

From the DEPARTMENT OF MEDICINE, SOLNA  
Karolinska Institutet, Stockholm, Sweden

**ANTITHROMBOTIC TREATMENT OF  
ATRIAL FIBRILLATION BEFORE AND  
AFTER THE INTRODUCTION OF NON-  
VITAMIN K ANTAGONIST ORAL  
ANTICOAGULANTS (NOAC) IN THE  
STOCKHOLM HEALTH CARE REGION**

Tomas Forslund



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ANTITHROMBOTIC TREATMENT OF ATRIAL  
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INTRODUCTION OF NON-VITAMIN K ANTAGONIST  
ORAL ANTICOAGULANTS (NOAC) IN THE  
STOCKHOLM HEALTH CARE REGION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Tomas Forslund**

*Principal Supervisor:*

Paul Hjendahl  
Karolinska Institutet  
Department of Medicine  
Clinical Epidemiology/Clinical Pharmacology

*Co-supervisor(s):*

Björn Wettermark  
Karolinska Institutet  
Department of Medicine  
Pharmacoepidemiology

Per Wändell  
Karolinska Institutet  
Department of Neurobiology, Care Sciences and  
Society  
Family medicine

*Opponent:*

Gunnar Gislason  
University of Southern Denmark  
National Institute of Public Health

*Examination Board:*

Lars Alfredsson  
Karolinska Institutet  
Institute of Environmental Medicine  
Cardiovascular Epidemiology

Cecilia Linde  
Karolinska Institutet  
Department of Medicine  
Cardiology

Håkan Walfridsson  
Linköping University  
Department of Medical and Health Sciences  
(IMH)



## ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia and the major risk factor for thromboembolic stroke. Effective treatment with the oral anticoagulant (OAC) warfarin has been available for decades. However warfarin treatment is complicated, and demands dose adjustments and regular monitoring. Warfarin also increases the risk for bleeding, especially intracranial bleeding which is rare but often fatal. Undertreatment of AF with OACs has long been a global problem and it has been common to use low-dose aspirin (ASA) instead, despite evidence of poor efficacy.

Several new directly acting oral anticoagulants (NOACs) have been introduced in routine care based on promising results from randomised trials – the first being dabigatran in 2011, followed by rivaroxaban in 2012 and apixaban in 2013. The introduction of these drugs has brought hope of facilitating OAC treatment, increasing the proportion of patients treated, and possibly also improving the effectiveness and/or safety of treatment.

This thesis is based on four population based epidemiological studies describing the antithrombotic treatment of AF before and after the introduction of NOACs in the Stockholm health care region using the health registry of the Stockholm health care region, Vårdanalyssdatabasen (VAL).

Study I-II describe the entire AF population in the region, including demographics, risk stratification, treatment, and outcomes before the introduction of NOACs. Study III-IV compare treatment persistence, adherence, effectiveness, and safety of different antithrombotic treatments.

The analyses show that undertreatment was common prior to the introduction of NOACs, but many of the patients without anticoagulant treatment were old, with complicating comorbidities, high bleeding risk and a poor prognosis in addition to a high risk of ischemic stroke. With NOACs there was a dramatic increase in the number of AF patients in the registries and a substantially larger proportion of the patients received OAC treatment. NOACs now dominate new treatment initiations, while warfarin has decreased substantially. In routine care warfarin and apixaban was associated with better persistence than dabigatran or rivaroxaban. Adherence with OAC treatment was high (>90%), and slightly better with the once daily regimen of rivaroxaban than the twice daily regimens of apixaban and dabigatran. NOAC treatment had similar or better effectiveness and safety compared to warfarin treatment, with similar outcomes among the elderly ( $\geq 80$  years) and patients with previous severe bleeds. NOACs were associated with fewer intracranial bleeds, but more gastrointestinal bleeds. The advantages with NOAC treatment were most pronounced with standard dosing in patients under the age of 80, and with reduced doses in patients aged 80 and above.

In conclusion, this thesis shows improvements in the management of AF in the Stockholm health care region and confirms that NOACs are attractive antithrombotic treatments for AF patients in routine care. More research is needed to further optimize the use of NOACs.

# SAMMANFATTNING PÅ SVENSKA

Förmaksflimmer är den vanligaste rytmrubbningen i hjärtat och samtidigt den viktigaste riskfaktorn för embolisk hjärninfarkt. Det har funnits effektiv behandling med blodförtunnande läkemedel – antikoagulantia - sedan många decennier. Det i Sverige dominerande läkemedlet är warfarin. Tyvärr är warfarin ett komplicerat läkemedel som kräver dosjusteringar och regelbundna blodprov. Warfarin ökar också risken för blödningar, speciellt intrakraniella blödningar som ofta är dödliga. Underbehandling med antikoagulantia har länge varit ett globalt problem med många samverkande orsaker och det har varit vanligt att i hög utsträckning använda acetylsalicylsyra istället, trots dokumenterat sämre effekt.

Flera nya direktverkande antikoagulantia (NOAK) har introducerats i sjukvården baserat på lovande resultat från randomiserade kliniska prövningar – de första var dabigatran 2011, rivaroxaban 2012 och apixaban 2013. Introduktionen av dessa läkemedel har inneburit hopp om att underlätta antikoagulantibehandling, öka andelen patienter med förmaksflimmer som får adekvat behandling, och möjligen också förbättra effektivitet och/eller säkerhet vid behandling.

Den här avhandlingen baseras på fyra populationsbaserade epidemiologiska delarbeten som beskriver den antitrombotiska behandlingen av förmaksflimmer före och efter introduktionen av NOAK i Stockholms Läns Landsting.

Studie I-II beskriver hela förmaksflimmerpopulationen i Stockholms Läns Landsting, inkluderande demografi, riskstratifiering, behandling och utfall innan introduktionen av NOAK. Studie III-IV jämför behandlingssjälvständighet, följsamhet till ordination, effektivitet och säkerhet mellan olika typer av antitrombotisk behandling.

Analyserna visar att underbehandling var vanligt innan introduktionen av NOAK. Många av patienterna utan antikoagulantibehandling var gamla med komplicerande samsjuklighet, hög blödningsrisk och dålig prognos, utöver en hög risk för ischemisk stroke. Introduktionen av NOAK innebar en dramatisk ökning i antalet patienter med förmaksflimmer som kunde identifieras i registren och en klart högre andel behandlades med antikoagulantia. NOAK dominerar nyinsättningarna och warfarin har minskat kraftigt. I rutinsjukvården var warfarin och apixaban associerade med högre självständighet än rivaroxaban eller dabigatran. Följsamheten till ordination verkade vara något bättre med det endoserade rivaroxaban än de tvådoserade apixaban och dabigatran. NOAK verkade vara lika eller mer effektivt och säkert än warfarin. NOAK var associerat med lägre förekomst av intrakraniella blödningar men fler gastrointestinala blödningar. Fördelarna med NOAK-behandling var mest framträdande med standarddos hos patienter under 80 år och med dosreduktion hos patienter som var 80 år eller äldre.

Sammanfattningsvis visar denna avhandling förbättringar i vården av förmaksflimmer i Stockholms Läns Landsting samt bekräftar att NOAK fungerar väl som antitrombotisk behandling i rutinsjukvård. Mer forskning behövs för att ytterligare förbättra användningen av NOAK.

## LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on four original studies which are reproduced with permission from the publishers.

- I.** Forslund T, Wettermark B, Wandell P, von Euler M, Hasselstrom J, Hjemdahl P. Risk scoring and thromboprophylactic treatment of patients with atrial fibrillation with and without access to primary healthcare data: experience from the Stockholm health care system. *Int J Cardiol.* 2013;170:208-14
- II.** Forslund T, Wettermark B, Wändell P, von Euler M, Hasselström J, Hjemdahl P. Risks for stroke and bleeding with warfarin or aspirin treatment in patients with atrial fibrillation at different CHA<sub>2</sub>DS<sub>2</sub>VASc scores: experience from the Stockholm region. *Eur J Clin Pharmacol.* 2014;70:1477-85
- III.** Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. *Eur J Clin Pharmacol.* 2016;72:329-38
- IV.** Forslund T, Wettermark B, Andersen M, Hjemdahl P. Stroke and bleeding with NOAC or warfarin treatment in patients with non-valvular atrial fibrillation: a population based cohort study. *Europace.* 2017; doi:10.1093/europace/euw416

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## LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AHA	American Heart Association
ASA	Acetylsalicylic acid
BID	Twice daily
CI 95	95% confidence interval
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
HR	Hazard ratio
ITT	Intention to treat
NOAC	Non-vitamin K antagonist anticoagulant
NPR	National patient register
OAC	Oral anticoagulant
OD	Once daily
OR	Odds ratio
PCC	Prothrombin complex concentrate
P-gp	P-glycoprotein
PT-INR	Prothrombin time (PT) - international normalized ratio
TIA	Transitory ischemic attack
VAL	Vårdanalysdatabasen (Stockholm administrative health data register)

# 1 INTRODUCTION

Drugs are an increasingly important part of health care, to either treat symptoms or underlying causes of disease, or to prevent disease. Despite the substantial advancements in drug treatment and increases in health and life expectancy in the last century there are still many unmet needs and challenges for the improvement of drug therapy [1]. As diagnostic opportunities and treatments improve, the expectations and demands increase. One can even say that the improvements in health and life expectancy create new and more complicated medical challenges due to the multimorbidity and polypharmacy associated with increasing age [2].

It is well documented that compliance to treatment guidelines often is inadequate and that many patients lack efficient evidence based treatment with medicines [3,4]. There are many possible reasons for this, including disturbing side-effects [5,6], lack of motivation resulting in low adherence to preventive drug treatments without symptomatic relief [6], high prevalence of relative or absolute contra-indications in target populations [7], and slow implementation of guidelines in health care [8].

New drugs are introduced to address unmet needs of varying importance, and to facilitate treatment and adherence to guidelines. According to reviews, however, only 10-15% of new drugs provide substantial advantages compared to older treatments [9-11]. In France it has been claimed that less than 4% of new drug indications or new indications for existing drugs really provide real therapeutic advantages [12,13].

From the clinicians point of view there are several problems with the randomized controlled trials providing the documentation for the registration of new drugs [14,15]. They may have sample sizes that are too small to fully assess the safety of drugs [15,16] or they may be so large that they result in statistically but not clinically significant treatment effects. The follow-up may be too short to show long-term benefits or risks [15,16]. Clinical trials are performed in settings which differ from routine care, with very well informed and motivated patients, and with much closer follow-up than that provided for the usual patient [15]. Importantly, patients in clinical trials are selected and may underrepresent or exclude vulnerable patient groups, especially elderly patients with multiple comorbidities [14,15]. The dosages used in the studies may also differ from those later used in routine care [15]. For these reasons the introduction of new drugs in routine care has to be regarded as another, fourth phase in the clinical and scientific development of new therapies.

