UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Sede Amministrativa: Università degli Studi di Padova

Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari

CORSO DI DOTTORATO DI RICERCA IN MEDICINA SPECIALISTICA "G.B. MORGAGNI"

CURRICOLO DI SCIENZE CARDIO-TORACO-VASCOLARI

CICLO XXX

ORAL ANTICOAGULATION FOR ATRIAL FIBRILLATION IN THE ERA OF NON-VITAMIN K ANTAGONIST ANTICOAGULANTS.

FOCUS ON VERY ELDERLY PATIENTS

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ABBREVIATIONS

AF	Atrial Fibrillation
AT	“As treated” statistical approach
FCSA	Italian federation of thrombosis centres (Federazione dei Centri per la Sorveglianza della terapia Anticoagulante)
ICH	Intra-Cranial Haemorrhage
INR	International Normalized Ratio
ITT	“Intention to Treat” statistical approach
LAA	Left Atrial Appendage
LMWH	Low Molecular Weight Heparins
MB	Major Bleeding
NOAC	Non-vitamin K antagonist Oral Anti-Coagulants
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NVAF	Non-Valvular Atrial Fibrillation
OAT	Oral Anticoagulant Therapy
TE	Thromboembolic Event
TTR	Time in Therapeutic Range
VKA	Vitamin K Antagonist oral anti-coagulants

RIASSUNTO

Introduzione. La fibrillazione atriale è l'aritmia cardiaca più comune, caratterizzata da un ritmo cardiaco irregolare, spesso ad alta frequenza, e associato alla formazione di trombi in atrio e auricola sinistra che possono causare l'ictus ischemico cardioembolico. La terapia anticoagulante orale ha dimostrato di ridurre l'incidenza di ictus ischemico in questI pazienti di circa due terzi, alle spese però di un'aumentata incidenza dei sanguinamenti. Nell'anziano la fibrillazione atriale è particolarmente frequente ma il suo trattamento presenta delle difficoltà: infatti, sebbene il rischio ischemico aumenti con l'età, anche il rischio emorragico è maggiore. ln questi pazienti il medico spesso preferisce non prescrivere o interrompere la terapia anticoagulante orale nel timore di complicanze. Il paziente anziano, inoltre, può essere portatore di più patologie, assumere diversi farmaci con potenziale rischio di interazioni farmacologiche e presentare una ridotta aderenza alla assunzione della terapia.

Scopo della tesi. Valutare l'impatto dell'anticoagulazione nel paziente anziano, con focus nel sottogruppo di pazienti con età $\geq$ 80 anni, che raramente vengono reclutati nei grandi trial clinici.

VENPAF. Abbiamo inizialmente condotto uno studio retrospettivo "*inception cohort*" includendo tutti i pazienti con età $\geq$ 80 anni in terapia con warfarin presso il locale Centro Trombosi (studio VENPAF). Dall'analisi è emersa un'incidenza di emorragie maggiori molto alta, che tende ad aumentare sensibilmente sopra gli 85 anni di età; nonostante ciò, il beneficio clinico netto della terapia appare comunque mantenuto, in quanto l'incidenza calcolata di trombo-embolismo in assenza di anticoagulazione è risultata maggiore, in entrambe le classi di età, rispetto all'incidenza osservata di emorragie maggiori.

Circa il 20% dei pazienti inclusi ha sospeso la terapia e questo è stato principalmente dovuto ad una decisione del medico di medicina generale o dello specialista; le ragioni addotte per la sospensione sono state la scarsa aspettativa di vita, la fragilità del paziente e l'eccessivo rischio emorragico. Abbiamo però constatato che la sospensione della terapia non era associata ad un miglioramento della prognosi ma anzi questi pazienti erano gravati da alti tassi di mortalità, eventi ischemici ed emorragici.

Restringendo l'analisi ai pazienti che avevano sperimentato un evento emorragico in corso di terapia anticoagulante, abbiamo potuto evidenziare come l'incidenza cumulativa di eventi ischemici ed emorragici

era significativamente più alta nei pazienti che dopo tale evento sospendevano la terapia rispetto a quelli che la riprendevano.

Studio caso-controllo. Per analizzare i fattori di rischio associati allo sviluppo di emorragia cerebrale in warfarin, abbiamo eseguito uno studio caso-controllo includendo tutti i pazienti seguiti per fibrillazione atriale presso il nostro Centro Trombosi. Abbiamo confrontato 51 pazienti con emorragia intracranica con 204 pazienti di controllo, appaiati per età, sesso ed esposizione alla terapia. Nessuna variabile analizzata è risultata associata allo sviluppo dell'emorragia. Abbiamo inoltre valutato il rischio emorragico per ogni paziente usando gli score HAS-BLED, ATRIA e ORBIT; tali score hanno presentato una capacità predittiva nei confronti dell'emorragia intracranica particolarmente scarsa o nulla ("c-statistic" minore 0.56 per tutti gli score utilizzati).

Registro Regione Veneto. Dallo studio VENPAF e dallo studio caso-controllo è emersa da una parte una forte tendenza al sanguinamento intracranico nel paziente anziano, dall' altra l'impossibilità di individuare specifici fattori predittivi di tale sanguinamento. È quindi con grande interesse che abbiamo guardato all'utilizzo clinico dei nuovi anticoagulanti orali (NAO), farmaci che dagli studi registrativi sembrano essere in grado di dimezzare questa grave complicanza rispetto al warfarin. Analizzando i dati della Regione Veneto attraverso il registro regionale delle prescrizioni farmacologiche, delle esenzioni e delle diagnosi di dimissione dai reparti, abbiamo potuto selezionare i pazienti che iniziavano una terapia anticoagulante orale perché affetti da fibrillazione atriale non valvolare. In confronto a warfarin, i NAO si sono dimostrati ugualmente efficaci e sicuri. Si è rilevata comunque una netta riduzione delle emorragie intracraniche e una lieve riduzione della mortalità rispetto alla terapia convenzionale, nonostante l'ottima qualità dell'anticoagulazione con warfarin raggiunta grazie ai centri trombosi veneti. In particolare, abbiamo riscontrato che nel Veneto i pazienti in terapia con NAO sono in media più anziani e a più alto rischio ischemico rispetto ai pazienti trattati con warfarin.

Abbiamo infine analizzato la popolazione di età $\geq$80 anni e riscontrato un deciso aumento delle emorragie gastrointestinali, soprattutto dal tratto inferiore, nei pazienti in terapia con NAO. Tale incremento, però, non ha modificato il profilo di sicurezza di questi farmaci, che presentano comunque un rischio

complessivo di emorragie maggiori e di ictus ischemici sovrapponibili al warfarin, con riduzione del rischio di emorragie intracraniche.

Conclusioni. Il presente lavoro di ricerca ha cercato di esplorare gli effetti della terapia anticoagulante nel paziente grande anziano con 80 anni o più. Dall'insieme degli studi condotti è stato possibile concludere che, nonostante l'elevato rischio di emorragia, il beneficio clinico per la prevenzione dell'ictus è a favore dell'uso di questi farmaci; andando infatti a considerare i pazienti che sospendevano il farmaco, abbiamo constatato una prognosi peggiore rispetto ai pazienti che rimanevano in terapia. Una parte non trascurabile delle emorragie in warfarin è dovuta ai sanguinamenti intracranici che sono spesso fatali o gravemente invalidanti; dai nostri dati tali eventi sono più frequenti nell'anziano e non sono prevedibili dai comuni fattori di rischio cardiovascolare, né da una buona qualità dell'anticoagulazione. I NAO sembrano invece mantenere anche nell'anziano un rischio di emorragie intracraniche inferiore al warfarin, nonostante un significativo aumento del rischio di emorragie gastrointestinali. Nel complesso, quindi, i nostri dati confermano i NAO come la terapia anticoagulante da preferire nella fibrillazione atriale non valvolare anche nel paziente molto anziano.

ABSTRACT

Introduction. Atrial fibrillation is the most common cardiac arrhythmia, characterized by irregular heart rhythm and associated with left atrial and left appendage thrombi formation that may cause ischemic stroke. Oral anticoagulant therapy has been shown to reduce the incidence of ischemic stroke in these patients by about two thirds, at the expense of an increase in bleeding. In the elderly, atrial fibrillation is particularly frequent, but anticoagulant therapy often encounter several issues: in fact, although ischemic risk increases with age, haemorrhagic risk is also high and often doctors prefers not to prescribe or discontinue oral anticoagulant therapy in fear of complications. The elderly patient, moreover, is often affected by multiple diseases, takes several drugs with potential risk of interactions and may have lower adherence to therapy.

Aim. To evaluate the impact of anticoagulation in the elderly patient, focusing on the subgroup of very elderly patients (i.e. $\geq$ 80 years of age) who are often not included in major clinical trials.

VENPAF. We initially conducted a retrospective "inception cohort" study involving all patients $\geq$ 80 years of age referred to the local Thrombosis Centre to start anticoagulant therapy with warfarin for atrial fibrillation (VENPAF study). From data analysis, we found that major haemorrhages rate is very high and tends to increase considerably over 85 years of age. Nevertheless, net clinical benefit appears to be maintained, as the calculated incidence of thromboembolism in the absence of anticoagulant therapy was higher in both age classes compared to the observed incidence of major haemorrhages.

About 20% of these patients had discontinued warfarin and this was often decided by the general practitioner or the specialist; main reasons for discontinuation were low life expectancy, fragility and excessive haemorrhagic risk. We found that therapy discontinuation was not associated with an improvement in prognosis, but indeed these patients faced high rates of mortality, ischemic and haemorrhagic events, regardless of persistence or discontinuation of anticoagulant therapy.

Analysing only patients who experienced a major bleeding event during anticoagulant therapy, we could highlight how the cumulative incidence of ischemic and haemorrhagic events was significantly higher in patients who suspended therapy than those who resumed it after the index event.

Case-control study. A case-control study was set to analyse which factors may possibly be associated with the development of intracranial haemorrhage with warfarin (the most serious complication of oral anticoagulant therapy). All patients followed by our Thrombosis Centre who developed intracranial bleeding in anticoagulant therapy were included; control group was created from anticoagulated patients paired for age, sex, and exposure to therapy in a 1:4 ratio. No variable was associated with the development of bleeding. We also could evaluate ischemic risk for each patient using HAS-BLED, ATRIA and ORBIT haemorrhage scores; these scores showed a predisposing capacity for particularly poor intracranial haemorrhage (c-statistic around 0.55 for all three scores).

Veneto Region Registry. After the analysis of cerebral bleedings during warfarin therapy, we focused on the use of non-vitamin K oral anticoagulants (NOAC), which demonstrated to halve cerebral bleeding as compared with warfarin in clinical trials. Using Veneto Region registries of pharmacological prescriptions, exemptions, and department discharge diagnoses, we were able to select patients who started oral anticoagulant therapy because of non-valvular atrial fibrillation and compared patients who started warfarin therapy versus those who started a NOAC. Results were broadly consistent with the literature, with similar efficacy and safety but a sharp reduction in intracranial bleedings and a mild reduction in mortality with NOAC, despite the good quality of warfarin anticoagulation achieved thanks to the thrombosis centers of our regions. Moreover, we found that patients treated with NOAC in Veneto region are on average older and at higher ischemic risk than patients treated with warfarin.

Finally, we analysed the subset of patients ≥80 years old and found a marked increase in gastrointestinal bleeding, especially from the lower tract, in patients treated with NOAC. However, ischemic stroke and total major bleedings rates were similar among the two groups and NOAC patients showed a lower risk of intracranial haemorrhage.

Conclusions. The present work analysed the effects of anticoagulant therapy in elderly patients with 80 years or more. Based on the different studies we conducted, it was possible to conclude that, despite the high risk of haemorrhage, clinical benefit for the prevention of stroke is in favour for the use of these drugs in this subset of patients. In fact, patients who suspended anticoagulant treatment had a worse prognosis

than patients who persisted. Intracranial hemorrhage is the most fearful side effect of anticoagulant treatment, being related to very high rates of mortality and disability; from our findings, these events are more frequent in the elderly and are not predictable by common cardiovascular risk factors or good anticoagulation quality. Data on NOAC users, on the other hand, seem to confirm that the risk of intracranial bleeding is inferior to warfarin even in the very elderly, despite a significant increase in the risk of gastrointestinal haemorrhage. Overall, therefore, our data confirms NOAC as the preferred anticoagulant therapy in very elderly patients with non-valvular atrial fibrillation.

1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia that has the following electrocardiographic characteristics:

- The RR intervals follow no repetitive pattern.
- there are no distinct P waves, although some electrical activity suggestive of P waves may be seen in some leads.
- even when an atrial cycle length can be defined, it is not regular and often less than 200 milliseconds

AF has been classified according to its duration and characteristics as: paroxysmal (i.e. self-terminating or intermittent), persistent (i.e. that fails to self-terminate within seven days, often requiring pharmacologic or electrical cardioversion), long-standing persistent (i.e. lasted for more than 12 months) and permanent (i.e. when the arrhythmia is accepted with no further attempts to restore sinus rhythm).

1.1 Atrial Fibrillation: epidemiology and physiopathology

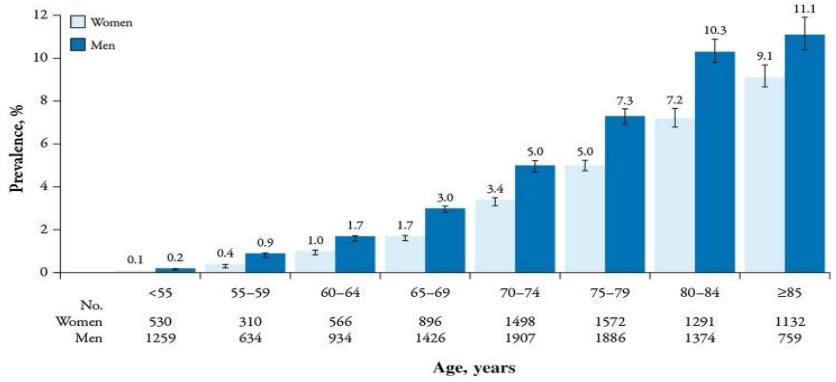
AF is a global health care problem with evidence suggesting an increasing prevalence and incidence world.[1] A systematic review of worldwide population-based studies estimated that the number of individuals with AF in 2010 was 33.5 million.

Prevalence. The prevalence of AF depends upon population characteristics, with differences apparent due to age, sex, race, geography, and time period. Prevalence is also influenced by the duration, sensitivity, and specificity of screening techniques.

- Age: AF is uncommon in infants and children and when present, almost always occurs in association with structural heart disease. Healthy young adults are also at low risk. The prevalence of AF increases with age[2] with a prevalence of more than 10% in patients ≥80 years of age (figure 1.1). General prevalence of AF has been recently estimated in Germany as 2.132% [3]
- Sex: prevalence is slightly higher in men than women, a difference seen in every age group. In Germany 55.5% of people affected by NVAF is male. [3]

- Race: whites are generally considered at higher risk of developing AF. A study evaluating the relationship between race and incident AF found that, compared with Whites, Blacks (hazard ratio [HR] 0.84), Hispanics (HR 0.78), and Asians (HR 0.78) each had a lower AF risk after adjustment. [4]
- Geography: Age-adjusted prevalence rate was highest in North America (700 to 775 per 100,000 population) and lowest in Japan, China and South Korea (250 to 400 per 100,000 population). [1]

Figure 1.1 prevalence of AF by age and gender[2]



- Time period: AF prevalence in the population is increasing. In a community-based study of 1.4 million patients in England and Wales, the age-standardized prevalence of AF between 1994 and 1998 increased by 22 and 14 percent in men and women, respectively.[5] In the ATRIA study, it was estimated that 2.3 million adults in the United States had AF in 1996 and 1997, and that this will increase to 5.6 million by the year 2050, with more than 50 percent being more than 80 years of age.[2]

Incidence. Incidence of AF, similar to the prevalence, increases with advancing age. [6] In a longitudinal study in which 3983 male Air Force recruits were followed for 44 years, 7.5 percent developed AF.[7] The risk increased with advancing age (from 0.5 per 1000 person-years before age 50 to 9.7 per 1000 person years after age 70). In a report from the Framingham Heart Study the risk of developing AF from age 80 to age 95 was 23 percent for men and 22 percent for women.[8]

Physiopathology. Irrespective of the underlying risk factors, changes in the anatomy and electrophysiology of the atrial myocardium are likely important. Thus, AF is usually associated with some underlying heart disease. Atrial enlargement, an elevation in atrial pressure, or infiltration or inflammation of the atria are often seen. Atrial premature beats appear to be most important as a trigger in patients with

paroxysmal AF who have normal or near-normal hearts. Hypertensive heart disease and coronary heart disease are the most common underlying chronic disorders in patients with AF. Hypertension increased the risk of developing AF 1.42-fold: although this is a relatively small increase in risk, the high frequency of hypertension in the general population results in hypertensive heart disease being the most common underlying disorder in patients with AF. [7].

Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF but rheumatic mitral valve disease, although now uncommon in developed countries, is associated with the highest incidence of AF.[9]

Other factors that may enhance and cause AF in patients are: heart failure, usually because associated with mitral regurgitation and increased left atrial pressures, hypertrophic cardiomyopathy, congenital heart disease (both with and without surgical correction) and venous thromboembolic disease (the mechanism is unclear but has been speculated to be related to the increase in pulmonary vascular resistance and cardiac afterload, which may lead to right atrial strain). AF also occurs in chronic obstructive pulmonary disease (especially obstructive sleep apnea), peripartum cardiomyopathy, lupus myocarditis, and both idiopathic and uremic pericarditis.

