.23	0.676 N.S.			
Diabetes	1.70 ± 0.14	1.45-2.00	0.000	1.38 ± 0.12	1.17 - 1.64	0.000
Prior stroke/TIA	3.65 ± 0.47	2.84 - 4.71	0.000	3.28 ± 0.43	2.53 - 4.24	0.000
Vascular disease	1.71 ± 0.15	1.44 - 2.02	0.000	1.23 ± 0.11	1.03 - 1.46-	0.021
Type of treatment						
No treatment (0)	**1**					
VKA; TTR<65 (1)	0.45 ± 0.04	0.38 - 0.53	0.000	0.43 ± 0.04	0.35-0.51	0.000
VKA; TTR ≥65 (2)	0.11 ± 0.04	0.06 - 0.21	0.000	0.15 ± 0.05	0.08-0.29	0.000
NAO; not adherent (3)	0.02 ± 0.02	0.00 - 0.12	0.000	0.02 ± 0.02	0.00-0.15	0.000
NAO; adherent (4)	0.35 ± 0.06	0.25 - 0.49	0.000	0.37 ± 0.06	0.26-0.52	0.000

As for the stroke risk, increasing age was a major risk factor for all-cause mortality (HR =3.23, 6.16 and 9.20 for patients aged 65-74, 75-84 and ≥85, respectively, $p<0.001$). With regard to comorbidities heart failure (HR=2.21, $p<0.001$), diabetes (HR=1.38, $p<0.001$), previous stroke/TIA (HR = 3.28, $p<0.001$) and vascular disease (HR= 1.23, $p<0.05$) were significantly associated with the risk of death. Further, female sex had a significantly preventive effect on the risk of death (HR = 0.82, $p<0.05$).

On the other hand, previous bleeding events were not significantly associated with death risk (HR = 1.20, $p>0.05$).

According to treatments, compared to the N-VKA group, VKA and NOAC treatments significantly reduced the risk of death: VKA- TTR< 65% group had an HR= 0.43 ($p<0.001$), VKA - TTR≥ 65% group had an HR= 0.15 ($p<0.001$), NOAC-not adherent group had an HR= 0.02 ($p<0.001$), NOAC-adherent group had an HR= 0.37 ($p<0.001$). Number of death in the treatment groups were: 450 (out of 2303- 19.5%) in the no treatment group, 188 (out of 2172 - 8.6%) in the VKA group and 36 (out of 774 – 4.6%) in the NOACs group.

8.10. Bleeding risk

Table 15 reported in a multivariate regression analysis the occurrence of major bleeding events (no. 181) collected at any time after the ID until 31 December 2016.

Table 15. Hazard ratio (HR) for bleeding risk evaluation (Cox regression model)
HR for bleeding risk was evaluated with regard to sex, age, comorbidities, and to therapeutic treatment. HR by combination of these covariates has been evaluated as well.

	Monovariate analysis			**Multivariate analysis**		
	HR ± SE	**95%CI**	**p-value**	**HR ± SE**	**95%CI**	**p-value**
Age, yrs						
<65	1					
65-74	3.23 ± 1.25	1.51 - 6.91	0.002	2.36 ± 1.13	0.92- 6.06	0.074
75-84	5.48 ± 2.02	2.66 - 1.31	0.000	3.16 ± 1.54	1.22- 8.22	0.018
≥85	4.95 ± 1.90	2.33- 10.53	0.000	2.94 ±1.48	1.09- 7.90	0.032
Sex						
Male	1					
Female	1.06 ± 0.16	0.79- 1.43	0.670 **N.S.**			
Thromboembolic risk factors at baseline						
Bleeding	3.24 ± 0.70	2.12- 4.94	0.000	2.71± 0.59	1.76- 4.17	0.000
Heart failure	2.13 ± 0.32	1.59- 2.85	0.000	1.44 ± 0.24	1.05- 1.99	0.024
Hypertension	1.07 ± 0.16	0.80 - 1.44	0.648 **N.S**.			
Pre-existing NVAF	1.08 ± 0.17	0.80- 1.47	0.583 **N.S.**			
Diabetes	1.90 ± 0.30	1.39- 2.59	0.000	1.39 ± 0.23	1.00- 1.93	0.047
Prior stroke/TIA	6.51±1.78	3.80- 11.13	0.000	5.47 ±1.52	3.17- 9.44	0.000
Vascular disease	1.89± 0.31	1.37- 2.60	0.000	1.40 ± 0.24	1.01- 1.96	0.045
Type of treatment						
No treatment (0)	**1**					
VKA; TTR<65 (1)	1.66 ±0.29	1.19- 2.33	0.003	1.39 ± 0.25	0.97- 1.99	0.072
VKA; TTR ≥65 (2)	0.53± 0.21	0.24- 1.16	0.113	0.57 ± 0.23	0.26- 1.27	0.172
NAO; not adherent (3)	1.54±0.56	0.76- 3.13	0.230	1.61 ± 0.59	0.78- 3.31	0.193
NAO; adherent (4)	1.50 ± 0.42	0.87- 2.59	0.145	1.40 ± 0.40	0.78- 2.46	0.240