In Sweden, regional Drug and Therapeutics Committees continuously assess the evidence for new treatments in relation to standard treatments and issue recommendations with high impact on drug treatment patterns [17,18]. Structured introduction of new drugs with possible health care benefits but associated with large costs is growing in importance [19]. Registry based studies provide the possibility to investigate the introduction of new drugs from

different angles and to assess the appropriateness of prescriptions. Other possibly more clinically meaningful outcomes can also be assessed [14]. Independent comparative effectiveness studies provide additional validation of the benefit and risks of new drugs in routine care [15]. Pharmacoepidemiologic registry based studies on large populations representative of routine care demand only limited resources and can be conducted rather fast. They may provide valuable information on effectiveness and safety in routine care and provide information on treatment results in vulnerable subgroups that have not been investigated in the randomized trials. However, they suffer from several methodological problems which are discussed in Chapter 6.1 [20].

## 1.1 ATRIAL FIBRILLATION

### 1.1.1 Etiology

The etiology of atrial fibrillation (AF) is multifactorial. AF often co-exists with numerous cardiovascular and other conditions [21-28], but the cause and effect are not always easy to distinguish [24-26]. AF also evolves in parallel with other conditions, which might be involved in the evolution of AF [26]. Associated conditions might lead to the development of AF through four general types of mechanisms [27]: ectopic firing and re-entry mechanisms caused by dysfunction of ion channels, abnormalities of intracellular  $\text{Ca}^{2+}$ -handling, structural remodeling, or dysregulation of the autonomic nervous system [27]. AF itself also causes remodeling; this might explain the common progression from paroxysmal to permanent AF [29]. Several of the associated conditions, such as hypertension, heart failure, and diabetes are also associated with an increased risk for ischemic stroke in AF-patients [28,30,31].

The most important risk factors for AF are age, hypertension, diabetes mellitus, and heart failure [26]. Increased age might lead to AF because of fibrosis and age-dependent loss of myocardial cells in the atria [26,27,32], but also due to other age related disorders [21,26]. Hypertension is common and an important risk factor, with higher blood pressure increasing the risk of AF and its complications [26,27]. Diabetes mellitus is found in 20% of AF patients, and might lead to disturbances of the atria [21,26,27]. Heart failure might cause AF, but be also a consequence of acute AF with tachycardia or permanent AF [24-27]. Symptomatic heart failure is very common in AF patients and can be found in approximately 30% [21-23]; conversely, AF has a prevalence of 30–40% of in patients with heart failure.

Coronary artery disease can be found in  $\geq 20\%$  of patients with AF [21-23,27]. Whether coronary artery disease leads to AF and in what ways AF might affect coronary perfusion are uncertain [21,33]. Valvular heart disease is common in patients with AF [21-23]. Mitral stenosis or regurgitation are strong risk factors for AF, possible due to distension of the atria [26], but AF also occurs in aortic valve disease [27]. Cardiomyopathies are generally rare, but can be found in 10% of AF patients [21-23,27]. Patients with atrial septal defects have AF in 10–15% of the cases [21]. There are also other congenital heart defects that increase the risk of AF [21,27].

Subclinical thyroid disease might increase the risk for AF [26]. Obesity is common with a prevalence of approximately 25% in AF patients [21,23], and seems to increase the risk of AF [26]. Sleep apnea may be a risk factor for AF. Possible causes are increased atrial pressure and size due to the apneas, or autonomic changes [21,26]. Chronic obstructive pulmonary disease has a prevalence of 10–15% in AF patients, and might be involved in the progression towards permanent AF [21,26]. Chronic renal disease affects 10–15% of patients with AF [21,26,27]. Renal insufficiency might also increase the risk of both ischemic events and bleeds [21].

### **1.1.2 Epidemiology**

AF is the most common arrhythmia with a prevalence that increases with age and that has been estimated to be approximately 2% of the adult population in several European countries [34]. In Sweden a prevalence of 2.9% of the adult population above 20 years of age has been reported [32]. The prevalence was higher in men than in women in all age groups. The mean age was approximately 75 years (men 71.9 years, women 82.2). The prevalence increased with age with a peak of 14.3% at 84 years [32]. Approximately 40 % of the AF-patients are above 80 years of age in Stockholm; they have a high risk for stroke, and complicating co-morbidities are also common [28,35]. There has been discussion about the prevalence of undetected asymptomatic atrial fibrillation. A large Swedish study found undiagnosed atrial fibrillation in 3.0 % of 75 year old Swedish citizens when screening with intermittent ECG recordings over 2 weeks [36].

### **1.1.3 Atrial fibrillation in the health care system**

Randomised trials as well as many observational studies have analysed selected patient groups, such as hospitalised patients or patients seeing cardiologists in selected centres participating in quality registers and clinical trials [30,31,37-45]. When new treatment alternatives are implemented in the health care system, such as non-vitamin K antagonist oral anticoagulants (NOACs) [37-39], it is important to remember that the pivotal trials leading to approval from the medical agencies have been conducted on relatively young patients, often with a good prognosis and without absolute or relative contraindications for warfarin treatment. Observational trials are therefore important to assess treatment effects in regular health care. Statistical methods are often used to reduce confounding and make the treatment groups comparable. However, assessments of patients from different parts of the health care system are important to evaluate the value of new treatments for all patients in routine care [35,46,47]

Patients with a diagnosis of AF are common throughout the health care system given the advanced age of the patients and the high prevalence of co-morbidities [26,28,35]. There is reason to believe that AF patients in regular health care differ from patients in randomized trials and/or observational registries [28,35], and population based studies describing the management of atrial fibrillation throughout entire health care systems have been lacking.

Many earlier observational studies of treatment routines and the risks of suffering stroke or severe bleeding have been conducted in hospital settings [30,31,40-43], even though many AF patients are treated in primary care [35,48-50]. The incidence and prevalence of AF depends on the health records chosen to identify patients with the diagnosis. Importantly, co-

morbidities included in the CHA<sub>2</sub>DS<sub>2</sub>VASc score may be missing without records from all healthcare providers, which could lead to underestimations of the stroke risk. Data from several consecutive years and derived from both inpatient care, specialist ambulatory care, and primary care are needed to accurately determine the prevalence of a certain disease when using healthcare registers [35,47,51].

#### **1.1.4 Cardioembolic stroke**

AF increases the risk of thromboembolism, especially embolic stroke. Antithrombotic treatment is often indicated for stroke prevention [21]. Traditionally, the risk for ischemic stroke was assessed using the risk scoring system CHADS<sub>2</sub>, but since 2010 the refined risk scoring system CHA<sub>2</sub>DS<sub>2</sub>VASc has been promoted instead [21].

##### **CHADS<sub>2</sub> score**

The previously used CHADS<sub>2</sub> score was calculated by adding 1 point for age above 75 years, 1 point each for a history of cardiac failure, hypertension, or diabetes, and 2 points for a history of TIA/ischemic stroke. The treatment of choice for individuals with high risk (CHADS<sub>2</sub> ≥ 2) of thromboembolism was oral anticoagulants [52], while treatment was considered for individuals with moderate risk (CHADS<sub>2</sub> = 1).

##### **CHA<sub>2</sub>DS<sub>2</sub>VASc score**

Since 2010 it is generally recommended that the thromboembolic risk of AF patients should be assessed by the CHA<sub>2</sub>DS<sub>2</sub>VASc risk scoring system (Table 1) [30,31,40,52]. According to the earlier ESC guidelines individuals with a score of 2 or more should be treated with an oral anticoagulant [52].

The CHA<sub>2</sub>DS<sub>2</sub>VASc risk score has been validated in several large registry based observational trials. However, analyses from Sweden have showed that the c-statistics for the composite thromboembolic endpoint only rose from 0.66 when using CHADS<sub>2</sub> to 0.67 with CHA<sub>2</sub>DS<sub>2</sub>VASc [30]. The results were almost identical in a similar Danish study [40]. With CHA<sub>2</sub>DS<sub>2</sub>VASc age ≥ 75 years counts as 2 (like a previous TIA/ischemic stroke), while age 65-74 years counts as 1. Additionally, female sex and vascular disease count as 1 each. With CHA<sub>2</sub>DS<sub>2</sub>VASc a greater proportion of patients with atrial fibrillation had an indication for anticoagulant treatment during the time period of this thesis [28,30,31]. Thus, patients with a definite indication increased from 65% when the risk was scored with CHADS<sub>2</sub> (score ≥ 2) to 85% when scored with CHA<sub>2</sub>DS<sub>2</sub>VASc (score ≥ 2) [28].

According to the ESC guidelines from 2010 and 2012 OAC treatment should be considered in AF patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1 (unless female sex is the only contributing factor). OACs should also be used instead of aspirin [52]. Recommendations in the AHA guidelines from 2014 are more moderate regarding treatment in patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1 [53]. This is supported by observational studies from Denmark and Sweden that failed to show any net clinical benefit of warfarin in individuals with CHA<sub>2</sub>DS<sub>2</sub>VASc scores 0-1, while there was a rising net clinical benefit with CHA<sub>2</sub>DS<sub>2</sub>VASc scores of 2 and above [41,42]. Other observational analyses addressing methodological issues in the definition of stroke have reached the same conclusion [54]. Also, aspirin-treated AF

patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1 in randomized trials had an annual incidence of systemic thromboembolism of only 0.9 %. The authors considered the risk low enough to consider withholding OAC treatment [55].

Risk assessments have in many studies been performed without access to diagnoses from primary care [30,31,41,42], which might lead to underestimation of the CHA<sub>2</sub>DS<sub>2</sub>VASc scores and overestimation of the benefit of treatment in low-risk patients. However, the debate is on-going whether to treat or not [56], and in Asia the risk seems to be higher than in Europe [57]. Age 65-74 is associated with the largest increase in relative risk for stroke in individuals with CHA<sub>2</sub>DS<sub>2</sub>VASc=1 (relative risk approximately 3), while other risk factors are only associated with small increases in relative risk (relative risk < 1.2) [52]. Therefore, it has been suggested that a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1 due to age 65-74 years, with a progressively increasing risk within the age span, should be considered an indication for anticoagulant treatment, while other factors are unlikely to confer a net clinical benefit [57].

The recently (October 2015) finalized Swedish guidelines [58] concur with the ESC guidelines from 2010 and 2012 and recommend OAC treatment for AF patients with CHA<sub>2</sub>DS<sub>2</sub>VASc scores of 2 and above and to consider treatment with a score of 1. However, these guidelines are even more restrictive against aspirin treatment which should not be used.