Diabetes, metabolic syndrome, and chronic kidney disease are medical conditions associated with the development of AF, probably because these comorbidities cause increased left ventricular mass and increased arterial stiffness. Systemic inflammation may also play a role.

Potentially reversible triggers for AF include: surgery (especially cardiac and thoracic surgery), hyperthyroidism (probably for an increase in beta adrenergic tone), acute alcohol intake[10], hypomagnesemia.[11]

Clinical evaluation. AF can have adverse consequences related to a reduction in cardiac output. Typical symptoms include palpitations, tachycardia, fatigue, weakness, dizziness, light-headedness, reduced exercise capacity, increased urination, or mild dyspnoea. More severe symptoms include dyspnoea at rest, angina, pre-syncope, or infrequently, syncope. In addition, some patients present with an embolic event or the insidious onset of heart failure (as manifested by pulmonary oedema, peripheral oedema, weight gain,

and ascites). The disease facilitates the development of left appendage thrombosis and therefore exposes patients to higher risk of systemic thrombo-embolism (TE). Indeed, AF patients showed higher mortality and morbidity rates compared to the control population, mainly driven by the increase in ischemic stroke incidence.[12]

1.2 Ischemic risk stratification in atrial fibrillation

Every patient with AF should be evaluated for the need of oral anticoagulant therapy (OAT) to prevent systemic embolization even for the first AF episode; however, AF patients have different risks of developing stroke. The presence of a mechanical valve or significant mitral valve rheumatic disease directly exposes the patient to a very high risk of TE and therefore in this class of individuals anticoagulation is always mandatory.[13] In the absence of these features, the disease is called "non-valvular atrial fibrillation" (NVAF) and it will be the main topic of the present work.

Currently, European guidelines recommend calculating TE risk in NVAF patients by using the CHA_2DS_2-VASc risk score.[13] (figure 1.2)

Figure 1.2 the CHA_2DS_2-VASc risk score [13]

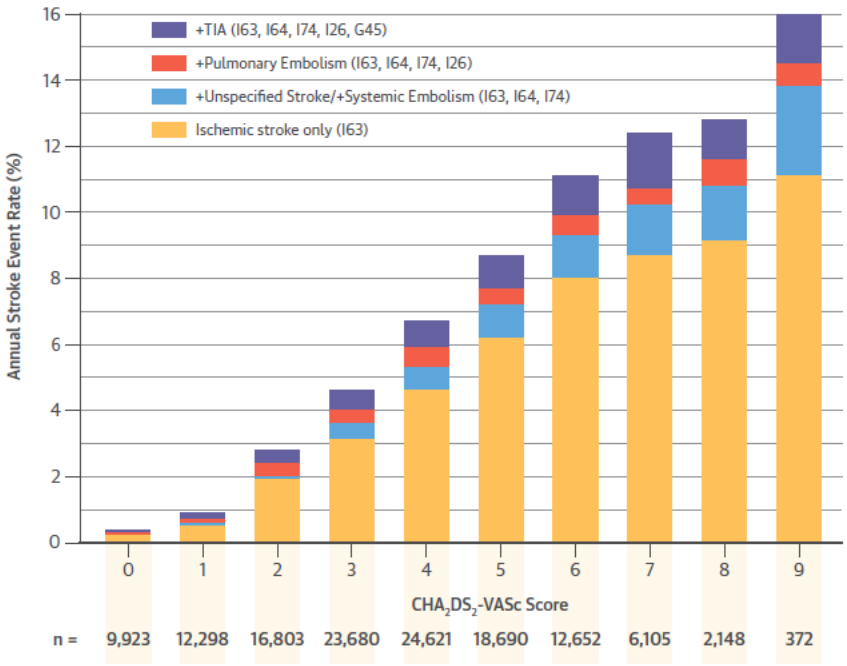
CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

CHA_2DS_2-VASc score have proven to directly correlate with the annual risk of ischemic stroke in untreated NVAF patients.[14] In one contemporary study, the annual risk of ischemic stroke in untreated

patients was 0.2, 0.6, and 2.2 percent for those with CHA_2DS_2-VASc scores of 0, 1, and 2.[15] (figure 1.3) Many antithrombotic (anticoagulant and antiplatelet) strategies have been evaluated in clinical trials. These trials and their meta-analyses have consistently demonstrated that among patients with NVAF at moderate to high TE risk (i.e. CHA_2DS_2-VASc ≥2), warfarin significantly reduces the incidence of clinical stroke (by about two-thirds) at an acceptable risk of bleeding compared to placebo.[16] OAT to prevent TE is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more and in all female patients with a CHA_2DS_2-VASc score of 2 or more. Only patients with a CHA_2DS_2-VASc score of 0 (i.e. with no risk factors for stroke) are truly considered at low risk of ischemic events and should not take OAT because the risk of bleeding outweigh the risk of stroke. Also, female patients with no other risk factors (CHA_2DS_2-VASc score of 1) should not be anticoagulated.[13]

The recommended treatment for patients with a CHA_2DS_2-VASc score of 1 (or 2 if female) is still debated, because in this cohort of patients the net clinical benefit of anticoagulation is unclear and risk factors does not carry the same risk of ischemic stroke thus complicating a standardized recommendation.[13] Presently, guidelines suggest to consider OAT, evaluating individual characteristics and patient preferences.

Figure 1.3 Annual stroke event rate in NVAF untreated patients stratified by CHA_2DS_2-VASc score[17]



1.3 Oral anticoagulant therapy: vitamin K antagonist

Many antithrombotic drugs, such as anticoagulants and antiplatelets, have been tested in the last 20 years: adjusted-dose of warfarin (achieving an international normalized ratio –INR between 2.0 and 3.0) has proven to be the most effective therapy against ischemic complications and death. These results have been obtained in several historical trials[18-25] and confirmed by further observational registries.[26,27]

Mechanism of action. Warfarin and other vitamin K antagonists (VKA, e.g. acenocoumarol, phenprocoumon, fluindione) block the function of the vitamin K epoxide reductase complex in the liver, leading to depletion of the reduced form of vitamin K that serves as a cofactor for gamma carboxylation of vitamin K-dependent coagulation factors.[28]. Without gamma carboxylation, the vitamin K-dependent factors, including factors II (prothrombin), VII, IX, and X, are immunologically detectable, but they cannot function because they cannot adequately bind calcium and phospholipid membranes needed for their haemostatic function.

Thus, the ultimate anticoagulant effect of VKAs is delayed until the previously synthesized, functional clotting factors are cleared from the circulation. Depletion of both factor X and factor II (prothrombin) is important for clinical efficacy, and factor II has the longest half-life of the vitamin K-dependent factors (approximately three days) and therefore the desired anticoagulant effect of a VKA does not occur for at least three days after drug initiation despite prolongation of the prothrombin time (PT) at earlier time points. The initial prolongation of the PT is due primarily to depletion of factor VII, which has a short half-life (four to six hours).[29]

VKAs also inhibit vitamin K-dependent gamma carboxylation of the anticoagulant factors protein S and protein C, which inhibit activated factors VIII and V. Thus, warfarin has a transient procoagulant effect during the first day or two of use. This is rarely of clinical significance, with the possible exception of patients who receive "loading doses" of warfarin (especially those with inherited protein C deficiency) who may (rarely) develop warfarin-induced skin necrosis.

Metabolism. VKAs are absorbed via the gastrointestinal tract, circulate bound to albumin, and accumulate in the liver. Warfarin reaches maximal blood concentrations approximately 90 minutes after oral

administration; only the non-protein-bound fraction is biologically active. Commercially available warfarin and acenocoumarol are racemic mixtures of S and R enantiomers. S-warfarin is more potent than R-warfarin and is metabolized primarily by the hepatic cytochrome P-450 2C9 isoform (CYP2C9). Therefore, the overall anticoagulant effect of warfarin is influenced by CYP2C9 genotype and CYP2C9 drug interactions (eg, medications, over-the-counter herbal remedies). VKA drugs significantly differ in their half-lives: for warfarin is 36 to 42 hours, for acenocoumarol 8 to 11 hours and for phenprocoumon three to five days or longer. VKA agents demonstrated different anticoagulant powers.[30]

INR control. At therapeutic levels of anticoagulation, VKA prolong the PT, which reflects the extrinsic pathway of coagulation in vitro. Most laboratories and portable devices report the results of the PT along with an INR, a parameter that standardizes the PT value to an international reference thromboplastin standard. For patients who are stably anticoagulated with a VKA, the percentage of time in the therapeutic range (TTR) is often used as a measure of the quality of anticoagulation control. TTR can be calculated using a variety of methods but the most used is the linear interpolation methods proposed by Rosendaal.[31] High quality anticoagulation (i.e. when INR controls are in therapeutic range for more than 70% of the time, as recommended by European guidelines[32]) is associated with lower risk of both ischemic and bleeding events. Patients with higher TTR (time in therapeutic range) have a significantly reduced risk of all anticoagulation-associated adverse events.[33] Moreover, in a recent post-hoc analysis of RE-LY trial (comparing dabigatran versus warfarin), high TTR (>72.4 %) correlated to a reduced risk of both TE and MB.[34] Nevertheless it is important to highlight that bleeding may occur also in patients with optimal INR control.

Therefore, VKA therapy requires constant INR monitoring through blood samples and the dosing must be adjusted in order to maintain a certain target INR (usually 2.5). Significant overcoagulation or under-coagulation expose the patient to the risk of bleeding or thrombosis, respectively.

In order to minimize bleeding risk, VKA therapy should be carefully monitored, as a large number of variables are associated with fluctuation of anticoagulant activity. Factors that most commonly influence warfarin dose requirement are: nutritional status (including vitamin K intake); medication adherence; genetic

variation; drug interactions; smoking and alcohol use; renal, hepatic, and cardiac function; hypermetabolic states.Significant chronic disease (e.g., severe heart failure, liver disease, alcohol abuse, cancer, diabetes) is associated with reduced warfarin metabolism and more difficult INR control.

1.4 Bleeding in anticoagulated patients

When prescribing anticoagulation, the clinician should always balance the risk of stroke against the risk of bleeding in that particular patient. While ischemic risk is rather well predicted by current risk scores, estimation of bleeding risk has been and currently is a challenge. There are numerous factor that may impact on bleeding risk. The most important are listed:

- Hypertension (especially when systolic blood pressure is >160 mmHg)
- Labile INR or time in therapeutic range <60% in patients on VKA
- Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatoy drugs
- Excess alcohol intake
- Anaemia
- Impaired renal function, Dialysis-dependent kidney disease or renal transplant

  Impaired liver function or Cirrhotic liver disease
- Reduced platelet count or function
- Older age
- History of major bleeding (MB)
- Previous stroke
- Malignancy
- Genetic factors

A large number of studies have tried to develop scores for bleeding risk assessment in warfarin-treated individuals, but presently only three have been derived and validated in AF populations: the $HEMORR_2HAGES$[35], the ATRIA[36] and the HAS-BLED[37] scores (Figure 1.4). However, attempts to validate such scores in external cohorts showed conflicting results:[15] in several studies these scores showed only modest

power to predict bleeding events[38,39] and in a prospective validation trial none of them showed a better performance compared to the physician's subjective assessment.[40] Moreover, considering only fatal bleeding or ICH, the HEMORR$_2$HAGES and the ATRIA scores failed to show a significant predictive performance.[38]

Figure 1.4 Comparison of different bleeding risk scores used in clinical practice. Adapted from[41]

HAS-BLED			HEMORR$_2$HAGES			ATRIA	
	Clinical characteristic	**Points**		**Clinical characteristic**	**Points**	**Clinical characteristic**	**Points**
H	Hypertension	1	**H**	Liver or renal disease	1	Anemia	3
A	Abnormal kidney or liver function	1 o 2	**E**	Ethanol abuse	1	Severe Renal disease	3
S	Stroke/TIA	1	**M**	Malignancy	1	Age ≥ 75 years	2
B	History of bleeding	1	**O**	Older age	1	History of bleeding	1
L	Labile international normalized ratio	1	**R**	Reduced platelet count or function	1	Hypertension	1
E	Elderly (> 65)	1	**R**	Re-bleeding	2		
D	Drugs (antiplatelets, NSAID, steroids) and/or alcohol	1 o 2	**H**	Hypertension	1		
			A	Anemia	1		
			G	Genetic factors	1		
			E	Fall risk	1		
			S	Prior stroke	1		
	Low-to-moderate bleeding risk	1 – 2		Low-to-moderate bleeding risk	1 – 3	Low-to-moderate bleeding risk	1 – 4
	High bleeding risk	≥ 3		High bleeding risk	> 3	High bleeding risk	> 4

Therefore, none of the proposed score is able to reliably predict the actual bleeding risk in the single patient, although they have the unquestionable quality to highlight risk factors that can be actively managed (particularly HAS-BLED).

Hemorrhagic stroke caused by spontaneous intracranial hemorrhage (ICH) is the most fearful OAT side effect, being related to very high rates of mortality and disability.[42] Multiple observational studies and randomized trials report the risk of ICH attributable to anticoagulant therapy with warfarin to be in the range of 0.2 to 0.4 percent per year.

It should be noted, however, that the prevention of ischemic stroke with OAT is so efficacious that in most AF patients the advantages of anticoagulation outweighs the risk of bleeding. It has been demonstrated that the net clinical benefit in NVAF patients (i.e. the estimated reduction in rate of TE minus 1.5 times the estimated increase in rate of ICH attributable to OAT), is always in favour of OAT therapy except for those patients at very low ischemic risk.[43]

Based on these results, guidelines suggest calculating both ischemic and bleeding risk before undertaking OAT, but whereas the former is determinant in anticoagulation decisions, the latter should not be used to exclude patients from OAT.[32]

1.5 The advent of non-vitamin K oral anticoagulation: new horizons

In the last few years, a complete new class of oral anticoagulants, known as NOAC, have been tested in large RCT for stroke prevention in NVAF. The advent of NOAC has finally widened the therapeutic options for TE prevention in patients with NVAF, once relegated only to the VKA drugs.

NOAC are profoundly different from VKA as they act as direct inhibitors of either thrombin (i.e. dabigatran), or FXa (i.e. rivaroxaban, apixaban and edoxaban), while VKA acts by inhibiting the production of all vitamin-K dependent coagulation factors. Key pharmacological characteristic are displayed in figure 1.5.

Figure 1.5 Pharmacological characteristic of oral anticoagulants drugs. Adapted from:[41]

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	VKORC1	FIIa (thrombin)	FXa	FXa	FXa
Prodrug	No	Yes	No	No	No
Bioavailability	100%	7%	80%	66%	> 45%
Protein binding	97%	35%	> 90%	87%	55%
Half-life	40 h	12 – 14 h	9 – 13 h	8 – 15 h	8 – 10 h
Dosing	Once daily	Twice daily	Once daily	Twice daily	Once daily
Renal clearance	0%	80%	33%	25%	35%
Drug interactions	Multiple	P-gp	P-gp + CYP 3A4	P-gp + CYP 3A4	P-gp ± CYP 3A4

FIIa: Activated factor II; FXa: Activated factor X; P-gp: Substrate of permeability glycoprotein; VKORC1: C1 subunit of the vitamin K epoxide reductase enzyme.

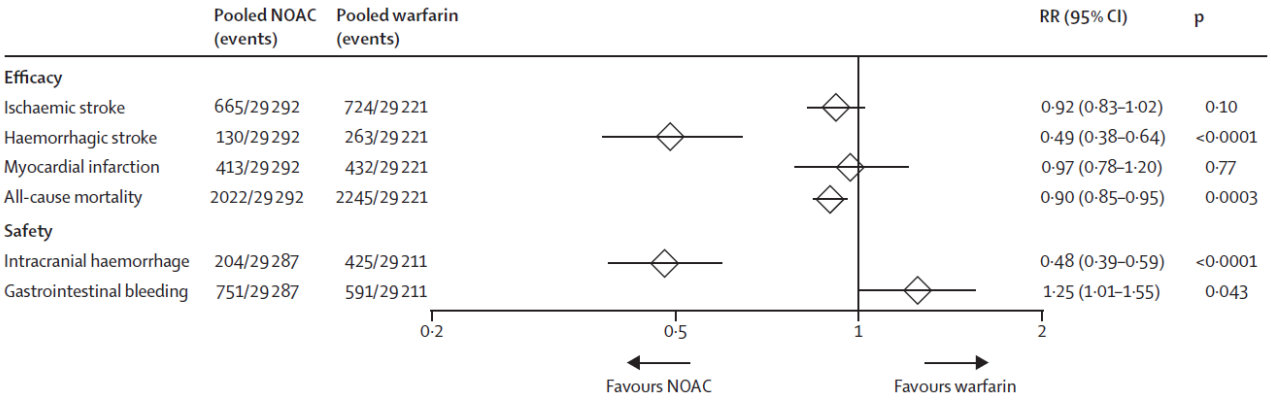
Important additional advantages of NOAC agents include convenience (no requirement for routine testing of the INR), a high relative but small absolute reduction in the risk of ICH, lack of susceptibility to dietary interactions, and markedly reduced susceptibility to drug interactions.[44] Disadvantages include lack of efficacy and safety data in patients with chronic severe kidney disease, lack of easily available monitoring of blood levels and compliance, higher cost, and the potential that unanticipated side effects will subsequently become evident.