Nor increasing age nor sex were significantly associated with the risk of major bleeding (HR=3.29, $p<0.001$).

With regard to comorbidities, previous bleeding events, heart failure, diabetes, previous stroke/TIA and vascular disease were significantly associated with the risk of major bleeding. In particular, previous stroke/TIA represents a major stroke risk factor, with a HR= 5.47 ($p<0.001$). In contrast, pre-existing NVAF and hypertension were not significantly correlated to the bleeding risk.

According to treatments, VKA-group TTR ≥65% was considered the group with preventive effect on the risk of major bleeding, but did not allow a significant decrease in such a risk (HR= 0.57, $p>0.05$). Patients on VKA therapy with a TTR<65%, or on NOACs therapy had an increased risk to develop a major bleeding, but they did not reach the statistical significance. Number of major bleeding in the treatment groups were respectively: 53 (out of 2303– 2.3%) in the no treatment group, 102 (out of 2172 – 4.7%)) in the VKA group and 26 (out of 774 – 3.4%) in the NOACs group.

9. DISCUSSION

The main objective of this retrospective observational study was to describe the anticoagulation therapy in patients with non valvular atrial fibrillation in clinical practice in the Local Health Authority of Treviso, across a period of time where the approach to treatment has been deeply changed: firstly the influence of guidelines which strongly recommended the thromboprophilaxys in high risk patients, and the introduction of the CHA2DS2-VASC score; then the NOACs -apixaban, dabigatran and rivaroxaban- introduction on the pharmaceutical market as innovative alternative therapy options in the prevention of NVAF-related stroke. Since the first NOAC (dabigatran) was available in Italy from July 2013, we aimed to compare anticoagulation practice during the pre- and post- new oral anticoagulant periods, including patients with a hospital admission for NVAF from 2007 to 2013, when the oral anticoagulant therapy option was limited to VKA. Then, we identified a second cohort of patient with a hospital admission or an emergency ward admission for NVAF from 2013 to 2016.

Overall we found that underuse of anticoagulants among high thromboembolic risk patients remains a persistent problem together with an elevate rate of discontinuation. In particular, regarding years 2007-2013, among patients with NVAF, about 60% received a first prescription of VKA after the ID; but 1,820 (≈ 37%) patients discontinued the anticoagulant treatment within 6 months. Regarding years 2013-2016, the percentage of patients who were treated with an oral anticoagulation therapy was about 56% and 294 (about 10%) patients had an occasionally therapy. The underuse of oral anticoagulant treatment is well-documented in the literature, and is a persistent problem: a recent meta-analysis of quantitative studies revealed that less than 70% of high-risk patients receive adequate oral anticoagulation therapy [Ogilvie IM, Am J Med. 2010]. Potential barriers to an appropriate treatment prescription include inadequate risk stratification, the advanced age of the patient, bleeding and falling risk, and the difficulties of warfarin management, including adverse events and patient compliance [Ogilvie IM, Am J Med. 2010; Hess PL, Am Heart J 2014; Barra S, J Saudi Heart Assoc 2015]. Additionally, the rate of discontinuation for VKA therapy found during the pre-NOAC period was similar to what has been reported in literature, where discontinuation rates range from 20% to more than 50% [Hess PL, Am Heart J 2014; O'Brien EC, Am Heart J 2014; Gallagher AM, J Thromb Haemost 2008; Fang MC, Circ Cardiovasc Qual Outcomes 2010].