In 2016 the cut-off for treatment of women in the European guidelines was changed, as women were considered to have a definite indication for anticoagulant treatment at CHA<sub>2</sub>DS<sub>2</sub>VASc scores 3-9, and a possible indication at a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 2 [59]. The inclusion of female sex as a risk factor in the CHA<sub>2</sub>DS<sub>2</sub>VASc score although it does not affect the indication for treatment raises the question of the need of revising the risk scoring of AF patients [60]. As mentioned above the CHA<sub>2</sub>DS<sub>2</sub>VASc score does not improve the overall prediction compared to the older CHADS<sub>2</sub> score, while it greatly increases the population eligible for treatment. The more restrictive indication for anticoagulant treatment in the new ESC guidelines raises the issue of possible overtreatment of low-risk individuals even further.

Improved risk stratification incorporating biological biomarkers has been proposed as an alternative to the CHA<sub>2</sub>DS<sub>2</sub>VASc score for predicting stroke [61,62], and could possibly also be used to predict bleeding [63], but the clinical feasibility and usefulness of such an approach is still uncertain.

<b>Risk factor</b>	<b>CHADS<sub>2</sub> score</b>	<b>CHA<sub>2</sub>DS<sub>2</sub>VASc score</b>
Congestive heart failure/LV dysfunction	1	1
Hypertension	1	1
Age >75	1	2
Diabetes mellitus	1	1
Stroke/TIA/thrombo-embolism	2	2
Vascular disease		1
Age 65–74		1
Sex category (i.e. female sex)		1
<b>Maximum score</b>	<b>6</b>	<b>9</b>

**Table 1 - CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc score [21]**

### **1.1.5 Bleeding**

Risks of bleeding should also be considered when deciding whether to treat with antithrombotic drugs or to withhold treatment [21,52]. Data regarding the prognostic impact of bleeding in patients with AF appear to be lacking, but lessons can be learned from the adverse prognosis seen in patients with acute coronary symptoms that experience major bleeding [64]. Major bleeding may act as a marker of adverse outcomes in frail patients; but might also cause poor outcomes directly (from blood loss; haemorrhagic shock; anemia leading to reduced tissue oxygenation, and activation of sympathetic, vasoconstrictive and prothrombotic mechanisms) or indirectly through the negative impact of transfusions and/or interruption of treatment and failure to resume it [64-66].

The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly age >65 years, drugs/alcohol concomitantly) scale can be used to assess bleeding risk [21,52], but there are numerous other scores [67]. However, the risk for stroke and severe bleeding are often associated and the risk for stroke is usually more important for individual patients [28,41,42]. A HAS-BLED score of  $\geq 3$  is an indication of high risk. These high risk patients should be treated with “caution” and closer follow-up is warranted [21,52]. For practical purposes, reducing the risk of bleeding by attention to reversible risk factors should be the main focus when treating with antithrombotic agents [64]. As mentioned above, new methods for risk stratification including biological biomarkers might be used to assess the risk/benefit balance of both stroke and bleeding [61-63].

## 1.2 ANTITHROMBOTIC TREATMENTS

Despite solid documentation for warfarin and poor documentation for low-dose aspirin [68,69] several studies have suggested problems with undertreatment with OAC and overtreatment with aspirin in patients with AF [31,35,41-43,69]. The standard treatment for many years has been vitamin K-antagonists, such as warfarin, while low dose aspirin has been recommended as recourse when warfarin could not be used [68]. Analyses have shown that the proportion of patients treated with OACs started to increase already before the NOAC era [48].

	<b>Pivotal study publication year</b>	<b>EMA-approval</b>	<b>Swedish reimbursement</b>
<b>Dabigatran</b>	2009	April 2011	December 2011
<b>Rivaroxaban</b>	2011	December 2011	October 2012
<b>Apixaban</b>	2011	November 2012	May 2013

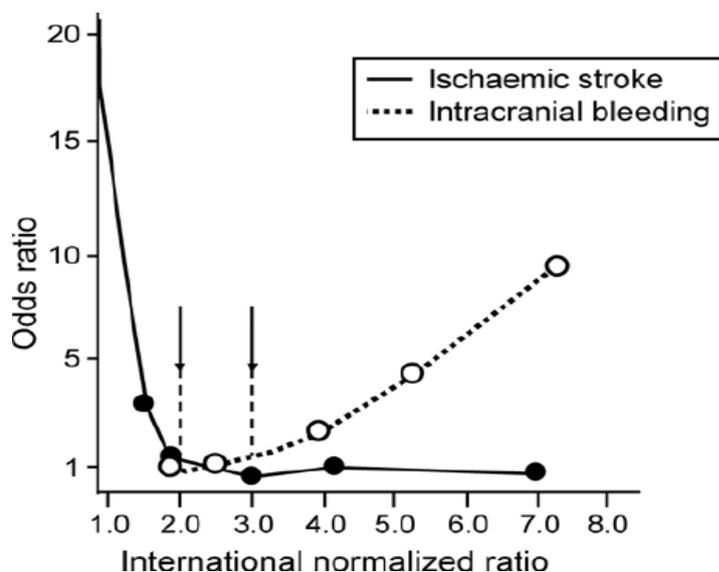
**Table 2 – The introduction of NOACs**

The introduction of NOACs since 2011 [37-39] (Table 2) has improved the possibility to provide adequate anticoagulant treatment of AF patients. With the introduction of NOACs more patients receive OAC treatment according to guidelines both internationally [70], and in Sweden (see Chapter 5.3). With the more aggressive treatment guidelines [52,53] overtreatment of low risk patients has also become an issue [35,54,57].

### 1.2.1 Warfarin

Warfarin or other vitamin-K antagonists were the only available alternatives for oral anticoagulant treatment during 65 years. Warfarin decreases the synthesis of the vitamin-K dependent clotting factors II, VII, IX, and X thereby decreasing the conversion of fibrinogen to fibrin [71].

Treatment with warfarin, as with all anticoagulant agents, implies balancing between risks for ischemic events and bleeding (Figure 1). Treatment with warfarin reduces the risk for stroke compared to both placebo and to aspirin according to meta-analyses of randomized trials [68]. Warfarin reduced the risk for stroke (ischemic and hemorrhagic) by 64% compared to placebo in an ITT-analysis; on treatment the risk was reduced by over 80 % with well managed warfarin treatment [68,72]. Compared to aspirin the relative risk reduction for stroke was 40% with warfarin (absolute risk reduction in primary prevention 0.7%, and in secondary prevention 7.0%), the risk of intracranial hemorrhage was doubled (absolute risk increase 0.2%), and all-cause mortality was reduced by 0.5% per year [68].



**Figure 1 – Odds ratios for ischemic stroke and intracranial bleeding related to International normalized ratio (INR) [72]**

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With time the quality of warfarin treatment and the outcomes have improved [73], as well as knowledge on how to address potential problems with the treatment [64,72,74]. Bleeding during warfarin treatment is primarily managed by securing adequate circulation, local control (e.g. endoscopic treatment or surgical haemostasis), and erythrocyte transfusion. The anticoagulant effect can be reversed by administering vitamin K intravenously. The INR will start to drop within 2 h and INR will be normalized within 12–16h. In the case of serious or life-threatening bleeding, immediate reversal can be achieved by the administration of prothrombin complex concentrates (PCCs) [64].

The randomized BAFTA study addressed the question of whether to treat old patients in whom the doctors had reservations about anticoagulant treatment with warfarin or aspirin. The population was still selected since the physicians had the choice to exclude the frailest patients, and only a minority of the possibly eligible patients above the age of 75 years were included [75]. However, the results were clear. Warfarin treatment halved the risk of suffering any stroke compared to aspirin treatment without significant differences in bleeding or mortality in patients above the age of 75 [75].

Yet there has been, and still is, reluctance to treat old and frail patients with OACs [69].

### 1.2.2 Non-vitamin K antagonist oral anticoagulants (NOACs)

With the introduction of NOACs [37-39] there are now more alternatives when choosing OAC treatment for AF patients and a possibility that more AF patients could be adequately treated. The directly acting thrombin inhibitor dabigatran received reimbursement in Sweden in December 2011 for treatment of AF. The directly acting factor Xa inhibitors rivoraxaban, and apixaban received reimbursement in October 2012 and in May 2013, respectively. The pharmacological properties of the three NOACs are further discussed below.

<b>Study design</b>	<b>Dabigatran (D) RE-LY [37]</b>	<b>Apixaban (A) ARISTOTLE [39]</b>	<b>Rivaroxaban (R) ROCKET-AF [38]</b>
<b>No. of patients</b>	18 113	18 201	14 264
<b>Age, years</b>	71 (mean)	70 (median)	73 (median)
<b>Prior warfarin</b>	50%	57%	62%
<b>Compared treatments</b>	D 150 mg x 2 D 110 mg x 2 Warfarin (INR 2-3)	A (2.5-) 5 mg x 2 Warfarin (INR 2-3)	R (15-) 20 mg x 1 Warfarin (INR 2-3)
<b>TTR, mean</b>	64%	62%	55%
<b>Dose reduction</b>	Randomization	4.7%	20.8% (?)
<b>Follow-up, years</b>	2.0 (median)	1.8 (median)	1.6 (median)
<b>CHADS<sub>2</sub> score</b>	2.2±1.2 32% CHADS <sub>2</sub> = 0-1	2.1±1.1 34% CHADS <sub>2</sub> = 1	3.5±0.9 0% CHADS <sub>2</sub> = 0-1

**Table 3 – Study design of the NOAC pivotal trials [37-39]**

All three NOACs have demonstrated similar or better stroke prevention and similar or lower risk for serious bleeding compared to warfarin in multinational studies involving 6 000-9 000 patients per treatment group and median follow-up times of 1.6-2 years [37-39] (Table 3). The risk for intracranial hemorrhage was lower with all three NOACs, while gastrointestinal bleeding was more frequent with the standard dose of dabigatran (150mg x2) and with rivaroxaban; but not with apixaban [37-39] (Table 4). The quality of warfarin treatment in the comparator arms, measured as Time in Therapeutic Range (TTR), has been highly variable between regions [37-39,76-78] (Table 3). Substudies have demonstrated that superiority of NOACs was found in centers and/or regions with poor TTR, while the results were similar in centers with optimal TTR and in Western Europe [76,78]. The mean TTRs were 75-80% in Sweden in all three pivotal trials, which is consistent with results from patients in the quality register Auricula [79]. However, quality registers like Auricula are only used in some regions and centers in Sweden, and the quality of warfarin treatment elsewhere remains less well documented.