All four NOAC evaluated in large phase III trial (overall more than 40.000 patients treated) have proven to be at least as effective as warfarin in the prevention of stroke (ischemic and hemorrhagic) and systemic embolism. This benefit was mainly driven by substantial protection against all type of ICH (including

hemorrhagic stroke), which were reduced by half. The most recent metanalysis[45] comparing all four NOAC against standard VKA therapy in patients with NVAF found:

- a significant reduction of stroke/systemic embolism (relative risk 0.81, 95% confidence interval 0.73-0.91, p<0.0001);
- a non-significant 14% reduction in major bleeding (relative risk 0.86, 95% CI 0.73-1.00; p=0.06).
- as secondary outcomes (figure 1.6), a significant and marked relative reduction in haemorrhagic stroke (relative risk 0.49, 95% CI 0.38-0.64, p<0.0001), a mild, although significant, gastro-intestinal bleeding increase (relative risk 1.25, 95% CI 1.01-1.55, p<0.0001) and a significant reduction in all-cause mortality (relative risk 0.90, 95% CI 0.85-0.95)

Figure 1.6 Meta-analysis of large trials comparing NOAC versus VKA. Efficacy and safety endpoints [45]



It is not possible to make a head-to-head comparison among these drugs in the absence of ad-hoc studies but the clear and strong superiority of NOAC in respect to warfarin for the prevention of hemorrhagic stroke was consistent in all the trials and with all the dosage tested. Interestingly, as shown in a post-hoc analysis of the RE-LY trial, the rates of ICH in the warfarin group were not associated with the time in therapeutic range (TTR) and were consistently higher in comparison with dabigatran.[34]

Low-dose regimens (i.e. dabigatran 110 mg x2[46] and Edoxaban 30mg[47]) showed the largest reduction in hemorrhagic stroke compared with warfarin even if associated with an increase in ischemic stroke (significant for edoxaban, non-significant for dabigatran).

Dabigatran 150 mg bid[46] and Apixaban 5 mg bid[48] showed superiority versus warfarin for the composite outcome of stroke and systemic embolism, while rivaroxaban 20mg qd[49] and edoxaban 60mg qd[47] showed non-inferiority. Different designs of the studies may account for such differences.

A recent analysis on a "real world" AF population treated with all different OAT therapy commercially available, found that for patients with $CHADS_2$ score ≥1 and CHA_2DS_2-VASc score ≥2 the three new drugs performed better than warfarin for net clinical benefit, regardless of risk of bleeding (assessed by HAS-BLED score). At CHA_2DS_2-VASc score =1 only apixaban and both doses of dabigatran appeared to have a positive net clinical benefit.[50]

The absence of a direct reversal agent for all NOAC is a matter of concern among clinicians. At present, only dabigatran has developed and commercialized a direct and specific antidote, idarucizumab.[51] The outcome of patients enrolled in phase III RCTs suffering from MB and its severity seems to be better in the group treated with NOAC than in the group treated with warfarin.[5,52,53]

Another concern is renal function, as all NOAC are partially excreted by the kidney. NOAC demonstrated a good efficacy and safety profile in moderate to severe renal impairment (Creatinine clearance 30-50 ml/min): in particular apixaban showed a reduction in the risk of bleeding compared with warfarin, while dabigatran and rivaroxaban reported no significant differences.[54] In patients with severe kidney impairment (CrCl <30 mL/min), all NOAC are contraindicated because they have not been tested in clinical trials. Rivaroxaban, apixaban and edoxaban trials used a reduced dose drug in presence of impaired renal function (rivaroxaban 15 mg daily[49] and half edoxaban dose – i.e. 30 mg or 15 mg depending on the two arms of the study[47] if estimated clearance was 30-50 mL/min, apixaban 2.5mg bid if reduced clearance was accompanied by age ≥80 years old or weight ≤60 Kg[48]). Even if it was not tested in the trial, reduced dose dabigatran (110 mg x 2, not available in the United States) should be used when estimated clearance is 30-50 mL/min, as a precaution, because it is the NOAC with greatest renal metabolism (see Figure 1.5).[46]

Therefore, NOAC appear to be safer than warfarin in the prevention of ICH in patients affected by NVAF. However, it is important to note that NOAC are at present contraindicated in all the group of patients in which they have not been tested, such as severe renal and/or liver impairment, and during pregnancy.

Dabigatran has been tested on patients with mechanical heart valves but the study was terminated prematurely because of an increased rate of TE and ICH with NOAC.[55] Therefore NOAC are not presently indicated in valvular AF.

Single or double daily administration, patients' co-morbidities, trial-proven efficacy in different subsets of patients and reported rate of extra-cranial bleeding will guide the clinician's decision for the choice of the most suitable NOAC in every single patient.

1.6 Alternatives to oral anticoagulation

Aspirin. Aspirin has been evaluated as an alternative to warfarin for the prevention of TE in NVAF. However, in the last decade, many studies and meta-analyses[56] showed that anticoagulants are significantly more effective than aspirin,[57] aspirin + clopidogrel[58] and aspirin + fixed low dose of warfarin[21,59] at stroke prevention. It has been advocated that antiplatelet therapy may be safer than OAT in regards to MB and ICH; however the "Birmingham Atrial Fibrillation Treatment of the Aged" (BAFTA) study clearly showed that in elderly patient with NVAF, the incidence of MB and ICH is the same with aspirin and warfarin.[57]

Left atrial appendage closure. Left atrial appendage (LAA) closure is a new way to reduce TE in NVAF patients without the use of OAT. During AF, the LAA becomes a major site of blood stasis, indeed it seems that it is the site for thrombogenesis in more than 90% cases evaluated with trans-esophageal imaging.[60] Therefore, surgical and transcatheter techniques have been explored to reduce the risk of stroke by excluding or occluding the LAA: while surgical procedures lacks of large RCT and results are still controversial, a RCT have shown that percutaneous LAA closure (with Watchman device) is non-inferior to standard anti-coagulant treatment for the prevention of TE in selected NVAF patients.[61] However many caveats remains such as the high periprocedural complication, mainly driven by inexperienced operators, the small but present risk of haemopericardium, the need of dual antiplatelet therapy for a range of time that expose the patient at high bleeding risk and the risk of incomplete closure/dislodgment of the device. At present LAA closure is not an alternative to OAT for stroke prevention in NVAF. Current ESC guidelines recommend that percutaneous LAA closure "may be considered in patients with a high stroke risk and contraindications for

long-term oral anticoagulation" with a level of evidence "B."[12] In particular this alternative should be evaluated in patients with recurrence of ischemic events or new appearance of hemorrhagic stroke during well-conducted OAT or in patients refractory or incapable to assume OAT. Preliminary studies seem to confirm the efficacy and safety of the procedure in patients with previous ICH, [62] however, until more data will be available, this procedure should be limited to restricted groups of patients in which OAT therapy is associated to very high risk of complications or is contraindicated (figure 3.2).

2. VITAMIN K ORAL ANTICOAGULANTS IN THE ELDERLY

Vitamin K oral anticoagulants (VKA) are reportedly still being underused in the elderly. [63,64] There is ongoing debate and contradictory evidence concerning whether older age exposes patients to a higher bleeding risk even with high-quality anticoagulation[65-67]. The incidence of bleeding is influenced by the quality of anticoagulant management but data on the elderly population are inconsistent. Elderly frequently discontinue treatment, but reasons and consequences are poorly investigated. In this special subset of patients, moreover, little is known whether to restart or not anticoagulation after a MB event, as the net clinical benefit of anticoagulation in frail and/or elderly patients may be reduced or absent.

To contribute to the debate, we design a subset of studies using data from patients referring to our local anticoagulation clinic, the Padua Thrombosis Centre.

2.1 Padua Thrombosis Centre

The Padua Thrombosis Centre is a leading multidisciplinary clinical and research group dedicated to the diagnosis and treatment of hypercoagulable conditions. The Padua Thrombosis Centre forms part of the Department of Cardiac, Thoracic and Vascular Sciences, an academic clinical unit of the Azienda Ospedaliera di Padova. It is affiliated to the Italian Federation of Thrombosis Centres (FCSA): FCSA centres are required to give patients who start the treatment adequate education on the purpose of the treatment, the risk of complications, INR values, and treatment management. They follow up patients by periodic INR measurements; establish the date for subsequent visits; prescribe the daily VKA dosages; and monitor and record changes in patients' habits, diet, comedications, intercurrent illnesses, bleeding, and thrombotic complications through patient interviews. Patients followed in FCSA-affiliated Thrombosis Centres demonstrated a better quality of anticoagulation measured as Time in Therapeutic Range (TTR): over a 5-year observation time, it has been observed a constant increase in TTR, from 64.8% (range 49.2–75.5%) in 2009 up to 67.9% (range 52.2–86.6%) in 2013; the percentage of Centres with a TTR above 60% was 83.9 in 2009 and 93.6 in 2013.[68] Presently, Padua Thrombosis centre present a centre TTR of around 70%.

2.2 The VENPAF trial

Initially, our aim was to determine the incidence of TE and MB in our elderly reference population: thus, we performed a single-centre, inception cohort retrospective follow-up study called VENPAF, very elderly naïve patients with NVAF.

Methods. We screened 4563 patients referring to the Padua Thrombosis Centre from January 2007 to January 2012. All patients ≥80 years old with NVAF (INR range 2-3) were considered for inclusion in the study. They were excluded if they were already on VKA therapy at the baseline, or had been in the previous 2 years, or if they suspended VKA within a month of starting the treatment, unless a bleeding event occurred earlier.

Of the 2757 patients with NVAF being followed up at our centre during the 5-year period considered, 891 were at least 80 years old; 93 of these patients did not meet our inclusion criteria (40 were not anticoagulant-naïve, 52 had been followed up for less than 1 month, and data were lacking for 1), so the final VENPAF cohort consisted of 798 patients. Patients' demographics and clinical baseline information were collected for analysis from the electronic records held at the Padua University Hospital and the Anticoagulation Clinic, or by means of telephone calls to family physicians. Comorbidities like hypertension, diabetes mellitus, and heart disease were defined according to the corresponding guidelines.[69-72] The TE risk profile was calculated using the $CHADS_2$ score.[73] The quality of anticoagulation was calculated as the time in the therapeutic range (TTR) from starting the treatment to the end of the follow-up, using the linear interpolation method devised by Rosendaal et al. [31] The resulting TTR included all INR data available during the observation period, including when the therapy was started, and any temporary suspensions for invasive procedures requiring heparin bridging.

TE and MB were detected through the Padua University Hospital electronic records and direct contact with the family physician. Ischemic stroke and transient ischemic attack were defined as a sudden neurologic deficit in the absence of cerebral hemorrhage on neuroimaging, with evidence of a focal ischemic lesion on subsequent examinations.[74] MB was defined according to the ISTH criteria as fatal bleeding and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-

articular, pericardial, or intramuscular with compartment syndrome) and/or bleeding causing a fall in the haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red blood cells.[75]

Patients' clinical characteristics. Baseline patient demographics are shown in Table 2.1, for the whole sample and by age group. The VENPAF sample included 485 females (60.8%) and the mean age was 84.4 (±3.3) years. Among the oldest patients, the prevalence of female gender and the heart failure rate were significantly higher (p=0.007 and p=0.002, respectively) and so was the CHADS2 score (2.72 vs. 2.51, p=0.003).

Table 2.1 Baseline characteristics of the cohort

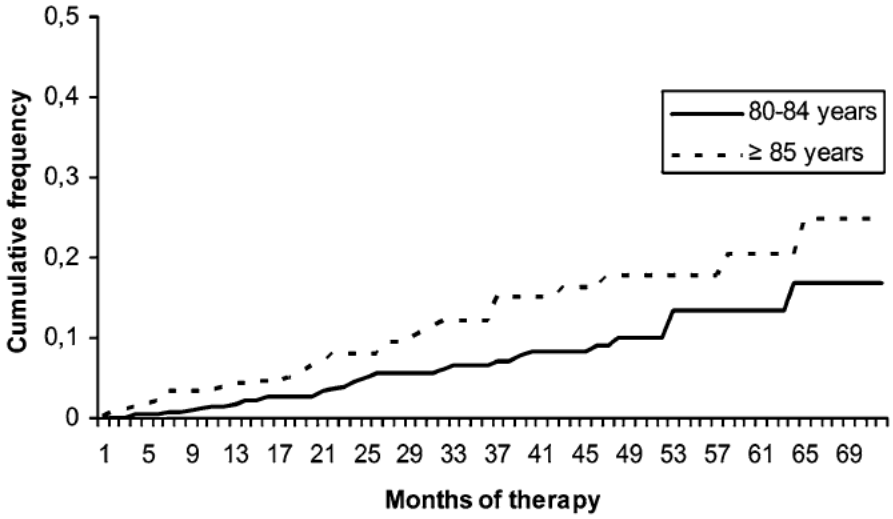
Characteristics	All patients (n = 798)	80- to 84-year olds (n = 463)	≥85-year olds (n = 335)	p value
Age				
Median (range), years	84 (80–99)	82 (80–84)	87 (85–99)	
Female				
% (n)	60.8 (485)	56.8 (263)	66.3 (222)	0.007
Follow-up				
Median (range), years	2.2 (0.01–6.00)	2.5 (0.01–6.00)	1.8 (0.01–5.94)	<0.001
Mean ± SD (years)	2.4 ± 1.6	2.6 ± 1.5	2.2 ± 1.6	
Time in the therapeutic range %				
Median (range)	63 (7–100)	64 (8–97)	62 (7–100)	0.19
Mean ± SD[a]	61.9 ± 15.1	62.5 ± 14.7	61.1 ± 15.6	
$CHADS_2$ score				
Median (range)	2 (1–6)	2 (1–6)	2 (1–6)	0.003
Mean ± SD	2.60 ± 1.04	2.51 ± 1.05	2.72 ± 1.02	
Heart failure				
% (n)	29.1 (231)	24.8 (114)	35.1 (117)	0.002
Hypertension				
% (n)	82.6 (657)	80.7 (372)	85.3 (285)	0.11
Diabetes mellitus				
% (n)	17.9 (142)	16.5 (76)	19.8 (66)	0.26
Prior stroke				
% (n)	15.5 (123)	15.2 (70)	15.9 (53)	0.84

[a] The TTR includes all INR data available during the observation period, including when therapy was started and any temporary suspensions for invasive procedures requiring heparin bridging

Major Bleeding (MB). The 798 patients considered were followed up for a median 2.2 years (IQR 1.2-3.5 years) for a total observation time of 1,912 years. Among those, 15% (120) died, 18.5% (148) suspended VKA before the end of the follow up and 6.6% (53) were monitored elsewhere (e.g. by their general practitioners or at other anticoagulation centres). There were 65 MB events (3.4 per 100 patient-years) during the follow-up (Table 2). Sixteen (24.6%) were fatal, 38 (58.5%) needed hospitalization or blood transfusions, 6 (9.2%) needed surgery or invasive intervention to stop the bleeding, and 5 (7.7%) were treated in an outpatient setting. It is noteworthy that 29 MB episodes were intracranial (1.5 per 100 patien-tyears), and 18 (0.9 per 100 patient-years) involved the gastrointestinal tract. Most of the MB events recorded were spontaneous (58.5%), while 29.2% were post-traumatic, and this information was not available for 12.3%.

The mean HAS-BLED score for the 65 patients who bled was 2.86 (±1.0). Patients experiencing MB episodes were a mean 84.8 (±2.7) years old. As shown in Table 2, patients over 85 years old had significantly more events than the 80-84 year-olds (4.7 vs. 2.6 per 100 patient-years, p<0.01). The older patients also had a higher rate of gastrointestinal bleeding, and significantly more spontaneous bleeding episodes (3.0 vs. 1.3 per 100 patient-years, p 0.008). The Kaplan-Meier survival curves very soon diverge significantly, as shown in Figure 1 (HR 1.8, 95%CI 1.1-3.0 p=0.014).

Figure 2.1 Cumulative frequency (Kaplan–Meier curve) of major bleeding events during the follow-up by age group (80–84 vs. C85)

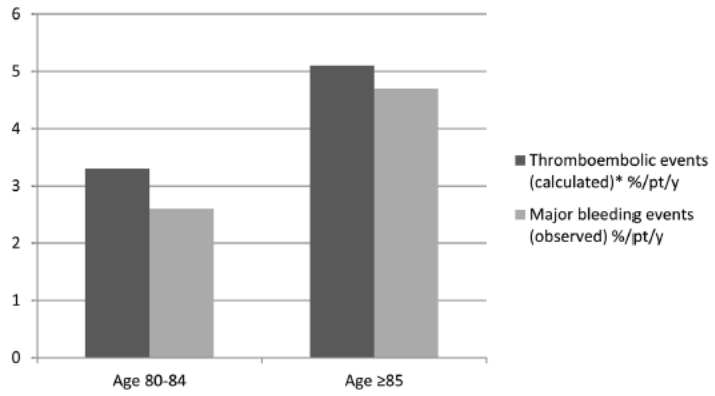


Thromboembolic events (TE). There were 25 TE during the follow-up (1.3 per 100 patient-years) (Table 2), in patients with a mean age of 84.5 (±2.7) years; 24 of them were strokes (1.2 per 100 patient-years), and 3 were fatal. To weigh the risks and benefits of administering anticoagulants in our observational cohort, we compared the rates of MB events actually observed with the TE rates that patients might have been expected to experience without taking oral anticoagulants (figure 2.2), given that oral anticoagulants are known to lower TE rate by 64 %, thus preventing approximately two in three of such events.[16]

We therefore ascertained that MB in elderly patients anticoagulated with VKA is 3.4 % patient-year and this picture is higher than what reported in previous studies[66,76-79], which described bleeding rates in the

range of 1.1–2.9 per 100 patient-years. However, the theoretical ischemic risk in this cohort seems to overcome the actual bleeding risk (figure 2.2) even in the most elderly patients.