Although European clinical guidelines would have influenced practice strongly recommending thromboprophylaxis in high risk patients and no treatment in low risk patients as calculated by CHA2DS2-VASC or CHADS2 score [Camm AJ, European Heart Journal 2012; January CT, J Am Coll Cardiol 2014], we still found a suboptimal use of antithrombotic therapy in both periods. In the pre-NOACs period, among low risk patients (score =0), ≈ 23% received a continuous anticoagulant treatment according to CHA2DS2-VASC score; data which increased up to about 32% if in the post-NOACs period (2013-2016). Similar data were found in a recent study: comparing the pre- and post-

direct oral anticoagulant eras, OAC overprescribing in low-risk patients were 35.0% and 42.9% in the pre- and post-DOAC eras, respectively (p = 0.59) [Admassie et al, Am J.Cardiol 2017].
Among high risk patients (CHA2DS2-VASC score ≥2), about 83% and 81% of N-VKA group did not receive any oral anticoagulant therapy during the pre- and post-NOACs periods respectively. Zimetbaum et al. [Zimetbaum PJ, Am J Med 2010] found similar proportions of patients in the low, moderate, and high stroke-risk groups receiving warfarin. Thus, patients who would benefit the most from anticoagulants due to high risk of stroke do not receive treatment, while those considered at low risk may perhaps be unnecessarily exposed to the inconvenience and risks associated with anticoagulant therapy [Barra S, J Saudi Heart Assoc 2015; Mochalina N, et al. Thromb Res 2016].

Furthermore, considering the antiplatelet use, despite data from literature clearly showing that the efficacy of antiplatelet agents in thromboembolic prevention is significantly lower than that of oral anticoagulant therapy [Connolly SJ, Circulation 2008], in the pre-NOACs period general practitioners preferred to use antiplatelet agents in about 45% of N-VKA-treated patients, in particular among high risk patients (1,300 out of 1,402 patients). This behavior could be partially explained by specific contraindications to VKA, difficulties in performing the INR control, concerns over bleeding risk and the elevated age of treated patients; however further analysis should be performed in order to investigate the reason of a large use of antiplatelet therapy instead of a VKA treatment and in order to identify which patients will benefit the most by switching form an antiplatelet drug to an oral anticoagulant treatment. Clearly, concerns over bleeding risk lead physicians to not prescribing a VKA treatment, since history of major bleeding events was more frequent among the group of no treated patients (6.39% and 2.62% of N-VKA and VKA patients).

In the pre-NOACs period, among patients treated with VKA, this study revealed that 73% of patients did not reach the therapeutic target in a median observational time of 31.51 months (6 to 83.82 months). In the post-NOACs period, the percentage of patients on VKA therapy with a TTR<65%, increased to 83.75% in a median observational time of 30.83 months. Such a result is particularly dramatic, since a recent study by Connolly et al. [Connolly SJ, Circulation 2008] highlighted that TTR<65% abolishes the protective effect of oral anticoagulant therapy, and reaches that comparable to antiplatelet agents. Comparable results were found only in the study of Sarawate et al. [Sarawate C, J Thromb Thrombolysis 2006] where the average TTR was 28.6. Differently from the present study, most prior observational studies reporting higher TTR were conducted in patients in hospital setting, under supervision of hospital-based physicians or by anticoagulation clinics [van Walraven C, Chest 2006]. What is evident in this real world study performed in a community setting covering a long period of time, is a persisting difficult of management of this complicated and elderly patients by general practitioners.

Overall, the baseline patient's characteristics were different for mostly all considered factors, both in the pre- and post-NOACs period. In the pre-NOACs period, the differences in the baseline patient's characteristics favored the oral anticoagulant treatments to younger patients (<75) who were men. This was still detected in the post-NOACs period, except for female sex in the NOACs group where the situation was inverted. These findings are consistent with those of others investigating the influence of age and sex on the treatment of heart disease [Dudley NJ, Age and Ageing 2002]: the clinical judgement of an individual doctor may be biased by age and sex, by perceptions of frailty and by the deficient evidence base in elderly patients [Dudley NJ, Age and Ageing 2002]. Most patients with atrial fibrillation are elderly, but it is the elderly ones who are most at risk from OAC treatment [Hampton JR. Age and Ageing 2002].