<b>Outcomes</b>	<b>Dabigatran (D) RE-LY [37]</b>	<b>Apixaban (A) ARISTOTLE [39]</b>	<b>Rivaroxaban (R) ROCKET-AF [38]*</b>
<b>Absolute outcomes vs. warfarin (%/year)</b>			
<b>Stroke/systemic embolism</b>	D110: 1.53 vs 1.69 D150: 1.11 vs 1.69	1.27 vs 1.60	2.1 vs. 2.4 (on treatment)
<b>Hem. stroke</b>	D110: 0.12 vs 0.38 D150: 0.10 vs 0.38	0.24 vs 0.47	0.26 vs 0.44 (on treatment)
<b>Total död</b>	D110: 3.75 vs 4.13 D150: 3.64 vs 4.13	3.52 vs 3.94	1.87 vs. 2.21 (on treatment) 4.5 vs. 4.9 (ITT)
<b>Relative outcomes vs. warfarin (RR (95% CI))</b>			
<b>Stroke/systemic embolism</b>	D150: 0.66 (0.53-0.82) D110: 0.91 (0.74-1.11)	0.79 (0.66-0.95)	0.88 (0.75-1.03) according to ITT; 0.79 on treatment
<b>Ischemisk or unspecified stroke</b>	D150: 0.76 (0.60-0.98) D110: 1.11 (0.89-1.40)	0.92 (0.74-1.13)	0.94 (0.75-1.17) (ischemic only)
<b>Hemorrhagic stroke</b>	D150: 0.26 (0.14-0.49) D110: 0.31 (0.17-0.56)	0.51 (0.35-0.75)	0.59 (0.37-0.93)
<b>Myocardial infarction</b>	D150; 1.38 (1.00-1.91) D110: 1.35 (0.98-1.87)	0.88 (0.66-1.17)	0.81 (0.63-1.06)
<b>Death</b>	D150: 0.88 (0.77-1.00) D110: 0.91 (0.80-1.03)	0.89 (0.88-0.99)	0.85 (0.70-1.02)
<b>Bleeds, serious</b>	D150: 0.93 (0.81-1.07) D110: 0.80 (0.69-0.93)	0.69 (0.60-0.80)	1.04 (0.90-1.20)
<b>Gastrointestinal bleeds, serious</b>	D150: 1.50 (1.19-1.89) D110: 1.10 (0.86-1.41)	0.89 (0.70-1.15)	(3.2 vs 2.2%, p<0.001)
<b>Minor bleeds</b>	D150: 0.91 (0.85-0.97) D110: 0.79 (0.74-0.83)	?	?

\*The primary comparisons in the ROCKET-AF trial were done on treatment, not according to intention-to-treat (ITT)

**Table 4 –Absolute and relative outcomes in the NOAC pivotal trials [37-39]**

The optimal dosages of the NOACs remain unclear. For dabigatran the patients were randomized to either 150 mg twice daily or 110 mg twice daily in the RE-LY trial [37]. The approved standard dosage is 150 mg twice daily both in Europe and the US, but the recommendations regarding dose reduction differ. In Europe dose reduction to 110 mg twice daily is warranted in patients above the age of 80 years [80]. Dose reduction should also be considered in patients above the age of 75 years, in patients with moderate renal insufficiency or in patients with increased bleeding risk [80]. In the U.S.A. the 110 mg dose was not approved, and dose reduction should only be considered in patients with severe renal insufficiency (eGFR 15-30 ml/min); the recommended dose is then 75mg twice daily [81].

For rivaroxaban the standard dosage is 20 mg once daily. Dose reduction to 15 mg once daily was recommended for patients with eGFR 30-49 ml/min in the ROCKET trial [38,82]. There is no published documentation regarding the proportion of patients with dose

reduction, but 20.8% of the study population had reduced renal function (eGFR 30-49 ml/min) [38].

Apixaban is recommended with the standard dosage 5 mg twice daily. The dosage should be reduced to 2.5 mg twice daily in patients with two of the following criteria: age  $\geq$  80 years, weight  $\leq$  60 kg, serum creatinine  $\geq$  133  $\mu$ mol/L [83]. Only 4.7% of the patients in the ARISTOTLE trial received the reduced dosage [39].

Dabigatran has also been investigated in patients with mechanical valve prosthesis, with or without AF [84]. The trial was interrupted due to a higher incidence of stroke with dabigatran, despite higher dosages guided by plasma concentration measurements to guarantee therapeutic levels. Warfarin remains the only available treatment for these patients.

Apixaban has demonstrated better stroke prevention without significantly more bleeding compared to aspirin in patients in whom the benefit of OAC treatment was unclear to the physicians [85]. Noteworthy, the patients were relatively young (mean age 70 years), with a mean CHADS<sub>2</sub> score of 2.0 and good prognosis; and without anemia, hemorrhagic tendencies, alcohol abuse etc. This differs from many of the aspirin treated patients in routine health care who often are much older, frequently with absolute or relative contraindications, and an overall poor prognosis [28].

Questions have been raised regarding the outcomes with NOACs in unselected and potentially different patients in routine care where follow-up is sparse, while warfarin treatment implies regular PT-INR controls and tighter contacts with health care personnel. There has also been an interest in comparing NOACs with warfarin in countries with high quality of treatment, like Western Europe.

Some early observational outcome studies were conducted in Europe and the U.S.A. in different health care settings regarding the use of dabigatran or rivaroxaban in routine care. Almost all results have been consistent with the pre-registration clinical trials and did not raise any important safety concerns [44,45,86-93]. However, one study showed that warfarin treated patients with earlier TIA/ischemic stroke who switched to dabigatran had higher rates of ischemic stroke [94]. Dabigatran and rivaroxaban has in some studies been associated with a lower risk for ischemic stroke than warfarin [86,90]. Intracranial bleeding has been less frequent with dabigatran than with warfarin [86,90,91,93]. GI bleeding has been similar [88,93]; or more common with dabigatran [86,90-92], especially in subgroup analyses of the elderly [86,88]. Two studies found the overall bleeding rate to be higher with dabigatran than with warfarin [91,92], but other studies found similar [44,87,90] rates. Rivaroxaban has been associated with a similar bleeding rate as warfarin [44,87].

More recently two large observational outcome studies in Europe and the U.S.A. have compared dabigatran, rivaroxaban and apixaban to warfarin treatment in routine care and found that they seem to be both safe and effective alternatives to warfarin [95,96]. Both studies used propensity score matching. NOAC patients with reduced doses were excluded in the Danish study of patients in hospital associated care [95], while dose reduction was included in the propensity score matching in the study of patients in a U.S. insurance claims database [96]. Thus, data on the consequences of dose reductions in elderly and frail NOAC treated patients with the largest risks of stroke were limited.

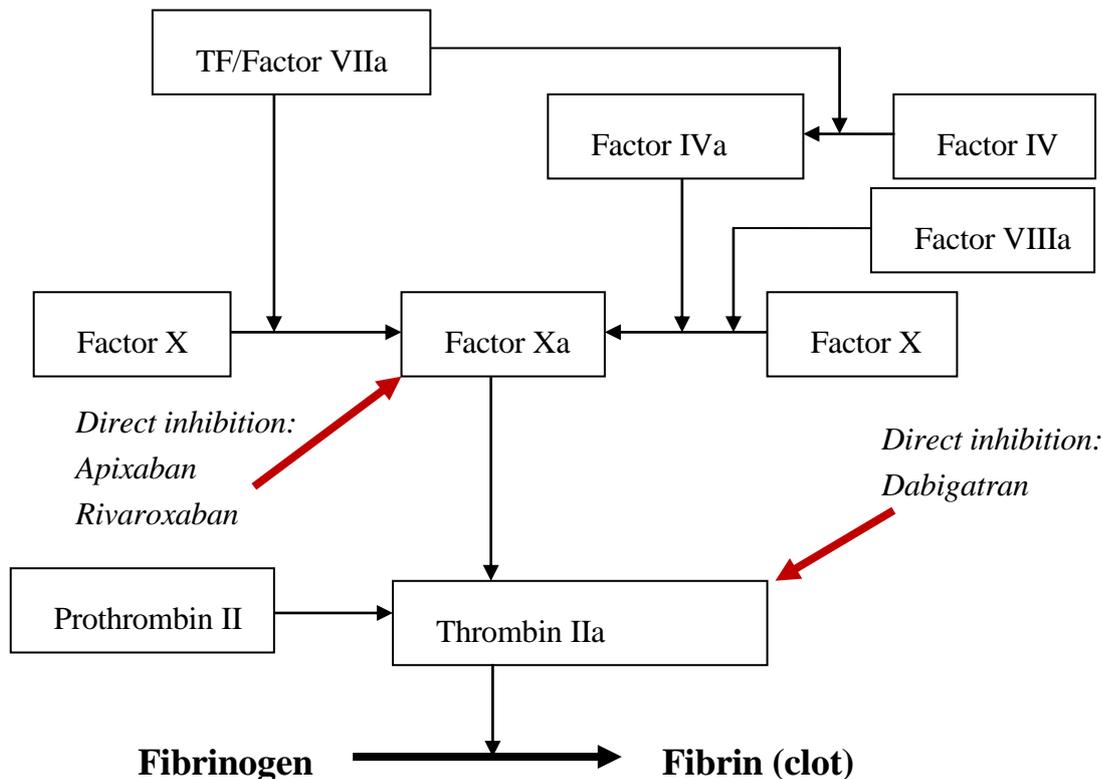
Another large study evaluated only bleeding risks with each NOAC compared to warfarin and found lower risks with dabigatran and apixaban, but not with rivaroxaban. The results were similar regardless of whether the NOAC patients received standard or reduced doses [97].

Studies comparing the NOACs are also being performed. An observational head-to-head study showed that treatment with rivaroxaban 20 mg once daily was associated with statistically significant increases in intracranial hemorrhage and major extracranial bleeding, including major gastrointestinal bleeding, compared to dabigatran 150 mg twice daily [98].

**Pharmacology**

Dabigatran is a directly acting thrombin inhibitor while rivaroxaban and apixaban are directly acting factor Xa inhibitors [99] (Figure 2, Table 5). All three NOACs might require dose reduction in patients with renal insufficiency, and they have not been documented in patients with eGFR < 25-30 ml/min [37-39,80,82,83]. Dabigatran is 80% dependent on renal elimination. Rivaroxaban and apixaban are less dependent on renal elimination (on average 35% and 27%, respectively), but more dependent on hepatic/biliary function [100]. The average half-lives are 12-17 hours for dabigatran, 5-9 hours (-13 hours in the elderly) with rivaroxaban, and 9-14 hours with apixaban [100]. The half-lives are longer in patients with decreased renal function, especially with dabigatran treatment.