Figure 2.2 Observed major bleeding events vs. calculated thromboembolic events by age group



2.3 Reasons and consequences of warfarin discontinuation

Another issue concerning anticoagulant underuse in the elderly is persistency that is defined as the length of time between therapy initiation and its discontinuation.[80] Discontinuation may be due either because patients never start taking the drug, or because they discontinue it after complications or side effects. Discontinuation rates for long-term VKA treatment in patients with NVAF are generally high [81,82] and tend to be higher in very old patients and among long-term-care residents.[57,64,83] Outcomes after VKA discontinuation in randomized trials have been reported,[84] but data for a 'real-world' population on reasons for discontinuation, subsequent therapeutic strategies and consequences are scarce.

The aim of our study was to report the reasons for warfarin discontinuation, the prescribed treatment after discontinuation and the clinical outcomes in the VENPAF cohort.

Methods. Warfarin discontinuation was defined as a period of at least 180 consecutive days in which there were no sequential INR measurements.[85] These patients were screened, and the following data were collected: (i) the person who took the decision to stop treatment; (ii) the reason given for discontinuation; and (iii) the alternative treatment used after warfarin discontinuation. Patients who

discontinued warfarin were followed for at least 6 months, and censored in cases of warfarin resumption, TE, MB, or death. In this period, the occurrence of TE or MB after warfarin suspension was registered.

TE and MB were defined as previously reported,[86] and detected through the Padua University Hospital electronic records and direct contact with the family physician. To reduce biases resulting from the observational nature of the study, all data were collected and processed by the same team of investigators, who crosschecked the electronic databases.

Results. One hundred and forty-eight patients (18.5%) discontinued warfarin after a median of 14 months of therapy. $CHADS_2$ and CHA_2DS_2-VASc scores were similar among patients who discontinued and patients who continued warfarin. Vascular disease was significantly more frequent in patients who discontinued oral anticoagulation.

During warfarin therapy, the frequency of outcome events was significantly higher and the quality of treatment was significantly lower in patients who discontinued the treatment. Despite similar CHA2DS2-VASc scores, TE occurred in 3.14 per 100 patient-years versus 1.05 per 100 patient-years (P = 0.01). MB occurred in 10.8 per 100 patient-years versus 2.4 per 100 patient-years (P = 0.001), and the TTR was 58% versus 62% (P < 0.001).

Multivariate Cox regression analysis (Table 2.2) identified the following as independent factors associated with therapy discontinuation: vascular disease (HR 2.5, 95% CI 1.5–3.9, P < 0.001), age ≥ 85 years (HR 1.4, 95% CI 1.1–1.9, P = 0.04), TTR < 60% (HR 1.8, 95% CI 1.3–2.5, P = 0.001), and bleeding events (HR 2.3, 95% CI 1.4–3.6, P < 0.001).

Reasons for warfarin discontinuation. As shown in Table 2.3, in most cases, the decision to discontinue was made by the specialist (80.4%) or by the general practitioner (12.8%), and in a few cases the decisionwas made by the patient (1.4%). The main reason for warfarin discontinuation was physician-perceived low life-expectancy (i.e. < 12 months) or frailty (45.9%), followed by bleeding side effects (19.6%) and sinus rhythm restoration (16.9%). Other physicians' concerns included logistic difficulties in therapy monitoring (4.1%), low patient compliance (3.4%), and polypharmacotherapy (0.7%). Treatment after

warfarin discontinuation was equally distributed among low molecular weight heparins (LMWH) (33.1%), antiplatelets (29.1%), and no antithrombotic therapy (27.7%).

Table 2.2 Multivariable Cox analysis of clinical factors associated with warfarin discontinuation

	Simple unadjusted regression			Multivariate stepwise regression		
Covariates	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Heart failure	0.9	0.6–1.2	0.47	–	–	–
Female gender	1.0	0.7–1.4	0.92	–	–	–
Hypertension	1.1	0.7–1.6	0.80	–	–	–
Prior stroke	1.1	0.7–1.8	0.62	–	–	–
Vascular disease	**2.4**	**1.5–3.8**	**< 0.001**	**2.5**	**1.5–3.9**	**< 0.001**
CHA_2DS_2-VASc score	1.1	0.9–1.3	0.11	–	–	–
Diabetes mellitus	1.3	0.8–1.9	0.29	–	–	–
Age (years), ≥ 85 versus 80–84	**1.4**	**1.0–2.0**	**0.03**	**1.4**	**1.1–1.9**	**0.04**
Thromboembolic events during warfarin treatment	1.4	0.6–2.9	0.41	–	–	–
TTR < 60%	**1.8**	**1.3–2.5**	**< 0.001**	**1.8**	**1.3–2.5**	**0.001**
Bleeding events during warfarin treatment	**2.3**	**1.5–3.5**	**< 0.001**	**2.3**	**1.4–3.6**	**< 0.001**

CI, confidence interval; HR, hazard ratio, TTR, time in therapeutic range. Significant associations are in bold.

Analysing patients according to reasons for suspension, frail patients and those with low life-expectancy were more frequently using anticoagulant therapy with LMWH after warfarin discontinuation than aspirin or no treatment (P = 0.006).

Table 2.3 Analysis of patients who discontinued warfarin

	% (*n*)
Who decided to discontinue treatment	
Specialist	80.4 (119)
General practitioner	12.8 (19)
Patient/caregiver)	1.4 (2)
Unknown	5.4 (8)
Reasons reported for discontinuation	
Frailty or low life-expectancy	45.9 (68)
Bleeding complications	19.6 (29)
Sinus rhythm restoration	16.9 (25)
Logistic issues	4.1 (6)
Low patient compliance	3.4 (5)
Polypharmacotherapy	0.7 (1)
Unknown	9.5 (14)
Antithrombotic treatment given after discontinuation	
LMWH	33.1 (49)
Antiplatelet drugs	29.1 (43)
No antithrombotic therapy	27.7 (41)
Other treatment*	4.7 (7)
Unknown	5.4 (8)

LMWH, low molecular weight heparin. *Includes six patients receiving LMWH plus antiplatelet therapy, and one patient receiving rivaroxaban.

Outcomes after discontinuation. The cohort of patients who discontinued warfarin was followed for a median of 25 months after discontinuation. Ninety-four of 148 patients (64%) died during follow-up, and death occurred especially in patients who experienced an ischemic or haemorrhagic event after discontinuation (21 deaths of 26 events, 81%). The cumulative incidence of at least one event among ischemic strokes, MB and deaths was especially high in frail patients, in those with low life-expectancy (most of whom were treated with LMWH) and in patients who discontinued warfarin because of bleeding complications.

Discussion. In the present study, we found that very elderly warfarin naïve patients with NVAF had a high warfarin discontinuation rate (18.5% of the entire cohort, with an incidence of 7.6% patients per year). This figure is slightly lower than those reported in less recent studies, which vary from 20% to > 30%. [64,85,87-89] At variance with these reports, a very recent registry on an anticoagulated population (the ORBIT-AF registry) showed a discontinuation rate, in VKA-naive patients, of 17% over 1 year of follow-up, a result that is close to our finding.[82] Whether or not the use NOAC enhances treatment continuation versus warfarin is not known, as the two treatments are not comparable in observational studies.[90,91] Even in randomized studies, in which treated patients are comparable,[46,49] continuation of NOACs was lower than that of warfarin.

The demographic and clinical characteristics at baseline were not different between patients who continued treatment and those who discontinued treatment. During anticoagulant treatment, TE and MB determined warfarin discontinuation. The quality of treatment measured according to the TTR was significantly different between the two groups. In this study, we did not observe an influence of CHA_2DS_2-VASc score on the quality of treatment, as previously reported.[92] A higher quality of anticoagulation correlates with better outcomes,[93] and this supports the current practice of patients with lower TTRs being evaluated for alternative treatments to avoid complications (e.g. NOACs and LAA closure).[41,94]

Multivariate analysis of clinical factors showed that older age and bleeding events are closely related to warfarin discontinuation. Although the TTR is strongly associated with warfarin discontinuation, it was

probably not taken into account by the physician who discontinued the treatment, and it was not reported as a reason for discontinuation. Knowing a priori the quality of treatment of patients starting warfarin, as demonstrated by the SAME-TT_2R_2 score, would be very useful for selecting the correct treatment strategy.[95] Vascular disease was the factor most strongly associated with warfarin discontinuation, possibly suggesting that physicians were concerned about the risk of using multiple antithrombotic treatments in these high bleeding risk patients. MB rate increases with age,[65] and the occurrence of haemorrhage automatically puts the patient at high risk of re-bleeding with warfarin.[96] Therefore, bleeding events are naturally associated with an increase in the bleeding risk perceived by the clinician, and have been confirmed in many studies[64,97] as one of the main reasons for discontinuation. Regarding age, some studies[64] are in line with our results, arguing that older patients are more likely to suffer from therapy complication or side effects, inducing themselves or clinicians to stop the medication. Other studies[82] have found an association of discontinuation with younger age, but this is probably related to low compliance. The decision regarding warfarin discontinuation and subsequent prophylaxis was usually taken by a hospital specialist, confirming previous reports.[64] Very elderly patients are often hospitalized for an acute illness, inducing hospital clinicians to decide whether to prolong anticoagulation. In our cohort, perceived frailty and low life-expectancy and hemorrhagic complications account for most of the reasons given by the clinicians for discontinuation. The decision regarding discontinuation did not always follow guideline recommendations, as almost 17% of patients discontinued warfarin treatment because of claimed sinus rhythm restoration.[98]. Large variability in treatment after discontinuation was revealed: an alternative anticoagulant was used in one-third of cases (long-term subcutaneous LMWHs), in contrast to current guidelines.[13] LMWHs were the preferred medications in frail patients and those with low life-expectancy. In contrast, the erroneous perception of low thromboembolic risk in sinus rhythm patients explains the discontinuation of any anticoagulant therapy.

As far as the authors are aware, our study is the first to report the outcomes of very elderly patients with long-term indications for warfarin who discontinued treatment. Patients selected for discontinuation showed a very high mortality rate, driven by frailty and previous bleeding complications. Ischemic and haemorrhagic events frequently led to clinical deterioration, and eventually to death. Patients who

discontinued treatment because of bleeding or frailty had a high rate of ischemic events, bleeding events, and death, irrespective of anticoagulant prophylaxis. A recent study by Staerk et al. is in line with our results, showing that patients who restarted oral anticoagulation after gastrointestinal bleeding had lower mortality and TE rates than patients who did not resume treatment.[99] Restoration of sinus rhythm probably identifies a healthy subgroup in elderly patients, and this may account for the absence of serious events during the first 3 years of follow-up. However, discontinuation of anticoagulant treatment in this setting is quite debatable. These are, in fact, high-risk patients, and recurrent AF may be asymptomatic, owing to rate or rhythm control treatments.

Limitations. The study was conducted on a single-centre cohort. Small numbers of events prevented us from using separate endpoints, and we therefore analysed data as a cumulative incidence of bleeding, ischemic events, and deaths. Our study is much smaller than other studies considering discontinuation in patients treated with VKA.[85,87-89] However, despite the relatively small numbers of patients and events, data collection was performed with extreme precision: no patients were lost to follow-up, and information was obtained using different databases and telephone contacts with general practitioners. This enabled us to reliably identify all events occurring during follow-up. Moreover, the inception cohort nature of our study allowed us to avoid the biases inherent in survival populations and selection biases, because our cohort was included all patients fulfilling the inclusion criteria from among the total population attending our anticoagulation clinic. We were not able to assess the currently used bleeding risk scores from the data of our database. However, as shown in our previous study, the HAS-BLED score did not appear to predict MB events: patients experiencing such events had a mean score below the high-risk cut-off of 3.[86] We observed a very high mortality rate (64%) in patients who discontinued warfarin, and this finding may be consistent with the high proportion of frail patients and their very advanced age. Mortality could have prevented more ischemic and/or hemorrhagic events from occurring, and the cause of death was often unknown, as most patients died outside the hospital.

2.4 To treat or not to treat after major bleeding?

MB rate increases with age[64,65] and the occurrence of haemorrhage automatically puts the patient at high risk of re-bleeding with warfarin.[96] Therefore, bleeding events are naturally associated with an increase in the bleeding risk perceived by the clinician, and have been confirmed in many studies[64,97] as one of the main reasons for discontinuation. The decision to restart or not OAT after MB is usually problematic. [41] Data referring to elderly patients are scarce and controlled trials in this setting are lacking.

We therefore analysed the subgroup VENPAF patients who experienced a MB while on warfarin. TE and MB after the index event were examined in relation to the restarting OAT.

Methods. This is a nested subgroup analysis of the VENPAF inception study. Patients who experienced a non-fatal MB during OAT were subsequently followed up and outcomes after the index event were recorded. Warfarin discontinuation was defined as previously reported.[100] TE and MB were detected through the Padua University Hospital electronic records and direct contact with family physicians and defined according to specific guidelines.[74,75] Fatal bleeding was defined as death occurring during hospitalisation for MB. All patients were followed from the time of the first MB until the occurrence of a second outcome event (either TE or MB), death or the end of follow-up period (36 months), whichever came first.

Results. During a median follow-up duration of 2.2 years, there were 65 MB with an incidence rate of 3.4 %patients/year. 16 MB were fatal (case fatality rate 25 %). Patients who experienced MB during OAT did not significantly differ from the total cohort in terms of age, gender, TTR and comorbidities. Patients with a fatal bleeding showed a significantly lower TTR (57.6 ± 15.1 % vs 64.5 ± 10.4 %, $p<0.05$) and significantly higher rate of ICH (81.3 % vs 32.7 %, $p<0.001$).

Of the surviving 49 patients, 25 restarted and 24 permanently discontinued OAT. Patients were similar in terms of demographic and clinical characteristics (Table 2.4). However, a trend toward suspending OAT after ICH was noted.

Patients were followed up for a total of 89 years. Twelve events were recorded: 2 in patients who restarted and 10 in patients who suspended OAT.

Table 2.4 Comparison of clinical and demographic characteristics of patients who discontinue or restarted oral anticoagulation after a major bleeding event.

Characteristics	Patients who restarted warfarin after MB (n=25)	Patients who discontinued warfarin after MB (n= 24)
Follow up (months), median (IQR)	35 (12 – 44)	14 (5 – 41)
Age, mean ±SD	84.6 ± 3.5	84.7 ± 3.0
Female, % (n)	60.0 (15)	66.7 (16)
CHA_2DS_2-VASc score, mean ± SD	4.0 ± 1.2	4.3 ± 1.4
HAS-BLED, mean ± SD	2.8 ± 0.9	2.9 ± 1.1
TTR^, mean ±SD	63.1 ± 10.9	65.9 ± 9.8
Anti-platelet therapy, % (n)	20 (5)	12.5 (3)
Aetiology of index MB		
Spontaneous, % (n)	52.0 (13)	75.0 (18)
Post-traumatic, % (n)	28.0 (7)	21.0 (5)
Unknown, % (n)	20.0 (5)	4.0 (1)
Site of index MB		
Intracranial, % (n)	24.0 (6)	41.7 (10)
Gastrointestinal, % (n)	28.0 (7)	37.5 (9)
Genitourinary, % (n)	16.0 (4)	4.1 (1)
Other, % (n)	32.0 (8)	16.7 (4)
Outcome events after index MB, n		
Ischaemic stroke, n	0	2
Pulmonary embolism, n	0	4
Intracranial MB, n	1	1
Gastrointestinal MB, n	1	2
Genitourinary MB, n	0	1
Deaths, n	11	6

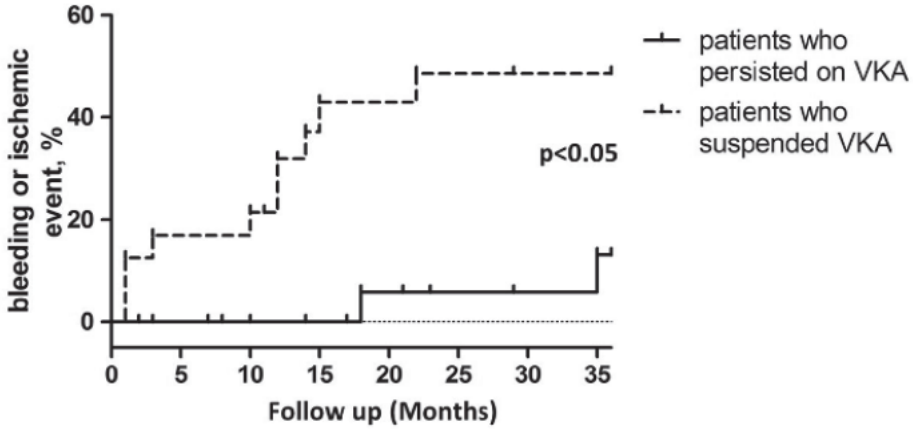
The events in patients who restart OAT were 2 MB while in patients who suspended were 4 MB and 6 TE (Table 2.4). As shown in Figure 2.3, a statistically significant increase of events is present in patients who suspended OAT ($p<0.05$).

The present analysis confirms that bleeding is a fearful and frequent complication in elderly patients.[101] Gastrointestinal bleeding and ICH are more common and severe in the elderly[102,103] and in our study accounted for 72 % of all MB. ICH was the most severe complication, responsible for 81 % of fatal haemorrhages, in line with previous reports.[42]

Overall, we found a case fatality rate of 25 % after MB which is extremely high. Together with ICH, low TTR value was independently associated with fatal events. TTR identifies patients at higher risk of complication during warfarin treatment,[104] but its association with ICH is still debated.[34,105]

Patients who resumed or discontinued warfarin after a non-fatal MB did not show statistical difference regarding basal demographic and clinical characteristics. However, differences between groups (e. g. higher number of ICH in patients who did not resume warfarin) may be non-significant due to low number of cases.