In the post-NOACs period, we also evaluated the patterns of prescription of oral anticoagulants (VKA and NOAC) as a starting treatment in naïve and prevalent patients with nonvalvular atrial fibrillation, and we described factors associated with treatment initiation with VKA or NOAC.
Comparing the patterns of prescription of oral anticoagulants (VKA *vs* NOACs) and factors associated with treatment initiation, prescription of NOAC as starting treatment was associated overall with a higher baseline risk of thromboembolic events, according to CHA2DS2-VASc score ≥2 (89.41% in the NOACs group *vs* 87.75 in the VKA-group, p<0.001), but we are of the opinion that a clinically significance difference between this groups might be difficult to underline. Nevertheless this finding is generally supported by evidences concluding that NOACs were associated with a more favorable efficacy and safety profile compared with warfarin [Madzak A, Expert Rev Cardiovasc Ther. 2015; Hernandez I, Am J Cardiol. 2017].

Of note, the majority of patients with a prior stroke or TIA were in the NOACs group. This finding was influenced by the adoption in the Veneto Region of specific guideline which did not allow to initiate the thromboprophylaxis with NOACs in naïve patients, except for patient with preexisting stroke or TIA, or patients contraindicated to on not tolerant to VKA therapy [Veneto Region Guideline, Decree no. 75/2013].

Considering clinical stroke outcomes, the Cox regression model outlined an incremental risk of stroke for N-VKA-treated patients compared to VKA patients, as extensively described in the literature [Connolly SJ, Circulation 2008; Aguilar MI, Cochrane Database Syst Rev 2007]. Among VKA-treated patients, stroke risk was higher in not at target patients compared to patients with TTR at target (OR = 0.79 and 0.60, respectively, compared to group N-VKA, N-antiplatelet). Similarly, an appropriate VKA therapy (TTR ≥65%) allowed reaching the longest time-to-stroke event, therefore providing the most effective thromboembolic prevention.

Comparing VKA patients and NOACs patients to no treated patients, in a Cox regression model, unexpectedly, the risk of stroke for NOACs patients is higher and get worse if patients were stratified by adherence (NOAC- adherent group had a HR=1.67, $p<0.05$). This finding is inconsistent with the published literature in this area. But this is probably justified by the small numbers of stroke events in the groups; also a higher percentage of patients on NOAC therapy with prior stroke/TIA, which is a major stroke risk factor (HR=15.58, $p<0.001$). Additionally, focusing on patients with a prior stroke/TIA, the multivariate analysis found a preventive effect for stroke risk for both VKA-group and NOACs-group, suggesting that a sampling bias had also influenced this finding.

Of note, given the limitation of the administrative databases, we had no information on the nature of the strokes suffered by patients and we cannot included in the analysis.

About all-cause mortality outcomes, VKA and NOACs treatment prevent significantly the risk of mortality, but TTR in the VKA nor adherence in NOACs groups were significant predictors of this outcome. This finding is not similar to other study in which the association of risk of death or stroke was seen influenced by adherence where the 27.8% of non-adherent patients on dabigatran, have an increased stroke risk (HR= 1.13 (95% CI 1.07–1.19) [41]. Finally, the higher bleeding risk in the treated patients *vs* no treated patients did not different among group. A preventive effect is observable limited to VKA group TTR≥65% (HR=0.57, $p>0.05$).

Regarding adherence to therapy, we found that adherence was higher among NOACs- patients compared with the VKA-patients. However, the adherence is still problematic, and may potentially lead to underestimation of bleeding risk and/or suboptimal stroke prevention in this observational study. Our finding is supported by several studies where adherence rates were situated in the range of 40% to 70% [Maura et al, Pharmacoepidemiol Drug Saf. 2017; Beyer Westendorf J, Eur Soc Cardiol. EP Europace 2016].

In conclusion, better quality of care of AF patients should be provided by increasing adherence to anticoagulation guidelines and improving patients' compliance with anticoagulation therapy through education and established protocols. A systematic approach should be implemented in order to assess the presence of stroke risk factors, to determine the presence of specific contraindications, and to schedule and ensure an appropriate follow-up and INR control. After the introduction of novel oral anticoagulant, adherence to oral anticoagulation therapy remain a significant challenge in the management of AF patients. Reinforced teaching for both patients and prescribers regarding the benefits of optimal OAT adherence is needed. Further analysis comparing VKA vs. non oral anticoagulant therapy should be performed.

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