*Warfarin decreases the synthesis of vitamin-K dependent coagulation factors prothrombin II, VII, IX, X, as well as protein C and S.*



**Figure 2 – Oral anticoagulants and the coagulation cascade [101]**

Another factor of importance is the bioavailability where dabigatran has very low bioavailability (3-7%), rivaroxaban almost total bioavailability with food (but only 66% without food), and apixaban has a bioavailability of  $\approx 50\%$  (not dependent on food) [80,82,83,99]. Low bioavailability might lead to considerable inter- and intraindividual variability in plasma concentrations, which is the case for dabigatran [102].

Drug-drug interactions by means of the transport protein P-gp are present for all NOACs, while the factor Xa inhibitors also interact through the CYP3A4 enzyme. Clinically important interactions exist or can be expected with antiarrhythmic agents such as dronedarone and amiodarone, or the non-selective calcium antagonists verapamil or diltiazem. HIV treatments and oral antifungal drugs also present clinically important interactions, if not as common, with the factor Xa inhibitors [80,82,83,100].

The variability is important with dabigatran. The plasma concentration varies 10 to 20-fold between individuals who are dosed according to recommendations [102, 103]; and the plasma concentration has been shown to relate to rates of stroke and bleeding in the RE-LY study [102]. The interindividual variability is moderate with rivaroxaban (30-40%) [82]. Apixaban has the lowest variability (20 % intraindividually, 30 % interindividually) [83].

	<b>Dabigatran</b>	<b>Apixaban</b>	<b>Rivaroxaban</b>
<b>Pharmacodynamics</b>			
Mechanism of action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Antidote	Idarucizumab	No	No
Reversal of effect	Idarucizumab Hemodialysis	Prothrombin complex concentrate (PCC) possible	Prothrombin complex concentrate (PCC) possible
<b>Pharmacokinetics</b>			
Bioavailability	3-7% (mean 6,5%)	50% (mean)	66% fasting 100% with food
Time to maximum concentration	2 h	1-4 h	2-4 h
Half-life	12-17 h; important prolongation in renal insufficiency	9-14 h; prolongation in renal insufficiency	5-9 h (-13 h in elderly); prolongation in renal insufficiency
Elimination	Renal (80 %).	1/4 renal. 3/4 non-renal	1/3 renal 2/3 hepatic
Standard dose (atrial fibrillation)	150 mg BID	5 mg BID	20 mg OD
Dose reduction	110 mg BID, if age $\geq$ 80 years or verapamil; consider when eGFR 30-49 mL/min, weight <50 kg, high risk of bleeding	2,5 mg BID if two of the following: S-krea $\geq$ 133 $\mu$ mol/L, age $\geq$ 80, weight $\leq$ 60 kg.	15 mg OD if eGFR 30-49 mL/min*.
Plasma concentration-effect data	Yes	No	No
Trough plasma concentrations	Mean: 91 ng/mL 25-75 percentile: 61-143 ng/mL High bleeding risk > 200 ng/mL	Not available	Mean: 32 ng/mL 5-95 perc.: 6-239 ng/mL High bleeding risk > 200 ng/mL
Interactions	P-glycoprotein inhibitors (P-gp): amiodarone/dronedaron, verapamil/diltiazem.	CYP3A4 or P-gp inhibitors increase and inducers decrease plasma concentrations	CYP3A4 or P-gp inhibitors increase and inducers decrease plasma concentrations
Coagulation analyses	Hemoclot TI	Anti-FXa.	Anti-FXa.

Prothrombin complex concentrate (PCC), twice daily (BID), once daily (OD), Estimated glomerular filtration rate (eGFR), P-glycoprotein inhibitors (P-gp)

**Table 5 – Pharmacological properties of the NOACs [99,100]**

## **Monitoring of NOACs**

Monitoring of NOACs with plasma concentration measurements is not needed in routine care. However, direct (drug measurements) and indirect (derived from coagulation tests) plasma concentration measurements have been developed for evaluation of drug exposure in acute situations and/or before surgical procedures [103-105]; or to provide information for dose adjustments in special cases.

Normal to high concentrations of dabigatran can be determined indirectly with Hemoclot TI, while low concentrations demand direct drug analysis by LC-MS/MS [105]. For rivaroxaban and apixaban special anti-Xa tests have been developed [100] and drug analysis with LC-MS/MS is also available. Plasma concentration-effect relationships have been documented for dabigatran [102], but not for rivaroxaban or apixaban.

### **1.2.3 Low-dose aspirin**

There is solid documentation of poor efficacy with aspirin for stroke prevention in AF [69]. A meta-analysis has indicated only approximately 20 % relative risk reduction compared to placebo [68]. Compared to aspirin, warfarin [68,75] or apixaban [85] provide substantially better protection against stroke without substantial increases in bleeding. Guidelines have since the comparative randomized trials in the 1990s recommended OAC over aspirin treatment [68], and recent guidelines have emphasized the importance of OAC treatment [52,53]. Still, aspirin has been widely used, even after the introduction of NOACs [35, 69]. Complicating co-morbidities such as cancer, dementia, anemia, alcohol abuse, renal disease, earlier severe bleeding and frequent falls has been shown to be more frequent in aspirin treated patients [28]. This suggests that physicians often might be reluctant to initiate OAC treatment in frail patients [28,69]. It should be mentioned that aspirin is still a valid treatment for ischemic heart disease [106], which is a common co-morbidity in AF-patients [42].



## 2 AIMS

### 2.1 GENERAL AIM

The general aim of this thesis was to increase knowledge on the use and outcomes with available antithrombotic treatments in AF patients in routine care in the Stockholm health care region before and after the introduction of NOACs.

### 2.2 SPECIFIC AIMS

- To describe the AF population in the Stockholm health care system: demographics, co-morbidity, risk stratification, antithrombotic treatment; and to investigate which implications data from primary care may have for analyses of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc risk scores.
- To evaluate and discuss the outcomes of patients with non-valvular AF receiving treatment with warfarin, aspirin or neither related to different CHA<sub>2</sub>DS<sub>2</sub>VASc-scores, age and complicating co-morbidities prior to the introduction of NOACs.
- To describe OAC treatment in patients with non-valvular AF in the Stockholm health care region before and after the introduction of NOACs.
- To compare the persistence with all OACs in patients with AF and a definite indication for OAC treatment (CHA<sub>2</sub>DS<sub>2</sub>VASc score 2-9); and to compare adherence to treatment with NOACs, evaluate the use of aspirin, and investigate patient characteristics associated with poor persistence.
- To compare outcomes regarding both effectiveness and safety with NOAC versus warfarin treatment in OAC-naïve patients with non-valvular AF in routine care, with special considerations regarding old and frail patients; and to explore the effects of dose reductions when prescribing NOACs.

## **3 MATERIAL AND METHODS**

### **3.1 SETTING**

The studies included in this thesis were all conducted in Sweden where healthcare is publically financed and accessible to all residents. Since the second half of the 20th century national health registers were developed. These registers have mandatory reporting for healthcare providers and are managed by the National Board of Health and Welfare. The unique personal identification number can be used to merge data from various registers and from medical records so that study subjects can be followed in the health care systems over time. The coverage is almost complete. These registers have provided data for numerous epidemiological studies and are considered to be of high quality [107-109].

### **3.2 PERSONAL IDENTIFICATION NUMBER**

The personal identification number is a unique identifier which is used in all public administration in Sweden for all citizens and immigrants who become permanent residents or intend to stay in Sweden for at least one year. It consists of the birth date and an identification number. Thus, information from all administrative and many other registers can be linked to an individual. When conducting research, the data is generally anonymised or pseudonymised (the encryption key is kept with a third party to allow for additional record linkage).

### **3.3 DATA SOURCES**

The data sources for the individual studies consist of four research databases based on record linkage of health care registry data.

#### **3.3.1 National Patient Register (NPR)**

The National Patient Register (NPR) is managed by the National Board of Health and Welfare and consists of codes for diagnoses and procedures on a national level. The NPR is well validated [108] and includes hospital discharges since 1964. The register also covers outpatient visits to both private and public caregivers from 2001. Diagnoses and procedures in primary care are, however, not covered in the NPR.

### **3.3.2 Causes of Death Register**

The Causes of Death Register (The National Board of Health and Welfare) contains information on all deaths since 1961. The register covers all Swedish residents, regardless of citizenship or of whether the death occurred in Sweden or abroad [110].

### **3.3.3 Prescribed Drug Register**

The Prescribed Drug Register (The National Board of Health and Welfare) contains complete data on all prescription drugs dispensed in Sweden from July 2005: amounts, dosages, expenditures, reimbursement, age and gender of the patient regardless of reimbursement status, co-payment and prescriber category [109]. The information has a high validity as almost 100% of the prescriptions are recorded together with a unique personal identification number.

### **3.3.4 VAL**

The administrative health data register of the Stockholm health care region (Vårdanalysdatabasen, VAL) was used in all four studies. VAL contains pseudonymized data regarding diagnoses, age, sex, prescription claims, hospitalizations and other healthcare consultations, migration and death for all individuals in the Stockholm health care region. Diagnoses from primary care are available since 2003, and for secondary care (outpatient visits and hospitalization) since 1993. The data for secondary care in VAL is the same as that found in the National Patient Register for the Stockholm region, and therefore well validated for use in epidemiological studies [107-108]. VAL also contains individual-level data on all prescription drugs dispensed anywhere in Sweden to inhabitants in the region since July 2010: amounts, expenditures and reimbursement, the age and gender of the patient, co-payments and prescriber category. This information is derived from the national Prescribed Drug Register [109].

In Studies I and II data from VAL were linked with data from the NPR [107-108] to cover other parts of Sweden, the Prescribed Drug Register [109], and the Causes of Death Register [110]. The reason for this record linkage was mainly that VAL did not include prescribed drugs before 2010. In study III-IV VAL was used without additional record linkage.

## **3.4 STUDY POPULATIONS**

Studies I-II included all patients with non-valvular AF recorded in inpatient care, specialist ambulatory care or primary care in the Stockholm health care region. In study I 43 353 patients with a diagnosis of non-valvular AF during 2006-2010 were included. Study II included 41 810 patients with a diagnosis of non-valvular AF recorded during 2005-2009 and outcomes were assessed in 2010.

Studies III-IV included individuals in the Stockholm health care region having initiated antithrombotic treatment and with a diagnosis of non-valvular AF prior to initiation. Study III included all first claims of either warfarin (n=9969), dabigatran (n=2701), rivaroxaban

(n=2074), apixaban (n=1352), or aspirin (n=4540) from April 2011 until December 2014, in individuals with CHA<sub>2</sub>DS<sub>2</sub>VASc-scores of 2-9. During this period there were no specific regional recommendations regarding choice of NOACs. Study IV was restricted to OAC naïve patients who initiated treatment with a NOAC (n=9292) or warfarin (n=12938) from January 2012 until December 2015.