Figure 2.3 Cumulative rate of ischaemic and bleeding events after the index event in patients who experienced a major bleeding, according to warfarin restart.



The main result from this study is that patients who restarted OAT had fewer events (either MB or TE) than patients who suspended OAT. This observation confirms other reports[99,106,107] which evaluated OAT after gastrointestinal bleeding. Our study is the only one to focus on elderly. Principal study strength is the absence of selection bias with no lost to follow-up and no missed events. The study presents some limitations, too: the analysis is retrospective and conducted on a single centre cohort; numbers of events are small and prevented us from using separate endpoints.

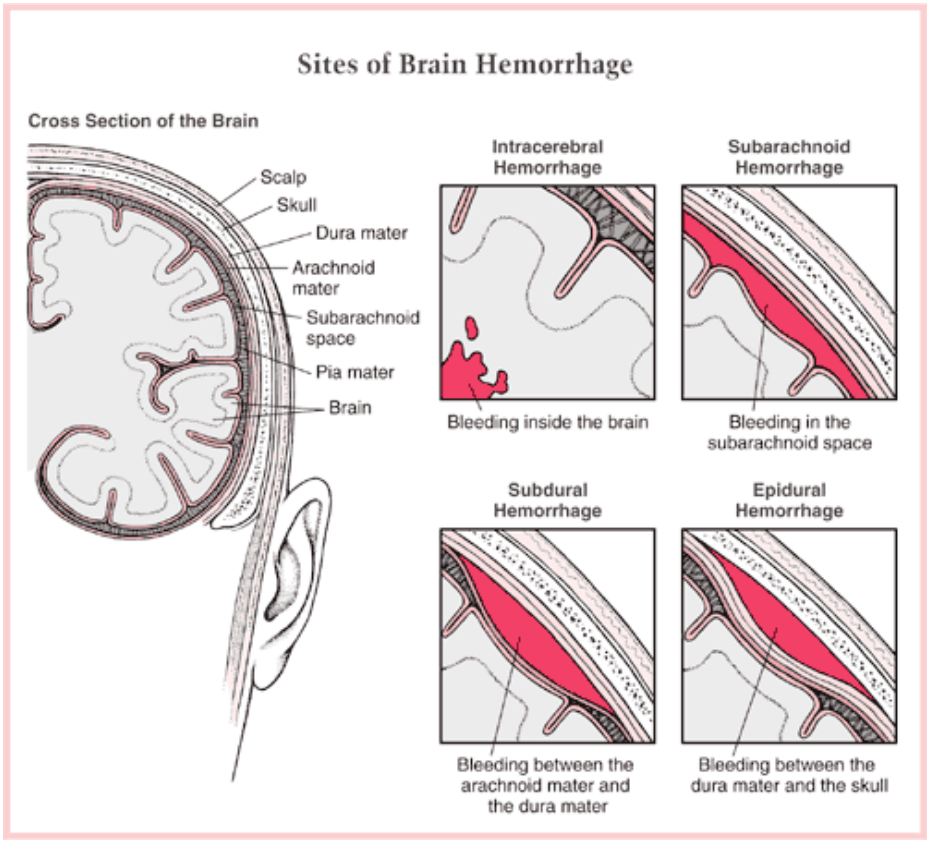
After these results, we concentrate our efforts to better determine the risk of haemorrhagic stroke in anticoagulated individuals.

3. THE RISK OF HAEMORRHAGIC STROKE IN ANTICOAGULATED PATIENTS

3.1 Haemorrhagic stroke and intracranial haemorrhage

Haemorrhagic stroke is the most fearful OAT side effect, being related to very high rates of mortality and disability.[108] Haemorrhagic stroke is a clinical syndrome defined as a sudden neurological dysfunction attributable to a intracranial haemorrhage (ICH) not caused by trauma.[109] ICH can be classified according to the affected intracranial compartment as intra-parenchymal, intra-ventricular, subarachnoid, subdural, and epidural (figure 3.1). Subdural and epidural haemorrhages are most commonly related to head injury whereas subarachnoid haemorrhages are generally caused by the rupture of cerebral aneurysms. The most frequent type of ICH causing haemorrhagic stroke during OAT is intracerebral haemorrhage, which comprises intra-parenchymal and intra-ventricular bleeding occurring in the absence of trauma.

Figure 3.1. Sites of Intracranial Haemorrhage (ICH)



With an overall incidence of around 25 per 100 000 person-years,[108,110] ICH is the second most common cause of stroke and it frequently bears a poor prognosis with very high case fatality rate, leading to permanent disability in almost 50% of the cases. In OAT patients, mortality raises to 67%, accounting for

about 90% of all bleeding related deaths.[42,108] Non-traumatic ICH is mainly associated with uncontrolled hypertension, although in recent decades the proportion of hypertensive haemorrhages has greatly reduced thanks to the increased awareness of the importance of blood pressure control.[110] On the contrary, ICH is much more frequent in the elderly, with a 9-fold increase in people aged ≥ 85y. vs. 45-54y.[108] This result is probably driven by high prevalence of hypertension and amyloid angiopathy (a disease associated to arterial degeneration and micro-bleeds seen on cerebral magnetic resonance imaging)[111] and by the increased use in this population of antithrombotic therapy.

The use of antithrombotic drugs (i.e. anticoagulants and antiplatelets drugs) increases the incidence of ICH of approximately 10-15 times, making the bleeding more severe and difficult to treat.[112] ICH and haemorrhagic stroke rates in patients treated with warfarin vary substantially among different studies: from 0.1%/year in clinical randomised trials[113] (Table 1) to 1.2%/year in "real-world" observational studies.[64] These important differences are likely to be explained by the different study design and disease definition (in particular MB, ICH and haemorrhagic stroke definitions may vary across the studies), by selection bias or intensity and quality of monitoring in different centres. However, despite the variability of these reports, it should be acknowledged that in the last decades the incidence of anti-thrombotic associated ICH has increased and the outcome worsened.[114] At present, it has been estimated that roughly 15% of all ICH are associated with the use of warfarin[110,114] and, given the increasing number of NVAF patients treated with OAT and the predisposition of elderly to ICH, this number is likely to increase.

3.2 Risk factors associated with haemorrhagic stroke

A wide range of factors may increase the general risk of bleeding in patients treated with OAT.[96,115-117] Risk factors highly associated with cerebral bleeding are age, ethnicity and hypertension. Table 3.1 summarize most supposed associations.

Aging. Elderly are particularly prone to ICH, which are more frequent among people aged ≥75 years and are often fatal.[42,112] High bleeding rates were found especially in the first year of treatment with warfarin.[64] Confounding factors may account for these results, as elderly patients usually present high

incidence of other risk factors for ICH (i.e. hypertension, amyloid angiopathy, co-medication, comorbidities). Nevertheless, current guidelines recommend oral anticoagulation therapy in the elderly, based on a positive net clinical benefit favouring VKAs over no therapy.[118] However, observational registries have shown higher incidence of MB in the "real world setting" compared with RCT.[119]

Table 3.1 Risk factors associated with haemorrhagic stroke and intracranial bleeding[41]

Risk factors	Remarks
Aging	Marked increase of intracranial hemorrhage in very **elderly** people (> 75 years)
Lifestyle factors	**Uncontrolled hypertension**; increased alcohol consumption; tobacco smoking; reduced low-density lipoproteins and low cholesterol level; waist-to-hip ratio
Past medical history	**Previous stroke or TIA**; **previous hemorrhagic stroke**; chronic kidney disease; hepatic impairment; chronic heart failure; diabetes
Co-medications	In particular, **anticoagulant (further increased for international normalized ratio > 3)**, **antiplatelet** and NSAID
Brain imaging alterations	Cerebral amyloid angiopathy; leukoaraiosis; microbleeds; cerebral malignancy
Others	Risk of falls; male gender; Asian or Mexican-American **ethnicity**; presence of apolipoprotein E2 or E4 allele; CYP2C9 and VKORC1 alteration during warfarin therapy

Most significant associations are provided in bold.
TIA: Transient ischemic attack; VKORC1: C1 subunit of vitamin K epoxide reductase.

Life-style factors. Uncontrolled hypertension (i.e. systolic blood pressure >160 mmHg) is the most import risk factors for all stroke types, particularly for ICH[116] and the concomitant treatment with OAT further increase the risk of bleeding. Tobacco seems to be associated with ICH (even if association is stronger with ischemic stroke) and a dose-response association for number of cigarettes smoked per day has been found.[116] Heavy alcohol intake is associated with the occurrence of ICH at a young age probably because of small-vessel disease early development and because of moderate haemostatic disorder through the associated liver impairment.[120] Increased total and non-HDL cholesterol levels seem to be associated with a reduced risk for haemorrhagic stroke.[116] However the association is poorly understood.

Past medical history. A recent or remote history of stroke, either ischemic or haemorrhagic, and history of bleeding (any site) are strong risk factor for ICH [121-123] Severe and moderate liver impairment (defined as a Child Pugh class of B or C) is associated either with bleeding disorders (probably related to reduced production of coagulation factors, thrombocytopenia and altered platelet function) and to thrombosis, due to a reduced production of natural anticoagulant factors such as antithrombin, protein S and protein C and net effect in the single patient is not predictable.[124] Renal impairment is a well-known risk factor both for bleeding and for thrombosis.[125] Severe CKD (defined as a creatinine clearance <30 ml/min)

has been associated to increased risk of ICH in patients treated with warfarin, partly due to the suboptimal anticoagulation control of these subjects.[126] However calculated net clinical benefit results positive in favour for OAT for all categories of renal function.[127]

Co-medications. Concomitant use of anti-platelets with OAT increases the risk of bleeding. It has been reported that patients treated with VKA and aspirin have a 1.8 fold increase of bleeding risk compared to VKA alone and this risk is even higher for the combination of VKA and clopidogrel (HR 3.1), being the highest in patient with "triple" anti-thrombotic therapy (VKA, clopidogrel and aspirin, HR 3.8).[128] RCT post-hoc analyses and data on outcome in the setting of acute coronary syndrome, demonstrated that NOAC, as VKA, are associated with higher bleeding risk when combined with either single or dual antiplatelet therapy.[129-131] Steroids and non-steroidal anti-inflammatory drugs (NSAD) may increase the risk of bleeding. While their use has been associated with gastrointestinal bleedings, they seem not to increase the risk of ICH.[132] A retrospective Chinese cross-over study, however, suggest that the use of parenteral ketorolac may expose the patients to higher risk of ischemic and haemorrhagic stroke[133], but further confirmations are still lacking.

Brain imaging alteration. There are growing data that some brain features expose the patient to higher risk of bleeding, such as leukoaraiosis (i.e. white matter abnormality seen on computed tomographic scan), vascular malformations, tumours or amyloid angiopathy.[134] Brain imaging is now able to detect microbleeds, a sign of severe microangiopathy.[135] Microbleeds and amyloid deposition are associated with a high ICH rate that is further increased by antithrombotic therapy, even if the INR is well controlled.[136,137] It should be noted, however, that Alzheimer's disease itself is not a strong risk factor for cerebral haemorrhage and should not be viewed as an absolute contraindication for antithrombotic therapy.

Other risk factors for ICH. Risk of falls is perceived as one of the main risk factors for withholding anticoagulation, and may lead to an increased risk of ICH. However, not all experts agree: some researchers have calculated that a person on warfarin must fall almost daily to outweigh the benefit of anticoagulation,[138] while others found a substantial increase of ICH, especially traumatic, in patients who are prone to fall.[139] Ethnicity has been advocated as one important risk factor for ICH. Rates of cerebral bleeding vary by different

race groups and it is particularly high in Black, Asians[115] and Mexican-Americans.[140] Genetic disorders may alter VKA metabolism thus exposing warfarin-treated patient to higher risk of bleeding. Current research mainly focus on cytochrome P450 2C9 polymorphisms and vitamin K epoxide reductase complex subunit 1 gene (VKORC1) that alter sensitivity to VKA thus delaying the stabilization of VKA treatment.[122] Apoliporotein alleles (i.e. Apo E4 and E2) are associated to an increased risk of cerebral bleeding, probably because their correlation with Alzheimer disease and parenchymal amyloid plaques.[141]

3.3 A case control study at the Padua Thrombosis Centre

To evaluate whether there are factors associated to ICH during OAT, we developed a case-control study using data retrieved from the electronical records of the Padua Thrombosis Centre. We then evaluate the predictive role of haemorrhagic bleeding scores in our population for the outcome ICH.

Methods. Patients eligible for the present study were retrieved retrospectively from the electronic medical records of the Padua Thrombosis Centre: PARMA software assists the clinicians in choosing the best dosage of VKA to maintain INR at target range. The software allows also to collect patient-related data and to store a clinical datasheet where all therapy-related complications, interfering drugs or relevant medical history are stored. Patient included in the present analysis were all ≥18 year-old patients who were on VKA because affected by NVAF. We selected the patients who, between January 2008 and December 2015, experienced an ICH while on anticoagulation. Patients were excluded if: the drug used for OAT was not a VKA; OAT indication was different from NVAF, e.g. in the presence of venous thromboembolism or mechanical cardiac valves. All ICH were confirmed by searching the electronical medical records of the Azienda Ospedaliera di Padova (GALILEO software), from which was possible to determine the site of bleeding, the cause (spontaneous or traumatic) and possible death (ICH was considered fatal if death occurred within 30 days from index date).

For each case patient, we randomly assigned four control patients by adopting a risk-set sampling method defined by age (± 2 years), gender and length of warfarin administration (from initiation to the case index date).[142] Patients' demographics and clinical baseline information were collected for analysis from the

electronic records held at the Padua University Hospital and the Anticoagulation Clinic. Comorbidities like hypertension, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, heart disease, chronic kidney disease and liver disease were defined according to the corresponding guidelines and as requested by the specific bleeding/ischemic scores.[69-72,74] Co-medications were extrapolated from emergency room and hospital discharge letters. The quality of anticoagulation was calculated as the time in the therapeutic range (TTR) from starting the treatment to the end of the follow-up, using the linear interpolation method devised by Rosendaal et al.[31] The resulting TTR included all INR data available during the observation period, including when the therapy was started, and any temporary suspensions for invasive procedures requiring heparin bridging. Haemoglobin, platelets, creatinine and PT-INR were collected soon afterwards the ICH event for cases; for controls, blood test were considered if performed ± 3 months from the ICH date of the respective case. Bleeding predisposition was considered present in case of: haemoglobin levels persistently < 100 g/l in the 3 months before the case index date; a previous bleeding event reported in the medical records as a cause of hospital or emergency room admission. From the data gathered, was possible to calculate three of the most used bleeding scores, such as HAS-BLED,[143] ATRIA,[36] and ORBIT.[144] The TE risk profile was calculated using the CHA_2DS_2-VASc score.[14]

Results. The search retrieved 59 individuals who experienced ICH during OAT. After excluding 6 patients because of mechanical heart valve implantation and 3 because affected by venous thromboembolism, the final cohort comprised 51 case patients. We randomly assign 4 controls patients for every case, by matching for age, gender and length of VKA therapy: thus, total control group comprises 204 individuals.

Table 3.2 show the characteristics related to ICH event in case patients: ICH was frequent in very elderly patients (especially ≥80 years of age), more than a quarter of them was fatal. As expected, intraparenchymal haemorrhage was often spontaneous and fatal, while subarachnoid and subdural bleedings were usually post-traumatic and not leading to death. Mean INR at the time of the event was in target range and the median time form beginning of OAT to ICH was around 2 years, ranging from 1 year to

more than 4. These data seem to go against current literature which report that serious bleeding are more frequent in over-coagulated patients and they usually develop in the first months after initiation.[145]

Table 3.2 Characteristics related to ICH event in case patients

	Cases (n=51)
Age at case index event, median (range)	84 (78 – 87)
- **Of which≥80 years old**	37 (73%)
Males, n (%)	24 (47%)
Fatal ICH	14 (28%)
- **Of which spontaneous**	10 (71%)
- **Of which post-traumatic**	4 (29%)
Site	
- **Intraparenchymal**	26 (51%)
- **Subarachnoid**	7 (14%)
- **Subdural**	18 (35%)
Etiology:	
- **spontaneous**	28 (55%)
of which intraparenchymal	20 (71%)
of which subarachnoid	0
of which subdural	8 (29%)
- **post-traumatic**	23 (45%)
of which intraparenchymal	6 (26%)
of which subarachnoid	7 (30%)
of which subdural	10 (44%)
INR at the index event, mean ±SD	2,8 ± 0,9
Length in months of VKA therapy from initiation to index event, median (range)	26 (15 – 55)

Demographic, laboratory and clinical characteristics of the case and control patients are listed in Table 3.3; there were no difference between groups regarding all characteristic analysed. 2 patients in the control group were on acenocumarol therapy, while all the rest were taking warfarin. Interestingly, TTR was higher, though not statistically significant, in patients who had ICH compared to controls. Laboratory tests did not show any statistical significance between group. Looking at clinical characteristic, patients who experienced ICH had more vascular disease, more bleeding predisposition and surprisingly less ischemic stroke, although none of such factors did reach statistical significance.

Table 3.3 Cases and controls baseline characteristics

	Cases (n=51)	Controls (n=204)	p-value
Age at case index event, median (range)	84 (78 – 87)	84 (78 – 87)	
Males, n (%)	24 (47%)	95 (47%)	
Type of VKA:			
- **Warfarin, n (%)**	51 (100%)	202 (99%)	
- **Acenocumarol, n (%)**	0 (0%)	2 (1%)	
INR range:			
- **1,5 – 2,5, n (%)**	0 (0%)	5 (2%)	
- **2 – 3, n (%)**	51 (100%)	199 (98%)	
TTR in the 6 months before the case index event, median (range)	70 (45 – 90)	64,5 (49 – 86)	0.43
LABORATORY TESTS			
Haemoglobin (g/l), mean ± SD	129 ± 16	131 ± 18	0.39
Platelets (x10^9/l), median (range)	217 (188 – 258)	219,5 (185 – 268)	0.98
Creatinine (µmol/l), median (range)	91 (75 – 105)	88 (72 – 107)	0.53
CLINICAL CHARACTERISTICS			**OR (I.C. 95%)**
Heart Failure, n (%)	16 (31)	53 (26)	1.30 (0.67 - 2.54)
Blood hypertension, n (%)	44(86)	185 (91)	0.65 (0.26 - 1.63)
Age ≥ 75 years old, n (%)	44 (86)	172 (84)	1.17 (0.48 - 2.83)
Diabetes Mellitus, n (%)	11 (22)	38 (19)	1.20 (0.57 - 2.56)
Stroke/TIA, n (%)	4 (8)	28 (14)	0.54 (0.18 - 1.60)
Vascular Disease, n (%)	24 (47)	72 (35)	1.63 (0.88 - 3.03)
Age 65 – 74 years old, n (%)	7 (14)	29 (14)	0.96 (0.40 - 2.34)
Female Gender, n (%)	27 (53)	108 (53)	1.00 (0.54 - 1.85)
Chronic kidney disease, n (%)	1 (2)	5 (2)	0.80 (0.09 - 6.97)
Liver disease, n (%)	1 (4)	4 (2)	1.00 (0.11 - 9.14)
Ischemic stroke only, n (%)	3 (6)	23 (11)	0.49 (0.14 - 1.71)
Bleeding predisposition, n (%)	19 (37)	53 (26)	1.69 (0.89 - 3.24)
Labile INR, n (%)	18 (35)	85 (42)	0.76 (0.40 - 1.45)
Concomitant antiplatelet therapy, n (%)	9 (18)	38 (19)	0.94 (0.42 - 2.09)
Anaemia, n (%)	16 (31)	65 (32)	0.98 (0.51 - 1.89)

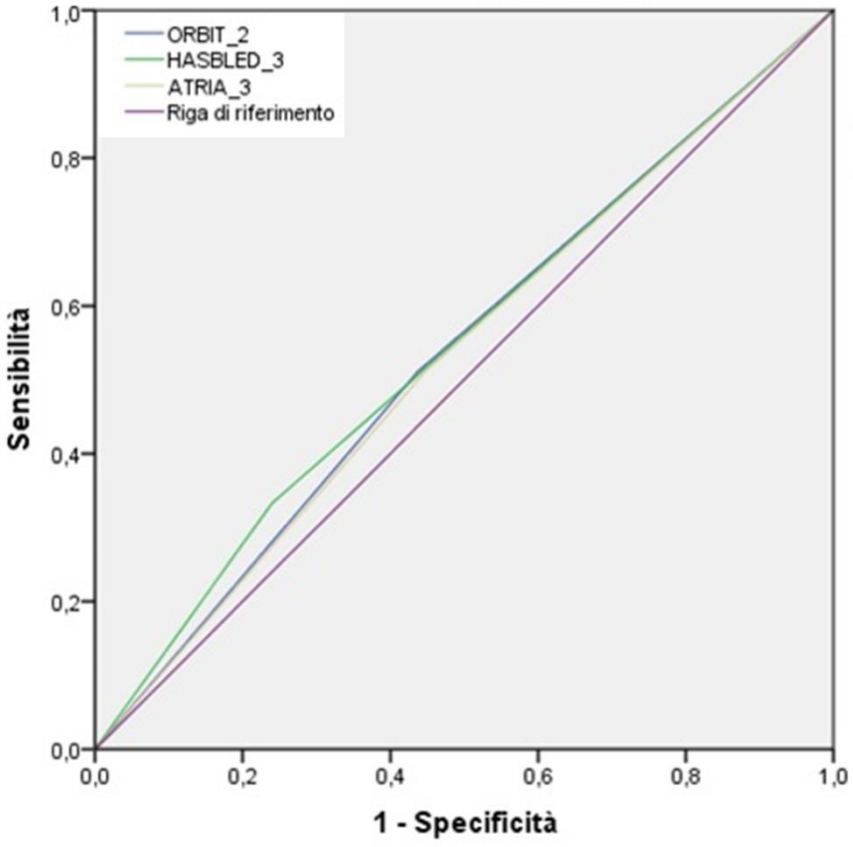
Comparing ischemic and bleeding risk scores, such as CHA_2DS_2-VASc, HAS-BLED, ATRIA and ORBIT, we did not find any statistical difference between cases and controls (table 3.4).

Table 3.4 Comparison of ischemic and bleeding risk scores.

	Cases (n=51)	Controls (n=204)	p-value
CHA_2DS_2-VASc, median (range)	4 (3 – 6)	4 (3 – 5)	p=0.64
HAS-BLED, median (range)	3 (2 – 4)	3 (2 – 3)	p=0.24
ATRIA, median (range)	4 (3 – 6)	3 (3 – 6)	p=0.51
ORBIT, median (range)	3 (1 – 3)	2 (1 – 3)	p=0.43

We finally performed *Receiver Operator Characteristic (ROC) Curve* to evaluate the predictive value by comparing the C-statistics of bleeding risk scores. The determination of cut-off points for risk categories were adapted to our cohort to increase prediction power, using HAS-BLED=3, ATRIA=3 and ORBIT=2 as cut off for high bleeding risk. As shown in figure 3.2, the area under the curve of all bleeding scores was similar with C-statistic less than 0.6 for all of them (C-statistic for HAS-BLED, ATRIA and ORBIT were 0.55, 0.53 and 0,54, respectively). Therefore, we concluded that none risk bleeding score had the power to accurately predict ICH in our cohort.

Figure 3.2 Receiver operating characteristic curves of the risk scores.



3.4 Strategies to minimize the risk of bleeding

OAT therapy is presently the most efficacious treatment for the reduction of TE in patients affected by NVAF. Nevertheless, OAT is associated with a significant increase of bleeding events, particularly ICH that may often result in deaths or severe disabling symptoms. We demonstrated in our cohort of anticoagulated patients that none risk factor is associated with ICH occurrence and commonly used bleeding risk scores could not efficaciously predict such events. However, several issues can be addressed to minimize the risk of haemorrhagic stroke in AF patients (Table 3.5).

Table 3.5 Issues to be considered to minimize the risk of haemorrhagic stroke in anticoagulated patients with atrial fibrillation[41]

Issue	Remarks
Use of DOAC instead of VKA	Expected an ~ 50% risk reduction
Blood pressure control	For both DOAC and VKA
Systematic evaluation of renal and hepatic function	Especially for DOAC
Drugs and food interactions	Especially for VKA
Reduce the risk of fall	For both DOAC and VKA
Discontinuation of antiplatelet therapy	If not strictly indicated
Prescriber education	Especially for DOAC
Time adherence to treatment	Especially for DOAC
Lower the intensity of anticoagulation	For both DOAC and VKA
Left atrial appendage closure	In special situations

DOAC: Direct oral anticoagulants; VKA: Vitamin K antagonist.

Drug Selection. NOAC have proved to be as effective as warfarin in the prevention of TE in NVAF, with a better safety profile through the reduction of haemorrhagic strokes by approximately half. These novel agents should be considered in place of warfarin to ameliorate the prognosis of patients considered at higher risk of hemorrhagic stroke, provided that NOAC is contraindicated in severe renal or liver disease, in patients with mechanical heart valves and during pregnancy.

Managing risk factors and co-morbidities. Even if new therapies greatly reduce the risk of haemorrhages, a careful bleeding risk assessment of NVAF patients is mandatory in order to minimize possible complications. Knowledge of ICH risk factors are useful in order to select patient at highest risk of bleeding, pursue the abolition or reduction of all correctable risk factors, take clinical decision about the prosecution/discontinuation of OAT and for the choice of the right agent. Blood pressure control is especially

important and OAT use, especially in elderly, should be as important as aggressive blood pressure management. Alcohol intake should be discouraged. Hepatic and renal impairment can increase bleeding events per *se* or by increasing OAT drugs concentration and therefore patients at higher risk of renal and/or liver deterioration should be monitored closely and therapy discontinued in presence of acute impairment.

Discontinuation of antiplatelet therapy. Patients with stable vascular disease should not be on anti-platelet therapy on top of OAT.[146] Patients with NVAF and a previous acute coronary syndrome and/or recent percutaneous coronary intervention with stent application should be treated as suggested by ad-hoc guidelines [147,148] in order to minimize bleeding risk. In case of dual antiplatelet therapy, clopidogrel and aspirin should be preferred over newer anti-platelets inhibitors (such as prasugrel, ticagrelor) that demonstrated higher bleeding rates. Moreover, whenever a patient taking NOAC must begin either single or dual antiplatelet therapy, NOAC dosage should be reduced to the lowest approved doses (i.e. dabigatran 110 mg bid, rivaroxaban 15 mg qd or apixaban 2.5 mg bid.).

Patient Education. AF patients often exhibit limited knowledge of their condition and treatment. Indeed, some experts reported that the majority of AF patients are unaware that they are at risk of stroke.[149] Lack of knowledge presents a key barrier to uptake and adherence; several studies suggest that patients with greater knowledge of warfarin therapy have more often INR values within the TTR[150-152] and consequently they have a reduced risk of treatment-associated bleeding and ischemic complications.[33] Educational interventions seem efficacious in improving adherence and increasing TTR.[151] Adherence and persistence is of utmost importance even during NOAC therapy and patient education is crucial. Presently there is no data on compliance of NOAC in everyday practice but the significance of the problem should not be underestimated. Patients' knowledge about their treatment and condition should be encouraged in order to improve adherence, with particular stress on time adherence for patients treated with non-VKA therapy:[153] NOAC patients should be instructed to avoid taking the pills at a distance of less than 12 h for dosing bid and less than 24 h for the administration qd. Instructions at initiation of therapy are mandatory as group sessions with constant re-education at every renewal of the prescription and involvement of family. Some patients may prefer INR monitoring to no monitoring and there may be a preference for VKA treatment over NOAC

from this perspective. Prescribing clinician should be aware of limitations concerning the use of anticoagulant therapy, especially NOAC: some authors[154] reported that many bleeding complication in patients treated with NOAC are probably explained by incorrect patient selection or dosage has not been adjusted based on patient's characteristics.

4. POPULATION-BASED ANALYSIS OF ANTICOAGULATION IN VENETO REGION

4.1 Material and methods

Study setting. We adopted a new-user retrospective cohort design to compare patients initiating treatment with NOACs and VKAs. For this purpose, we performed a population-based analysis on linked claims data in the Veneto Region (north-eastern Italy, with about 5 million inhabitants) using:

- The drug prescriptions archive: it includes all the prescriptions reimbursed by the National Health System. It holds information on purchase data, Anatomical Therapeutic Chemical (ATC) classification, and forms of dispensing including the number of pills per package.
- The regional inpatients register: it includes all hospital admissions and discharge dates (both from private and public hospitals), and discharge diagnoses coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD9-CM).
- The database of residents registered in the regional health system: it gathers information on emigration status or death for any cause.
- The archive of co-payment exemptions: it includes information on comorbidities. In Italy, hospital care is free while patients must contribute to out of hospital care and drug costs unless they are eligible for co-payment exemption because affected by specific chronic diseases certified by a specialist.

All analyses were carried out on routinely collected health records submitted to an anonymization process allowing linkage of archives without any possibility of identification of individuals. There was no patient involvement in this study.

Identification of naïve patients with NVAF. We identified all people aged 18 years or older by their index prescription of VKA (ATC B01AAxx) or NOACs (dabigatran B01AE07, rivaroxaban B01AF01, apixaban B01AF02) from July 2013, date of the first NOAC commercialization approval in Italy, to December 2015. The first OAC prescription, or index date, identified the date of enrolment

in the cohort. We excluded from enrolment individuals with any dispensed prescription of OAT in the 12 months preceding the index date. Patients with dispensed prescriptions of antiplatelet drugs post-index date

were also excluded. Linkage with the regional inpatients register allowed the exclusion of patients with mechanical heart valves, diagnosed mitral stenosis, venous thromboembolism or other indications for anticoagulation (adopted codes in the Table 4.1).

Table 4.1 International Classification of Diseases 9th Revision (ICD-9CM)/Anatomical Therapeutic Chemical (ATC) Codes sed to identify comorbidity and co-medication

	International Classification of Diseases 9th Revision (ICD9CM) code	Anatomical Therapeutic Chemical (ATC) codes	Co-payment exemption codes
Deep vein thrombosis	4534; 4511; 4512; 4519; 4532; 45181; 45183; 45189		
Mitral stenosis	3940		
Pulmonary embolism	415.19		
Heart valve surgery (excluding aortic bioprosthesis)	35 (excluding 3521)		
Congestive heart failure/Left ventricular dysfunction**	428	C03C	021
Cancer	140-209		048
Hypertension**	401-405	C02A C02B C02C C02DA C02L C03A C03B C03D C03E C03X C07C C07D C08G C09BA C09DA C09XA52 C02DB C02DD C02DG C04 C05 C07 C07F C08 C09BB C09DB C09	031 A31
Diabetes mellitus**	250		013
Stroke/TIA/Thromboembolism	433-438		B02
Bleeding, History of	578; 430; 431; 432; 5997; 7863		
Myocardial infarction	410.0-410.9; 411.0; 412;429.79		
Peripheral artery disease	440.20-440.24; 440.29; 440.30-440.32; 440.4; 443.81; 443.89; 443.9		
Aortic plaque	440.0		
Abnormal renal function	582; 583; 585; 586		023
Abnormal hepatic function	570-573; 7904		008; 016
Outcomes			
Major bleeding	430; 431; 432; 372.72; 362.81; 379.23; 784.7; 511.8; 531.0 532.0 534.0 533.0; 852.0 853.0 852.2; 852.4; 459.0 599.7 280.0; 531.0x, 531.2x, 531.4x, 531.6x; 532.0x, 532.2x,		

	532.4x, 532.6x, 533.0x, 533.2x; 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x; 535.01, 535.11, 535.21, 535.31, 535.41, 535.51; 535.61, 537.83,		
Stroke	433.x1 434.x (except sub-code: x0), 436		
Medications			
Dabigatran		B01AE07	
Rivaroxaban		B01AF01	
Apixaban		B01AF02	
Warfarin		B01AA03	
Acenocoumarol		B01AA07	
Aspirin*		B01AC06	
Clopidogrel*		B01AC04	
Nonsteroidal anti-inflammatory drugs*		M01A	
Alpha adrenergic blockers		C02A C02B C02C	
Nonloop diuretics		C02DA C02L C03A C03B C03D C03E C03X C07C C07D C08G C09BA C09DA C09XA52	
Vasodilators		C02DB C02DD C02DG C04 C05	
Beta-blockers		C07	
Calcium Channel blockers		C07F C08 C09BB C09DB	
Statins		C10	
Renin-angiotensin system inhibitors		C09	

*at least 3 packages

**We identified subjects with hypertension using ICD codes, a combination treatment with at least 2 of the classes of antihypertensive drugs (Alpha adrenergic blockers; Nonloop diuretics; Vasodilators; Beta-blockers; Calcium Channel blockers; Renin-angiotensin system inhibitors), and co-payment exemptions. Likewise, congestive heart failure individuals were identified using ICD codes, ATC codes, and co-payment exemptions, while diabetes using ICD and co-payment exemption codes.

Patient exposure. We adopted two analytical approaches. In the *intention to treat* (ITT) approach, patients were considered as being continuously exposed from the index date until the occurrence of an endpoint or the end of the programmed follow up, whichever came first. In the *as treated* (AT) approach, exposure was calculated from the index date until the absence of a new prescription by the end of a 60-day period from the last identified index medication fill (grace time), occurrence of an endpoint, or the end of follow-up, whichever came first. In this setting, we measured drug exposure in terms of defined daily doses (DDD).[155] The number of DDD was converted to the number of days the patient was treated, counting 1 DDD

per day and distributing all available DDDs to days of follow-up (including the days covered by the last prescription). The last date of enrolment was 31 December 2015 while follow up extended until 31 March 2016 to allow a follow up of at least 3 months for all individuals.

Baseline demographics and clinical features of patients. Demographics were recorded at the time of enrolment in the cohort. By linkage of drug prescriptions, inpatients records, and co-payment exemptions, we identified patient comorbidities and drugs of interest (as detailed in the footnote of Table 4.1). Comorbidities included diabetes, congestive heart failure, cerebrovascular disease, peripheral and carotid artery diseases, hypertension, myocardial infarction, coronary bypass graft and percutaneous coronary intervention, chronic renal disease, chronic liver disease, history of MB, and diagnosis of cancer. Assessed drugs of interest included concomitant prescription of antiplatelet agents, NSAID, and antihypertensive drugs. All comorbidities were used to compute propensity scores. CHA_2DS_2-VASc score was calculated using the relevant comorbidities identified through diagnoses coded in the previous 2 years before the index date. The bleeding risk was assessed at the time of inclusion in the cohort using a modified HAS-B(L)ED score that did not include labile INR. History of bleeding included diagnoses coded in the previous 10 years.

Endpoint definition. Study endpoints were ischaemic stroke, MB including ICH, myocardial infarction defined according to ICD-9CM codes (Table A1), and death from any cause. We identified endpoints by inpatient hospital relevant primary and secondary discharge diagnoses that included ICD codes of interest. MB events were identified using the Cunningham algorithm for automated database definition of serious bleeding related to OAT use.[156] A Quarantine period of 30 days was set for ischaemic stroke and myocardial infarction, thus events recorded in the 30 days following index date were not considered in the final analysis.[17] For the other endpoints, we started counting the days at risk from the index date.