### **3.5 METHODS**

This thesis consists of four population based studies of patients with non-valvular AF.

Study I was a cross-sectional study. The prevalence of AF in different levels of health care and the importance of diagnoses from primary health care in the assessment of CHA<sub>2</sub>DS<sub>2</sub>VASc-scores were investigated; as well as the demographic characteristics of AF patients and their antithrombotic treatment at different CHA<sub>2</sub>DS<sub>2</sub>VASc-scores.

Study II was a cohort study describing the risks of ischemic stroke, serious bleeds, or death with warfarin, aspirin, or no antithrombotic treatment during 2010. The risks were stratified by CHA<sub>2</sub>DS<sub>2</sub>VASc-scores, age and complicating co-morbidities.

Study III was a cohort study comparing the persistence and adherence to different OAC treatments and low-dose aspirin. Prescription claims were analyzed both crudely and in multivariate analysis adjusting for age, sex, prescriber category, prior OAC treatment, and number of drugs claimed by the patients.

Finally, study IV was a cohort study comparing the effectiveness and safety of NOAC and warfarin treatment. Cox regression analyses were performed evaluating TIA/ischemic or unspecified stroke/death (adjusted for individual CHA<sub>2</sub>DS<sub>2</sub>VASc criteria with age as a continuous variable), and severe bleeds (adjusted for sex and adapted HAS-BLED criteria with age as a continuous variable); and for components of the composite co-primary endpoints. Subgroup analyses were performed focusing on patients 80 years and above, and patients with a prior severe bleed. Exploratory analyses of dose reductions of NOACs were conducted and dabigatran, rivaroxaban and apixaban were compared individually with warfarin treatment.

### **3.6 STATISTICAL METHODS**

In all four studies descriptive statistics were used and data were presented as proportions or mean values with 95% confidence intervals (CI), as appropriate. In study II two-sample tests of proportions for relative frequencies were also performed.

In study III multivariate logistic regression was employed to evaluate persistence in 10 444 OAC initiations (9 710 individual patients) at one year. Adjustments were made for age, sex, prior OAC treatment, prescription from primary care, and the total numbers of drugs claimed by the patients. Persistence was defined as the proportions of patients on each drug who

claimed the treatment in question during 6 month intervals, excluding those who died during the interval. Complementary analyses were performed for OAC naïve patients and also with the inclusion of patients who died during follow-up in the definition of persistence. In order to confirm the model individual patients on first and second line OAC treatment were compared separately. Sensitivity analyses were performed, comparing persistence with 3, 4 or 6 month intervals in the assessment of prescription claims. Different definitions of adherence were compared using two-sample tests of proportions for relative frequencies.

In study IV Cox regression analyses were conducted for crude and adjusted estimates evaluating two co-primary endpoints: the composite endpoint TIA/ischemic or unspecified stroke/death (adjusted for individual CHA<sub>2</sub>DS<sub>2</sub>VASc criteria and age as a continuous variable), and severe bleeds (adjusted for sex and adapted HAS-BLED criteria with age as a continuous variable). Secondary analyses were performed for the components of the co-primary endpoints. Patients were censored at primary endpoints; migration out of the region; when claiming a drug from the comparator group(s) or low-dose aspirin; or at the end of follow-up (December 31, 2015).

Alternative analyses were performed of outcomes during the first year of treatment, outcomes according to the intention-to-treat principle (no censoring for claims of other OAC treatments or low-dose aspirin), fully adjusted outcomes, as well as an analysis of overall mortality as a non-competing end-point in order to address the risks of informative censoring and/or confounding. Propensity score adjusted analyses yielded essentially the same results.

To evaluate possibly non-proportional hazards plots of Schoenfeld residuals were analysed and Cox regression with covariate-time interactions was performed.

The statistical analyses were performed using Excel 2007 (Microsoft Corporation, Redmond, WA), SAS Enterprise Guide 4.2, or SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC).

## ETHICAL CONSIDERATIONS

The results in this thesis are based on record linkage from databases with health care registry data (see 3.3 - Data sources). All studies were approved by the Regional Ethical Review Board in Stockholm (Study I-II: EPN 2010/1158-31/2, Study III-IV: EPN 2015/579-31/2)

These databases include diagnoses registered at outpatient health care consultations and hospital discharges, as well as claims of prescription drugs at any pharmacy in Sweden. The databases are pseudonymised, which means that the personal identification numbers are encrypted with a database encryption key which allows the possibility to update the databases with additional information if needed. The encryption key is managed by a third-party key manager and the researchers never come in contact with identifiable data. The analyses were performed on a local password protected computer. The raw data are transferred to a CD and archived after the end of the studies.

All analyses are presented at the group level and individual prescribers or patients can never be identified. Informed consent was not applicable since the patients are not identified and the studies comprised thousands of individuals. However, all studies were approved by the Regional Ethical Review Board in Stockholm and a personal data permit has been obtained from the Public Healthcare Services Committee, Department of Healthcare development of the Stockholm County Council.

There is a risk of breaching personal integrity when studying data from health care registries. However, all analyses were performed on encrypted data and grouped such that no data can be derived to any specific patient.

Some prescribers might experience a breach of integrity if inadequate compliance with guidelines is identified. However, no individual prescribers can be identified and no reporting of results at a prescriber level has been done.

The major ethical question regards the practice of not obtaining informed consent from patients when conducting large registry based epidemiological studies. Some individuals might feel that investigations of their age and sex in relation to their diagnoses and treatments constitute an invasion of privacy. This thesis concerns antithrombotic treatment for atrial fibrillation which probably is less sensitive than analyses of crime, abuse, psychiatric conditions or psychiatric drugs, but the objection might still exist.

Arguments against obtaining informed consent are that the large amount of patients would demand vast resources, which would make it impossible to conduct large academic registry based studies. An important argument for registry studies is that population based registries include patients that might be difficult to study under other conditions, i.e. patients with dementia, addictions, severe illnesses or decreased autonomy; and thus provide excellent complements to randomized controlled studies with selected, often homogenous and rather

uncomplicated patients. Loss of patients in registry based studies, especially of patients that are difficult to include in other studies, would significantly decrease the utility value of these studies.

In order to send letters of informed consent the individuals in the databases would have to be identified. It is possible that some individuals would see this identification and letter as a larger breach of integrity than to have anonymously been included in a large scientific material.

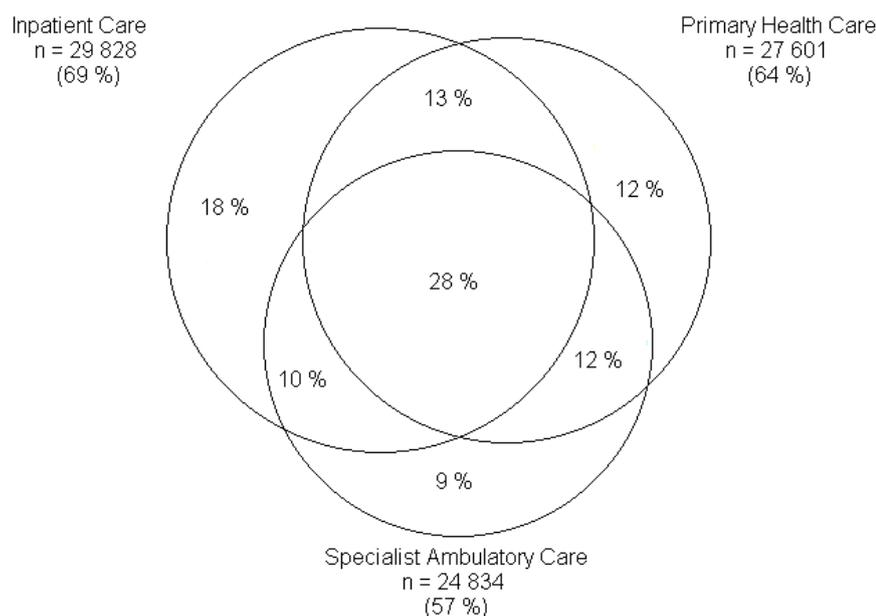
There is no direct benefit for the individuals included in the four studies of this thesis. However, the findings might contribute to better thromboprophylactic treatment for patients with AF in the future, whether they were included in the studies or not.

## 4 RESULTS

### 4.1 STUDY I

In Study I we described the AF population in the Stockholm health care region, and investigated the importance of diagnoses from primary health care in the assessment of CHA<sub>2</sub>DS<sub>2</sub>VASc-scores.

During a 5-year interval (2006-2010) 43 353 patients with a diagnosis of non-valvular AF could be found in inpatient care, specialist ambulatory care or primary care, with a grossly equal distribution between the levels of care (Figure 3). Of interest, 64% of the entire cohort of patients with AF had the diagnosis in primary care, and 12% of the patients had the diagnosis only in primary care (Figure 3).



**Figure 3 - Overlap between inpatient care, primary health care and specialist ambulatory care of the prevalences of a diagnosis of non-valvular atrial fibrillation during the years 2006–2010 among 43 353 patients who were alive at the end of 2010 in the Stockholm health care region.**

Warfarin appeared to be underused and aspirin overused. In 2010 warfarin prescriptions were claimed by 47.2%, and aspirin by 41.6% of the entire cohort. On the other hand, many patients with a doubtful indication received OAC treatment: 34% of patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1 and 20% with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 0 had warfarin, despite

poor documentation of clinical benefit. Aspirin was more frequently used instead of warfarin among women and elderly patients.