Statistical analysis. We assessed the incidence of endpoints on the NOAC and VKA cohorts. To adjust for differences in baseline characteristics between the cohorts, two analytic methods were adopted, both based on propensity scores. In the first stage, multivariate logistic regression including all measured covariates was performed to assess the probability (propensity) of being a NOAC rather than a VKA user. In the second stage: i) the regression models were stratified by propensity score; ii) NOAC users were matched

by propensity score and semester of enrolment to VKA users in a one-to-one ratio by means of nearest neighbour matching within specified calliper. The rate of events for the assessed endpoints is expressed as number per 100 patient-years. In the ITT approach, a time to event analysis was adopted to measure the risk of study endpoints from the initial prescription until the occurrence of ischaemic stroke, myocardial infarction, MB, death, emigration, or end of follow-up (31 March 2016), whichever came first. In the AT approach, additional censoring events were either switch to a different anticoagulant drug or discontinuation of the use of an anticoagulant.

Cox regression was used to compare event rates between treatment groups with results expressed as hazard ratios (HR) with 95% confidence intervals (CI).

4.2 results on the total cohort

From July 2013 (date in which NOACs were introduced in Italy) to December 2015, 137.800 individuals newly initiated on oral anticoagulant treatment were identified. Of these, 22.896 were excluded mainly for heart valve surgery and venous thromboembolism. The rest were excluded because they had a former diagnosis of mitral stenosis and a few patients for residing outside the Veneto Region. From the remaining 114.904 patients, 65.737 were excluded for being prior users of VKA and 8.756 for being concurrent users of antiplatelet drugs. In this way, 40.411 naïve patients were identified: 6.923 treated with NOAC and 33.488 with VKA. The distribution of patients receiving specific NOAC agents was 33%, 41% and 26% for dabigatran, rivaroxaban and apixaban, respectively.

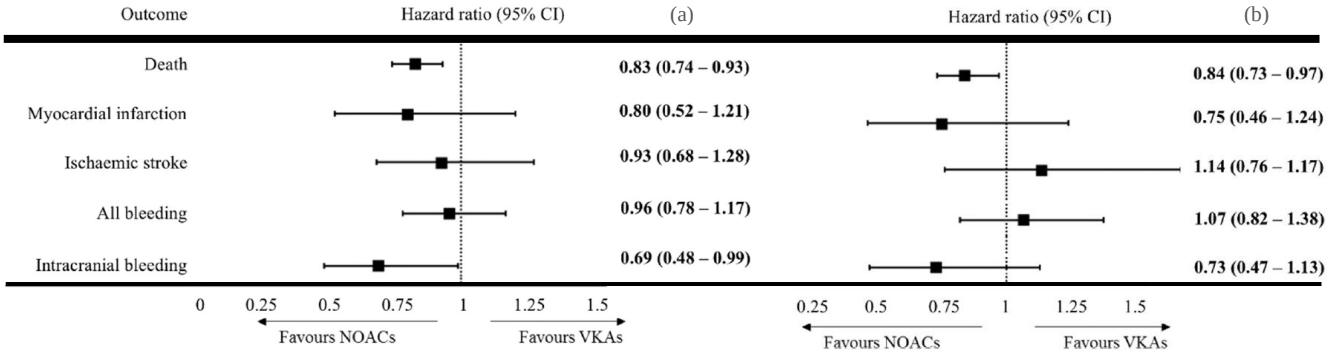
Baseline and clinical characteristics. The NOACs cohort included more female individuals, elderly, as well as those with previous stroke. These data translated into a higher mean CHA2DS2VASc and HASBED score in this group (3.23 vs 3.05 and 2.36 vs 2.19, respectively). NOAC cohort significantly differed from the VKAs cohort in almost all assessed characteristics. After matching by propensity score, the two cohorts were comparable, with 6740 individuals in each arm (Table 4.2)

Table 4.2 Baseline demographics and clinical characteristics of study subjects treated with NOAC or VKA (propensity score 1:1 match).

	All study subjects			Propensity score-matched		
	NOAC (n = 6923)	VKA (n = 33,488)	P value	NOAC (n = 6740)	VKA (n = 6740)	P value
Subjects no.	6923	33,488		6740	6740	
Gender						
Male	47.3%	52.2%	<0.001	47.9%	48.2%	0.809
Female	52.7%	47.8%		52.1%	51.8%	
Age: mean (SE)	75.3 (0.14)	74.3 (0.06)	<0.001	75.2	75.1	0.491
Age groups						
<65 yrs	14.8%	15.8%	<0.001	15.1%	15.1%	0.987
65–74 yrs	24.5%	26.8%		24.7%	24.6%	
75–84 yrs	39.3%	41.0%		39.5%	39.5%	
85 + yrs	21.3%	16.4%		20.7%	20.8%	
Risk scores at baseline						
CHA_2DS_2VASc mean (SD)	3.23 (1.45)	3.05 (1.42)	<0.001	3.20 (1.45)	3.19 (1.45)	0.7
HAS-BED mean (SD)	2.36 (1.10)	2.19 (1.03)	<0.001	2.33 (1.09)	2.32 (1.09)	0.12
Comorbidities						
Congestive heart failure	9.8%	11.5%	<0.001	9.9%	10.1%	0.646
Hypertension	73.0%	73.1%	0.812	72.8%	72.3%	0.512
Stroke/TIA/thromboembolism	22.5%	9.9%	<0.001	20.5%	20.1%	0.492
Myocardial infarction	2.2%	2.3%	0.808	2.2%	2.3%	0.485
Peripheral artery disease	1.4%	1.8%	0.046	1.5%	1.4%	0.512
Diabetes	16.2%	17.6%	<0.001	16.1%	16.6%	0.456
Cancer	9.4%	9.5%	0.652	9.4%	9.5%	0.791
Chronic renal disease	2.5%	4.3%	<0.001	2.6%	2.7%	0.591
Chronic liver disease	1.4%	1.3%	0.390	1.4%	1.3%	0.501
History of bleeding	3.5%	2.1%	<0.001	3.1%	3.1%	0.961

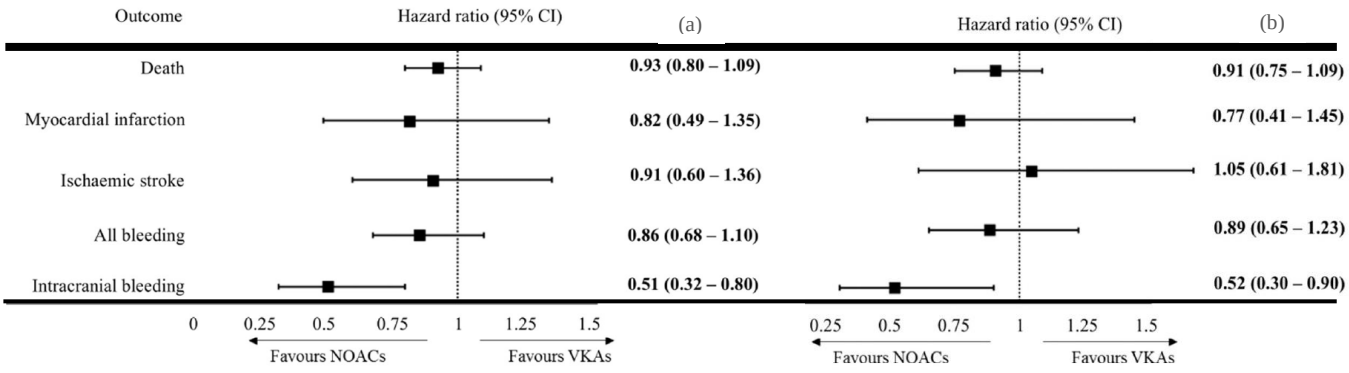
Intention to treat (ITT) analysis. In the ITT analysis, follow up extended for 7.645 patient-years in the NOAC cohort and 47.428 patient-years in the VKA cohort. The overall crude rate of events was fairly similar between the groups. The rate of ischaemic stroke was quite similar among NOAC and VKA users (0.7% patient years and 0.6% patient years, respectively). MB rate was 1.6% patient-years in both NOAC and VKA groups. In the Cox regression analysis (Fig. 4.1), the relative risk of stroke did not significantly differ in the stratified and one-to-one matched analysis (HR 0.93; 95%CI 0.68–1.28 and HR 1.14; 95%CI 0.76–1.71, respectively). Moreover, the relative risk of bleeding was also not different in the stratified and one-to-one matched analysis (HR 0.96; 95%CI 0.78–1.17 and HR 1.07; 95%CI 0.82–1.38, respectively). However, the rate of ICH was significantly lower with NOAC in the stratified model (HR 0.69; 95%CI 0.48–0.99); a similar result was observed in the one-to-one matched analysis although not reaching statistical significance (HR 0.73; 95%CI 0.47–1.13). The risk of death was significantly lower in the NOAC cohort using both analytical approaches (HR 0.83; 95%CI 0.74–0.93 and HR 0.84; 95%CI 0.73–0.97, respectively).

Figure 4.1 Effectiveness and safety outcomes in the ITT analysis (HR; 95%CI) with (a) stratification by propensity score and (b) stratification with 1:1 matching



As Treated (AT) analysis. Follow-up extended for 6.178 patient years in the NOAC cohort, and for 20.611 patient years in the VKAs cohort. A higher overall crude rate of MB was recorded among the VKA users as compared to NOAC users (2.0% patient-years and 1.5% patient-years, respectively). In Cox regression analysis (Figure 4.2), the relative risk of stroke did not statistically differ in the stratified and one-to-one matched analysis (HR 0.91; 95%CI 0.60–1.36 and HR 1.05; 95%CI 0.61–1.81, respectively). Moreover, the relative risk of bleeding was also not statistically different in the stratified and one-to-one matched analysis (HR 0.86; 95%CI 0.68–1.10 and HR 0.89; 95%CI 0.65–1.23, respectively). The rate of ICH was significantly lower with NOACs both in the stratified model and in the one-to-one matched analysis (HR 0.51; 95%CI 0.32–0.80 and HR 0.52; 95%CI 0.30–0.90, respectively). The risk of death was lower with NOACs using both analytical approaches although not reaching statistical significance (HR 0.93; 95%CI 0.80–1.09 and HR 0.91; 95%CI 0.75–1.09, respectively).

Figure 4.2 Effectiveness and safety outcomes in the AT analysis (HR; 95%CI) with (a) stratification by propensity score and (b) stratification with 1:1 matching



Discussion. Despite the good control of anticoagulation with VKAs in our region, we found a better safety and equivalent effectiveness with NOAC in patients with NVAF. In this study, patients with NVAF and a first prescription of oral anticoagulants were selected by excluding those with venous thromboembolism, cardiovascular surgery, or mitral stenosis. Patient enrolment started at the time of introduction of NOACs in the Italian healthcare system. NOACs were preferentially started in very elderly patients (over 85 years of age) and in those with previous stroke. As a result, NOAC group presented a higher CHA_2DS_2-VASc and HAS-BED score. The perceived advantage of NOAC in terms of safety and better manageability may account for the higher prescription rates in the elderly. Comparative analysis of end-points was performed using stratified and 1:1 matched analysis. The strategy of matching within stratum regression (stratification) adjustment may be used to account for residual differences between patients treated with NOAC and VKA. Moreover, analysis was computed according to the first prescription (ITT) or to drug exposure (AT). ITT analysis is more pertinent for the evaluation of effectiveness in terms of the public health impact with the introduction of new drugs, while in the AT we sought for treatment effect according to adherence.

Despite the higher risk for ischaemic stroke in the NOAC group (higher CHA_2DS_2-VASc score), the rate of ischaemic events (%patient-years) was similar to that observed in VKA group. Similar results were obtained in the stratified and 1:1 matched analysis using both ITT and AT. These data emphasise the concept of equal effectiveness of NOAC versus VKA in stroke prevention in NVAF.[45] The rate of MB in the VKA group is in line with that reported in anticoagulation clinics in Italy (2% patient-years) and stems for a good clinical and laboratory control of treatment in our region.[66,68] Clearly, a good performance of VKA-treatment might have reduced the relative benefit of NOAC in terms of bleeding complications.[34] However, the crude rate of MB was higher with VKAs in the as treated analysis (2.0% vs 1.5% patient-years), even with a well-managed VKA therapy. This result is further emphasised considering the lower bleeding risk in the VKA group as far as age and previous stroke are concerned.[65,66,86,157] The propensity score analysis fully confirmed the reduction of ICH, already observed in the registration trials of NOAC, in both ITT and AT. The analysis of the effectiveness and safety of each NOAC needs larger numbers and will be the subject of a further study including more patients and/or with an extended follow-up. A significant reduction in death rates with NOAC was reported

in at least one randomized study[48] and confirmed by real world data.[158] In our study, mortality was significantly lower in the NOACs cohort as compared to VKA users in the intention to treat approach; however, such finding did not reach statistical significance in the as treated analysis despite maintaining the same trend of reduction. This difference might be due to unaccounted reasons for therapy discontinuation. No difference in the incidence of myocardial infarction was observed between NOAC and VKA treated individuals. Despite the robust analysis, our findings have limitations related to the study's retrospective design and to data collected on routine health records without direct patient involvement. Furthermore, individual patient TTR data were not available. Nevertheless, our results have important clinical and healthcare policy implications when considering the observed overall benefit with NOAC over a generally well conducted VKA therapy as a comparator.

In conclusion, the present analysis confirms that, despite the good control of anticoagulation with VKA in our region, NOAC have a better safety and equivalent effectiveness than standard anticoagulant therapy.

4.3 results in elderly patients

After demonstrating a good safety-efficacy profile with NOAC in the general population, we aimed to focus on elderly patients and their pattern of bleeding. To this end, we performed an analysis comprehending only patients with 80 years of age or more.

From the 40.411 naïve patients of the global analysis, 25.275 were excluded because younger than 80 years of age. In this way, 15.136 elderly patients affected by NVAF were identified, 2.882 with a first NOAC prescription and 12.254 with a first VKA prescription. Due to the reduced number of individuals, we calculate propensity score with only one technique (propensity score coefficient) and no 1:1 matching. ITT and AT analyses were both performed.

Baseline and clinical characteristics. The NOAC cohort included more female individuals, very elderly (≥85 years old), as well as those with previous stroke, heart failure and history of bleeding. These data translated into a higher mean CHA_2DS_2-VASc in this group (4.3 vs 4.1, $p<0.001$). As expected, people with

chronic kidney disease were more frequently on VKA therapy, as NOAC have a relative contra-indication in this subset of patients (Table 4.2). After matching by propensity score, the two cohorts were comparable.

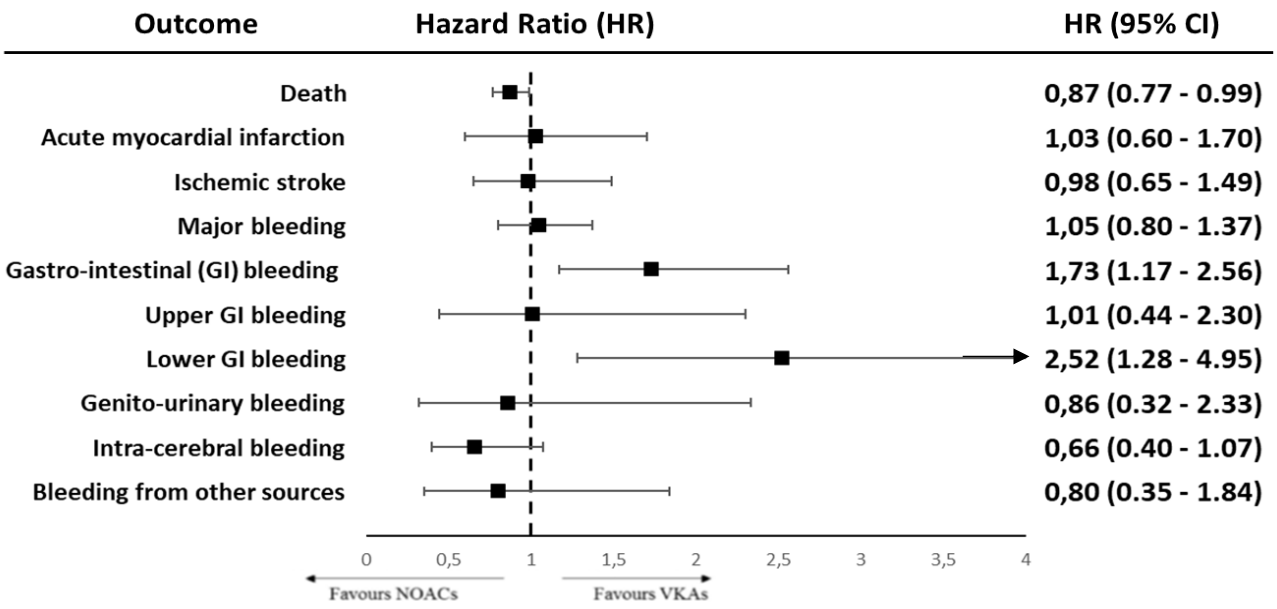
Table 4.3 Baseline demographics and clinical characteristics of study elderly subjects treated with NOAC or VKA

	NOAC	VKA	p-value
Subject number	2882	12254	
Gender			
Male	37,4%	40,9%	<0.001
Female	62,6%	59,1%	
Age groups			
Age 80-84 years old	48,8%	55,1%	<0.001
Age ≥85 years old	51,2%	44,9%	
ISCHEMIC RISK SCORE			
CHA_2DS_2-VASc, mean±SD	4.3±1.3	4.1±1.2	<0.001
CHA_2DS_2-VASc 2-3	27,8%	32,9%	
CHA_2DS_2-VASc 4-5	51,1%	55,1%	<0.001
CHA_2DS_2-VASc 6+	21,0%	12,0%	
COMORBIDITIES			
Congestive heart failure/Left ventricular dysfunction	15,0%	17,0%	<0.01
Cancer	9,8%	9,7%	n.s.
Diabetes	17,2%	18,3%	n.s.
Stroke/TIA/Thromboembolism	26,7%	13,3%	<0.001
History of bleeding	4,2%	2,7%	<0.001
Myocardial infarction	2,7%	2,9%	n.s.
Peripheral artery disease	1,8%	2,2%	n.s.
Chronic kidney disease	4,0%	6,2%	<0.001

Intention to treat (ITT) analysis. In the ITT analysis, follow up extended for 3.053 patient-years in the NOAC cohort and 16545 patient-years in the VKA cohort. The overall crude rate of events (death+ischemic+bleeding) was lower in NOAC than in VKA group (13.6% patient-years and 14.8% patient-years, respectively). The rate of ischaemic stroke was quite similar among NOAC and VKA users (1.01% patient-years and 0.97% patient-years, respectively). MB rate was 2.4% patient-years in NOAC users and 2.3% patients-year in the VKA group. Looking at the site for MB, gastrointestinal bleeding was more frequent in NOAC users (1.28% patients-year versus 0.77% patients-year), driven by an increase in lower and unspecified gastrointestinal bleedings. In the Cox regression analysis (Figure 4.3), the relative risk of stroke, myocardial

infarction and MB did not significantly differ between groups. There was a little but significant benefit of NOAC in terms of mortality (HR 0.87; 95%CI 0.77–0.99). Looking at different bleeding sites, the relative risk of gastrointestinal bleeding was higher with NOAC (HR 1.73; 95%CI 1.17–2.56), particularly when considering lower gastrointestinal bleeding only (HR 2.52; 95%CI 1.28–4.95). The hazard ratio for other bleeding sites, including ICH, did not reach statistical significance.