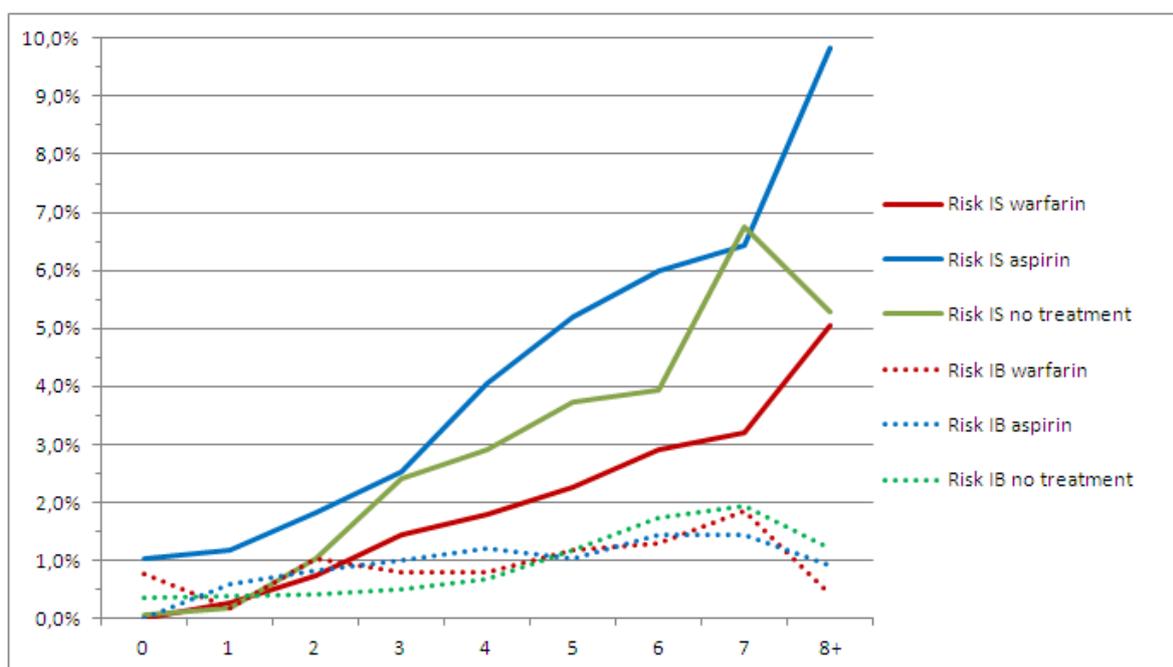
The mean CHA<sub>2</sub>DS<sub>2</sub>VASc-score was 3.82 (4.67 for women and 3.14 for men). Registry CHA<sub>2</sub>DS<sub>2</sub>VASc scores were underestimated without co-morbidity data from primary care (Table 6). The mean CHA<sub>2</sub>DS<sub>2</sub>VASc-score of patients with a diagnosis only in inpatient care or specialist ambulatory care increased from 3.63 to 3.83 when comorbidities registered in primary care were added. This underestimation of CHA<sub>2</sub>DS<sub>2</sub>VASc-scores might thereby have overestimated treatment benefits in low-risk patients in earlier studies.

CHA <sub>2</sub> DS <sub>2</sub> VASc	Excluding diagnoses from primary care		Including diagnoses from primary care	
0	6.95%	(6.70%-7.21%)	6.34%	(6.09%-6.58%)
1	10.51%	(10.21%-10.82%)	9.62%	(9.32%-9.92%)
2	13.80%	(13.45%-14.14%)	12.49%	(12.16%-12.82%)
3	16.61%	(16.24%-16.98%)	15.14%	(14.79%-15.50%)
4	17.58%	(17.20%-17.96%)	17.43%	(17.06%-17.81%)
5	14.84%	(14.49%-15.20%)	16.09%	(15.72%-16.46%)
6	10.66%	(10.35%-10.97%)	11.89%	(11.57%-12.22%)
7	5.94%	(5.70%-6.18%)	6.96%	(6.71%-7.22%)
8	2.51%	(2.35%-2.66%)	3.25%	(3.08%-3.43%)
9	0.60%	(0.52%-0.67%)	0.77%	(0.68%-0.85%)

**Table 6 - CHA<sub>2</sub>DS<sub>2</sub>VASc scores in live patients diagnosed with non-valvular atrial fibrillation in special ambulatory care and/or inpatient care 2006-2010. The scores suggest that patients had no (score = 0), possible (score = 1) or definite (score ≥ 2) indications for anticoagulant treatment. Comparison of scores obtained when excluding and including diagnoses from primary care. 38 337 unique individuals. Values within parentheses are 95% CI.**

## 4.2 STUDY II

In Study II, we investigated the stratified risks for stroke and bleeding with warfarin, low-dose aspirin or no treatment at different CHA<sub>2</sub>DS<sub>2</sub>VASc-scores (Figure 4), and in patients with very high age or complicating co-morbidities (Table 7). The observations confirmed earlier findings of undertreatment with warfarin.



**Figure 4 - Risks of suffering ischemic stroke (IS) and intracranial bleeding (hemorrhagic stroke + traumatic intracranial bleeding) (IB) during 2010 in 39 875 AF patients with warfarin, aspirin or no treatment (clopidogrel excluded).**

Half of the high-risk patients (CHA<sub>2</sub>DS<sub>2</sub>VASc-scores  $\geq 2$ ) treated with aspirin were obvious candidates for anticoagulant treatment with no identified contraindications; they had a high risk for ischemic stroke (4.0%), a low bleeding risk (1.8%), and a moderate mortality rate (8.4%) (Table 7). The other half of the aspirin treated patients had possible or probable contraindications and high risks for ischemic stroke (5.2%), bleeding (5.0%) and death (19.3%) (Table 7). The issue of undertreatment with anticoagulants is difficult to evaluate in such patients, and the risk/benefit is less advantageous compared to uncomplicated patients.

Outcomes during 2010	Warfarin		Risk ratio (complicated/uncomplicated)	Aspirin		Risk ratio (complicated/uncomplicated)
	Uncomplicated	Complicated		Uncomplicated	Complicated	
<b>n</b>	10024	4189		6551	6173	
<b>Ischemic stroke</b>	2.0(1.7-2.3)%	2.1(1.6-2.5)%	1.0 (0.8-1.3)	4.0(3.5-4.4)%	5.2(4.6-5.8)%	1.3 (1.1-1.5)
<b>Thrombo-embolism</b>	3.0(2.6-3.3)%	3.1(2.6-3.6)%	1.0 (0.8-1.3)	5.5(5.0-6.1)%	6.8(6.1-7.4)%	1.2 (1.1-1.4)
<b>Hemorrhagic stroke</b>	0.5(0.4-0.6)%	0.9(0.6-1.2)%	1.8 (1.2-2.8)	0.4(0.2-0.5)%	1.0(0.8-1.3)%	2.7 (1.7-4.2)
<b>Traumatic intracranial bleeding</b>	0.3(0.2-0.4)%	0.6(0.3-0.8)%	1.8 (1.1-3.0)	0.2(0.1-0.3)%	0.7(0.5-0.9)%	3.4 (1.8-6.4)
<b>Any severe bleeding</b>	1.9(1.6-2.2)%	3.8(3.2-4.4)%	2.0 (1.6-2.4)	1.8(1.5-2.2)%	5.0(4.5-5.6)%	2.7 (2.2-3.4)
<b>Deceased (all cause)</b>	2.9(2.6-3.3)%	6.2(5.5-6.9)%	2.1 (1.8-2.5)	8.4(7.8-9.1)%	19.3(18.3-20.3)%	2.3 (2.0-2.5)

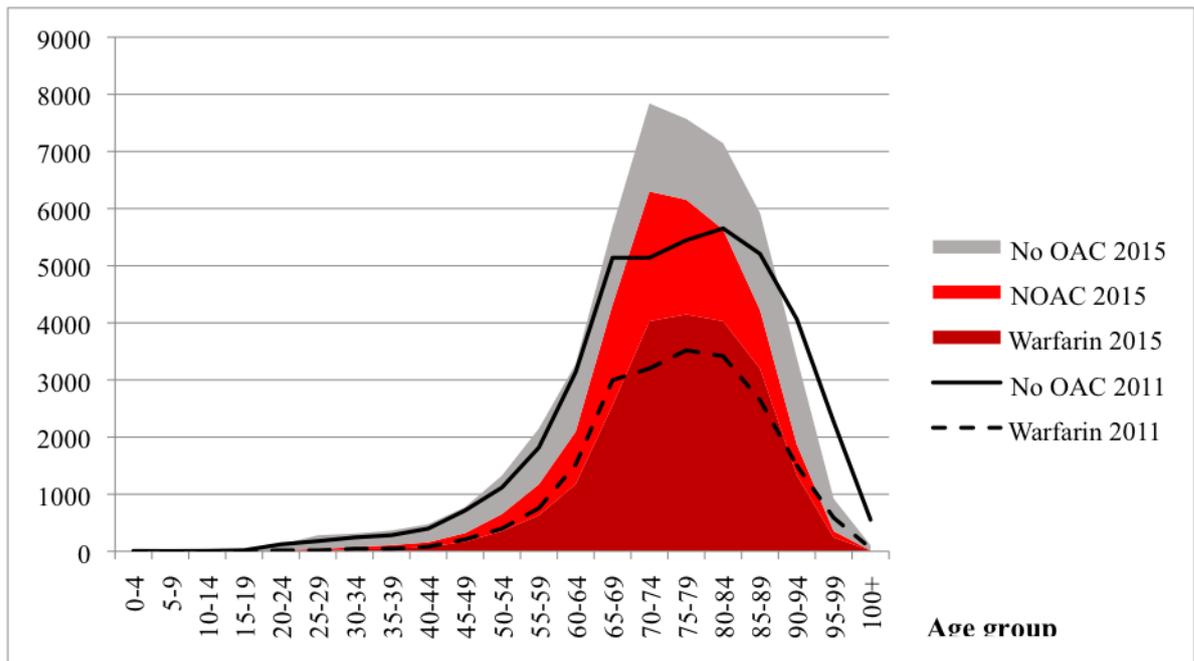
**Table 7 – Outcomes among 26 937 atrial fibrillation patients with CHA<sub>2</sub>DS<sub>2</sub>VASc-scores 2-9 in the Stockholm health care region with and without potential contraindications (dementia, alcohol abuse, renal disease, anemia, earlier severe bleeding, or frequent falls), respectively. Values within parentheses are 95% CI.**

One-year risks for ischemic stroke were low in patients with low CHA<sub>2</sub>DS<sub>2</sub>VASc-scores: 1.0-1.2% with aspirin, 0-0.3% with warfarin, and 0.1-0.2 % without treatment at CHA<sub>2</sub>DS<sub>2</sub>VASc-scores 0-1. These low risks should be considered when discussing more aggressive use of OAC treatment. The higher stroke rate in the aspirin treated group reflects the imbalance between groups regarding unmeasurable baseline covariates, and comparisons between the groups should not be made (see 6.1 - Methodological considerations).

### **4.3 ANTICOAGULANT TREATMENT OF ATRIAL FIBRILLATION BEFORE AND AFTER THE INTRODUCTION OF NOACs IN THE STOCKHOLM HEALTH CARE REGION**

After the publication of the European Guidelines for AF in 2010 and the introduction of NOACs, which commenced in late 2011, the initiations with NOACs have increased steadily while warfarin has decreased [18]. The choice between the three NOACs was fairly equal up until January 2015 when apixaban was recommended as an alternative to warfarin in the regional recommendations, with dabigatran as a secondary alternative for selected patients. From November 2015, AF patients were more likely to receive apixaban than any other OAC, while less than 20% of the initiations were with warfarin. [18]. From January 2016 apixaban is recommended as the OAC of choice for AF-patients in the Stockholm region, with warfarin and dabigatran being recommended as secondary alternatives.