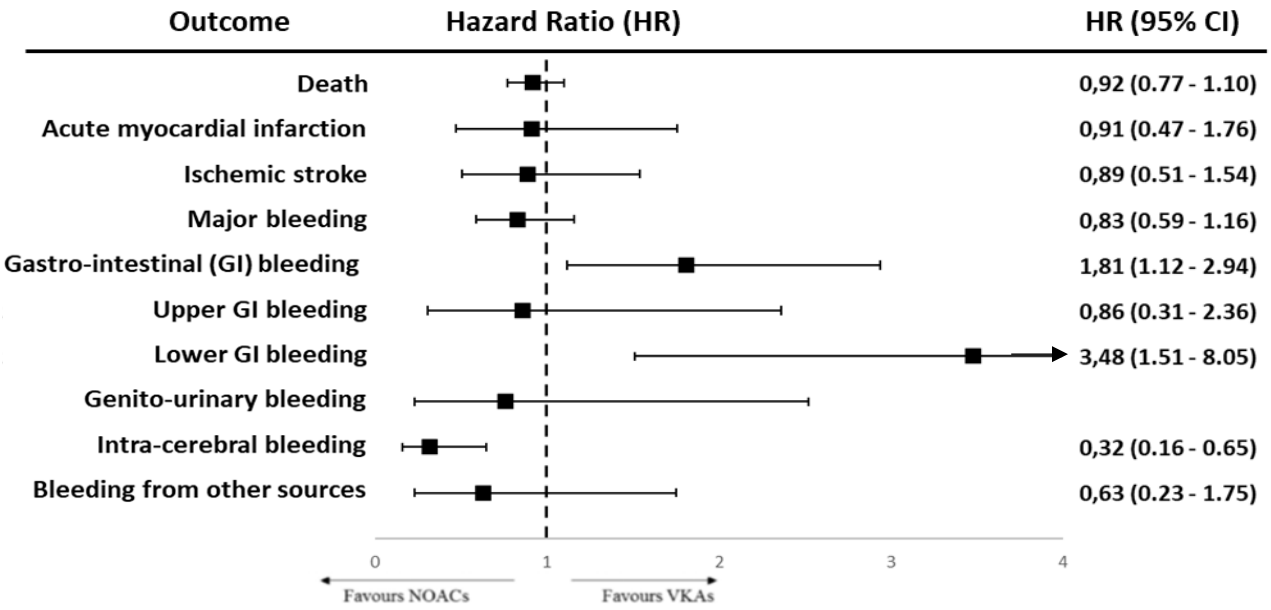
Figure 4.3 Effectiveness and safety outcomes in the ITT analysis (HR; 95%CI)



As treated (AT) analysis. In the AT analysis, follow up extended for 2.472 patient-years in the NOAC cohort and 6.686 patient-years in the VKA cohort. Results are consistent with the ITT analysis for all endopints. The overall crude rate of events (death+ischemic+bleeding) was lower in NOAC than in VKA group (11.8% patient-years and 13.9% patient-years, respectively). The rate of ischaemic stroke was 0.6% patient-years in both groups. MB rate was 2.1% patient-years in NOAC users and 2.8% patients-year in the VKA group. Looking at the site for MB, gastrointestinal bleeding was more frequent in NOAC users (1.25% patients-year versus 0.9% patients-year), driven by an increase in lower and unspecified gastrointestinal bleedings, while ICH incidence rate was more than halved in the NOAC group (0.5% patients-year versus 1.3% patients-year). In the Cox regression analysis (Figure 4.4), the relative risk of death, stroke, myocardial infarction, and MB did not significantly differ between groups. Looking at different bleeding sites, the relative risk of gastrointestinal bleeding was higher with NOAC (HR 1.81; 95%CI 1.12–2.94), particularly when considering

lower gastrointestinal bleeding only (HR 3.48; 95%CI 1.51–8.05). On the other side, the risk of ICH was lower in the NOAC group (HR 0.32; 95%CI 0.16–0.65). The hazard ratio for other bleeding sites did not reach statistical significance.

Figure 4.4 Effectiveness and safety outcomes in the AT analysis (HR; 95%CI)



Discussion. The present analysis confirms that ageing is associated with an increase of ischemic and haemorrhagic complication while on OAT (stroke incidence rate of 1% patient-year in elderly versus incidence rate of 0.7% patient-year in total cohort; MB incidence rate of 2.8% patient-year in elderly versus incidence rate of 2% patient-year in total cohort). Veneto region develop a good network of Thrombosis Centres in its territory, therefore we may argue that VKA therapy has been well managed in this cohort. Once more, NOAC demonstrated a very good efficacy and safety profile even in elderly, performing equal or better than VKA in almost all endpoints. The only exception has been an increased risk of gastrointestinal bleedings, particularly from the lower tract; this may be due to the anticoagulant effect of NOAC, that is very fast and it starts from the site of absorption. Therefore caution should be paid in prescribing NOAC in patients prone to GI bleeding (previous bleeding, peptic ulcer, diverticulosis, intestinal angiodysplasia, polyps, etc.) and clinical history should be taken into account. However, it should be noted that total MB rate and overall mortality have not been affected form the increase in GI bleeding; overall NOAC benefit is therefore maintained, probably driven by a major reduction in ICH, which are usually more severe and disabling then GI bleedings.

7. CONCLUSION

OAT is the mainstay therapy for the prevention of ischemic stroke and other TE in patients affected by AF.[12,148,159] Standard anticoagulation is usually achieved by warfarin, a vitamin K antagonist drug that works by inhibiting the production of all vitamin-K dependent coagulation factors. Along with a reduction of TE, OAT inevitably exposes patients to the risk of bleeding events ranging from minor and self-limiting bleeds to fatal haemorrhages. Therefore, when clinicians prescribe these drugs, they should balance the risk of ischemic stroke against the risk of MB in that particular patient.

Elderly patients have a higher risk both of bleeding and of stroke and a relevant underuse of VKA therapy has been reported. From our set of studies, we tried to better elucidate the risk and the benefit coming from warfarin use in elderly population.

We could demonstrate that, in a real-world cohort of very elderly patients with a well-managed VKA therapy, the risk of complications (both haemorrhagic and ischemic) is very high and much higher than what reported in clinical trials. However, net clinical benefit seems preserved, meaning that the calculated risk of stroke without OAT remains higher than the observed risk of bleeding during OAT.

Notwithstanding these results, discontinuation rate in these patients is very high and mainly driven by perceived frailty and high bleeding risk. Patients who discontinue treatment showed lower TTR, higher complication rates while on VKA therapy and faced a severe prognosis after discontinuation. Therefore, there is the need to increase OAT persistency by improving patient education and clinician knowledge or by switching to newer class of drugs when indicated.

We were not able to find any evidence that suspending warfarin enhance survival; indeed, looking at patients who suffered a MB while on warfarin, we were able to demonstrate a worse survival at 3 years of patients who stop warfarin versus patients who persist on VKA.

Haemorrhagic stroke caused by spontaneous ICH is the most fearful OAT side effect, being related to very high rates of mortality and disability.[108] We performed a case-control study and we were not able to find any factor, except for age, whose exposition was connected to higher risk of ICH: these events therefore are

not predictable and actual bleeding risk scores are not able to select a truly high risk patients for this particular condition.

The advent of non-vitamin K oral anticoagulants (NOAC), such as activated factor II (FIIa) inhibitors (i.e. dabigatran) and activated factor X (FXa) inhibitors (i.e. rivaroxaban, apixaban and edoxaban) widened the therapeutic options for TE prevention in patients with NVAF. Among many advantages, NOAC significantly reduce ICH. In order to confirm literature results and to evaluate the impact of NOAC in our local healthcare system, we performed a population-based study on Veneto Region using claim data from hospital discharge codes, exemptions and drugs prescription, to compare standard VKA therapy against NOAC in NVAF patients. Despite the good control of anticoagulation with VKA in our region, we found a better safety and equivalent effectiveness with NOAC, mainly driven by a a consistent reduction in ICH rates.

Looking at the subset of patients ≥80 years old, we found a marked increase in gastrointestinal bleeding, especially from the lower tract, in patients treated with NOAC. However, ischemic stroke and total major bleedings rates were similar among the two groups and NOAC patients showed a lower risk of ICH and lower risk of death. Therefore, special care should be paid in the evaluation of elderly patients at increased risk of gastrointestinal bleeding and clinical history is to be taken into account.

In conclusion, NOAC should be regarded as a first choice in very elderly patients with NVAF mainly because of reduced ICH events but also because their ease of use that may impact on drug adherence. Attention should be paid to contra-indication of this therapy (i.e. severe renal disease, mechanical valves, rheumatic disease) and to select the right dose according to patients' characteristics. Patient education on the importance of OAT and the risk connected to poor adherence to therapy remains a main task of Thrombosis Centre.

8. REFERENCES

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RINGRAZIAMENTI

Tutto il lavoro compiuto in questi tre anni non sarebbe stato possibile se non grazie all'aiuto e alla collaborazione di tante persone.

Ringrazio il prof. Iliceto e la Clinica Cardiologica dell'Azienda Ospedaliera di Padova per avermi permesso di accompagnare la ricerca alla clinica, perché il fine ultimo di tutto il nostro lavoro è di migliorare le cure delle persone.

Grazie al prof. Thiene e alla prof.ssa Angelini che hanno selezionato, accolto, seguito e formato noi dottorandi in questo lungo percorso.

Un ringraziamento in particolare al prof. Pengo, da cui ho imparato tanto non solo nell'ambito della ricerca ma anche dell'etica e delle relazioni umane.

Grazie alla dr.ssa Padayattil e al dr. Denas, con cui ho condiviso le gioie e i dolori del lavoro quotidiano e con cui è stato possibile portare a termine così tanti obiettivi. Grazie anche al dr. Tiso, alla dr.ssa Bracco, alla dr.ssa Baroni e al dr. Zanella per la preziosa collaborazione.

Grazie a tutto il gruppo del laboratorio di emostasi per il costante supporto: dr.ssa Banzato, dr.ssa Bison, dr.ssa Cattini e dr.ssa Pontara.

Grazie al dr. Nante e a tutto il gruppo della Clinica Geriatrica dell'Azienda Ospedaliera di Padova con la cui collaborazione è stato possibile pubblicare buona parte dei lavori su anziani e coumadin. In particolare la dr.ssa Bertozzo, la dr. ssa Marigo, la dr.ssa Petruzzellis e la dr.ssa Rossi.

Ringrazio inoltre il dr. Gennaro, la dr.ssa Ferroni e il dr. Fedeli del Servizio Epidemiologico Regionale (SER) e il dr. Giorgio Costa del Coordinamento Regionale Unico del Farmaco (CRUF) dalla cui collaborazione sono nate le analisi della popolazione della regione Veneto.

Un grazie ai miei genitori, sempre vicini, e a mia sorella, dr.ssa Zoppellaro, con cui ho condiviso una parte del percorso in cardiologia.

E infine grazie a Serena e alla dr.ssa Granziera, che sono la stessa persona ma che hanno lavorato per due, in ambito familiare e in ambito lavorativo, per consentirmi di portare a termine questo progetto.

CURRICULUM VITAE

PERSONAL INFORMATIONS

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Nationality	Italian
Date of birth	06.07.1983

WORKING EXPERIENCES

From 10/03/2009	**REGISTERED AT THE ITALIAN MEDICAL COUNCIL (ORDINE DEI MEDICI DI TREVISO), N. 04934**
From 04/07/2013	**REGISTERED WITH THE BRITISH GMC (GENERAL MEDICAL COUNCIL, UK), N. 7417095**
Date	30/06/2009 – 30/09/2013
Type of business	**SPECIALTY MEDICAL TRAINING IN "CARDIOVASCULAR DISEASES"**
Employer	Clinica Cardiologica, Centro "V. Gallucci", Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari Università degli Studi di Padova – Italy Director: prof. S. Iliceto
	5-year practical training in one of the biggest cardiology clinic in Italy. I gained experience as a cardiology registrar in all the fields of cardiology: patient care in cardiology ward and intensive care unit, experience in cath lab and electrophysiology lab, outpatient clinic, cardiovascular imaging, programming of ICDs and pacemakers, exercise tests and so on.
Date	5/06/2012 – 5/06/2013
Type of business	**Training Abroad – Advanced Echocardiography**
Employer	Royal Brompton Hospital Echocardiography Department London SW3 6NP Director: prof. R. Senior
Description	I participated to the department daily activities and I obtained experience on execution and reporting of basal transthoracic echocardiography and on stress echocardiographies (types of stressor: dobutamine, regardenoson and bycycle, treadimill). In particular I focused my experience on the use of contrast in echocardiography (for endocardial border enhancement and for perfusion evaluation) and the use of myocardial deformation analysis.

EDUCATION AND TRAINING

Date	From November 2014, current
Title	**PhD student in "Oral anticoagulant therapy and pharmacoepidemiology of Non-Vitamin K antagonist Oral Anticoagulants"**
Name and Type of organisation providing education and training	Cardio-vascular PhD programme, Padua University. Director: prof. G. Thiene (past), prof. A. Angelini (current) Tutor: prof. V. Pengo
Date	From July 2014 until July 2019
Title	**European Accreditation in trans-thoracic adult echocardiography**
Name and Type of organisation providing education and training	European Association of Cardio-Vascular Imaging (EACVI)
Date	16 /06/2014
Name and Type of organisation providing education and training	Clinica Cardiologica, Centro "V. Gallucci", Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari Università degli Studi di Padova – Italy Director: prof. S. Iliceto
Title of qualification awarded	**Degree in medical specialization on "Cardiovascular diseases"**
Level in national qualification	110/110 cum laude
Date	22/09/2008
Name and Type of organisation providing education and training	Università degli Studi di Padova Italy
Title of qualification awarded	**Degree in Medicine and Surgery**
Level in national qualification	110/110 cum laude
Date	From May to September 2008
Name and Type of organisation providing education and training	Universität Heidelberg Germany
Title of qualification awarded	**Winner of the grant "Erasmus Placement" – practical training in the cardiovascular cellular biology laboratory of Heidelberg University under the supervision of prof. Bea.** With the data collected during my stay I wrote my medical thesis ("Critical role of macrophages in glucocorticoid driven vascular calcification in a mouse-model of atherosclerosis").
Date	From March 2007 to April 2008
Name and Type of organisation providing education and training	Dipartimento di Medicina Clinica e Sperimentale (DMCS) Università degli Studi di Padova – Italy
Title of qualification awarded	Training in the cardiovascular cellular biology laboratory directed by prof. Pauletto where I gained experience in cellular culture and histopathology.

Date	From August to December 2005
Name and Type of organisation providing education and training	Oulu University Finland
Title of qualification awarded	Winner of the Erasmus grant.
Date	2002
Name and Type of organisation providing education and training	University of Cambridge UK
Title of qualification awarded	First Certificate in English (FCE).
Date	1997-2002
Name and Type of organisation providing education and training	High school "Liceo Classico Statale - A. Canova" Treviso - Italy
Title of qualification awarded	High school qualification on classical studies
Level in national qualification	100/100

MOTHER TONGUE **ITALIAN**

OTHER LANGUAGES	ENGLISH	GERMAN	SPANISH
Reading	EXCELLENT (C2)	BASIC (A1)	BASIC (A1)
Writing	EXCELLENT (C1)	BASIC (A1)	BASIC (A1)
Understanding and Speaking	EXCELLENT (C1)	BASIC (A1)	BASIC (A1)

DRIVING LICENSE B (Car), boat license

LISTA DELLE PUBBLICAZIONI

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