Figure 5 summarizes changes in the AF population and the treatment patterns before and after the introduction of NOACs, i.e., in 2011 and 2015. The number of living resident patients with non-valvular AF in VAL during a 5-year identification period has increased from 41702 to 47698 (patients having moved into the region during the 5-year period were excluded in order to improve risk stratification). The proportion of patients treated with OAC increased from 50.8% in 2011 to 70.3% in 2015. Among patients with a definite indication for anticoagulant treatment (CHA<sub>2</sub>DS<sub>2</sub>VASc 2-9) 75% were treated with an OAC in 2015 compared to 54% in 2011. The largest increases of OAC treatment were found among patients with complicating co-morbidities and in patients aged 80 years and above. In absolute numbers there were more AF patients treated with warfarin after the introduction of NOACs than before (over 20 000), but the proportion had decreased slightly to 46.3% while 24.0% had claimed a NOAC in 2015.

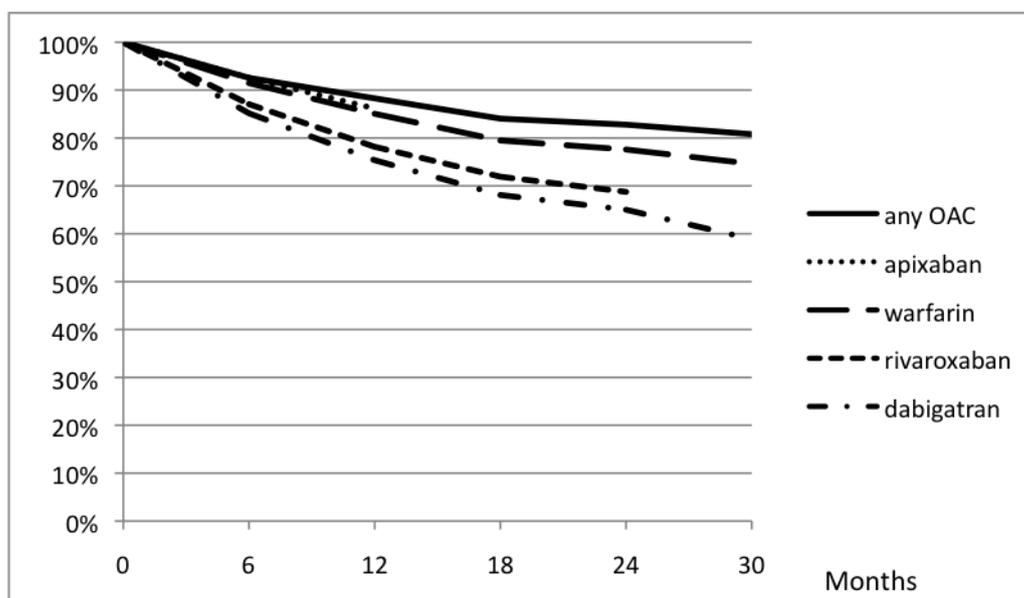


**Figure 5 – Anticoagulant treatment of non-valvular AF in the Stockholm health care region. Numbers of patients with warfarin, NOAC and no OAC treatment 2011 and 2015 in different age groups**

#### 4.4 STUDY III

In Study III, persistence with the different NOACs during 2011-2014 was compared to the persistence with warfarin treatment in patients with non-valvular AF and CHA<sub>2</sub>DS<sub>2</sub>VASc scores 2-9. Also persistence with, and switches from low-dose aspirin were analyzed.

The persistence with any OAC, including switches, was high: 88.2% (CI 87.5%-88.9%) at one year and 82.9% (CI 81.8%-83.9%) at two years (Figure 6). The crude persistence was 85.0% (CI 84.2%-85.9%) with warfarin, 85.9 % (CI 81.8%-90.1%) with apixaban, 74.4% (CI 72.3%-76.5%) with dabigatran, and 77.4% (CI 74.6%-80.2%) with rivaroxaban after one year the (Figure 6).



**Figure 6 – Unadjusted persistence with anticoagulant treatment in non-valvular atrial fibrillation patients with CHA<sub>2</sub>DS<sub>2</sub>VASc scores 2-9. The analysis comprises 16 096 OAC initiations in 14 426 individual patients.**

Multivariate analysis of the persistence at 1 year confirmed statistically significant differences, with initiations on warfarin and apixaban having higher odds for persistence than initiations on dabigatran or rivaroxaban (Table 8). Factors significantly associated with lower persistence were female sex and number of drugs, while initiation of treatment from primary care was associated with a higher persistence (Table 8).

<b>Treatment persistence</b>	<b>Odds Ratio Estimate</b>	<b>95% CI</b>	<b>P-value</b>
<b>Warfarin vs apixaban</b>	0.88	0.62-1.25	0.47
<b>Warfarin vs dabigatran</b>	1.81	1.57-2.10	<.0001
<b>Warfarin vs rivaroxaban</b>	1.50	1.24-1.81	<.0001
<b>Apixaban vs dabigatran</b>	2.07	1.45-2.94	<.0001
<b>Apixaban vs rivaroxaban</b>	1.71	1.18-2.47	0.004
<b>Rivaroxaban vs dabigatran</b>	1.21	1.00-1.46	0.053
<b>Female sex</b>	0.86	0.78-0.96	0.006
<b>Age (per year)</b>	1.00	0.99-1.00	0.12
<b>Prior OAC treatment</b>	0.97	0.82-1.14	0.68
<b>Prescription in Primary Care</b>	1.21	1.08-1.35	0.001
<b>Number of Drugs (per drug)</b>	0.95	0.93-0.97	<.0001

**Table 8 – Odds ratio estimates of treatment persistence at 12 months in patients with non-valvular atrial fibrillation and CHA<sub>2</sub>DS<sub>2</sub>VASc scores 2-9 who were initiated with warfarin (n=7 452), dabigatran (n=1 778), rivaroxaban (n=925), or apixaban (n=289). The analysis comprises 10 444 OAC initiations in 9 710 individual patients.**

The adherence (proportion of days covered >80%) was above 90% for all NOACs; significantly higher with rivaroxaban compared to dabigatran (p<0.001), but not compared to apixaban (p=0.14). Full adherence ( $\geq 100\%$  of days covered by dispensed drug) was significantly more common with rivaroxaban (79.7%) than with apixaban (71.4%), and dabigatran (72.7%).

## 4.5 STUDY IV

In study IV we compared the efficacy and safety of NOAC and warfarin treatment in OAC-naïve patients with non-valvular AF. NOAC treated patients were younger (72.9 vs. 74.1 years) and had lower CHA<sub>2</sub>DS<sub>2</sub>VASc-scores (3.42 vs. 3.68) than warfarin treated patients.

NOAC vs. warfarin treatment was associated with similar risks for TIA/Ischemic or unspecified stroke/death (HR 0.93; 0.84-1.03) and severe bleeds (HR 1.04; 0.88-1.22) (Table 9). In secondary analyses NOAC treatment was associated with lower risks of intracranial bleeds (HR 0.72; 0.51-1.00) or hemorrhagic stroke (HR 0.50; 0.28-0.87), but a higher risk for gastrointestinal bleeds (HR 1.24; 1.00-1.52).

Endpoint	NOAC vs. warfarin				
	Crude HR (CI 95)	Adjusted HR (CI 95)	Intention-to-treat Adjusted HR (CI 95)	Fully adjusted HR (CI 95)	(CHA <sub>2</sub> DS <sub>2</sub> VASc 2-9) Adjusted HR (CI 95)
<b>TIA/Ischemic stroke/stroke unspecified/death</b>	<b>0.82* (0.73-0.91)</b>	<b>0.93 (0.84-1.03)<sup>1</sup></b>	<b>0.91* (0.83-0.99)<sup>1</sup></b>	<b>0.91 (0.82-1.01)<sup>3</sup></b>	<b>0.96 (0.86-1.07)<sup>1</sup></b>
TIA/Ischemic stroke/stroke unspecified	0.86 (0.72-1.03)	0.93 (0.78-1.12) <sup>1</sup>	0.96 (0.82-1.13) <sup>1</sup>	0.92 (1.03-1.05) <sup>3</sup>	0.98 (0.81-1.18) <sup>1</sup>
Ischemic stroke	0.76* (0.60-0.96)	0.83 (0.66-1.06) <sup>1</sup>	0.91 (0.74-1.12) <sup>1</sup>	0.81 (0.64-1.03) <sup>3</sup>	0.84 (0.66-1.08) <sup>1</sup>
Death	0.79* (0.70-0.90)	0.93 (0.81-1.05) <sup>1</sup>	0.88* (0.79-0.98) <sup>1</sup>	0.91 (0.80-1.03) <sup>3</sup>	0.95 (0.83-1.08) <sup>1</sup>
<b>Any severe bleed</b>	<b>0.99 (0.84-1.16)</b>	<b>1.04 (0.88-1.22)<sup>2</sup></b>	<b>0.95 (0.82-1.10)<sup>2</sup></b>	<b>1.05 (0.89-1.24)<sup>3</sup></b>	<b>1.06 (0.89-1.25)<sup>2</sup></b>
Intracranial bleed	0.65* (0.47-0.91)	0.72* (0.51-1.00) <sup>2</sup>	0.63* (0.46-0.85) <sup>2</sup>	0.69* (0.50-0.97) <sup>3</sup>	0.76 (0.54-1.06) <sup>2</sup>
<i>Hemorrhagic stroke</i>	<i>0.45* (0.26-0.80)</i>	<i>0.50* (0.28-0.87)<sup>2</sup></i>	<i>0.48* (0.29-0.80)<sup>2</sup></i>	<i>0.49*(0.28-0.86)<sup>3</sup></i>	<i>0.48* (0.27-0.86)<sup>2</sup></i>
<i>Other intracranial bleed</i>	<i>0.82 (0.54-1.23)</i>	<i>0.90 (0.59-1.36)<sup>2</sup></i>	<i>0.74 (0.51-1.10)<sup>2</sup></i>	<i>0.86 (0.56-1.30)<sup>3</sup></i>	<i>1.01 (0.66-1.54)<sup>2</sup></i>
Gastrointestinal bleed	1.21 (0.98-1.48)	1.24* (1.00-1.52) <sup>2</sup>	1.12 (0.93-1.35) <sup>2</sup>	1.28* (1.03-1.58) <sup>3</sup>	1.28* (1.03-1.59) <sup>2</sup>

**Table 9–Hazard ratios (HR) of study outcomes in 22 230 OAC-naïve patients with non-valvular AF initiated on anticoagulant treatment; NOAC vs. warfarin.**

Significant differences compared to warfarin are denoted \*.

<sup>1</sup> Adjusted for individual CHA<sub>2</sub>DS<sub>2</sub>VASc criteria and age as a continuous variable

<sup>2</sup> Adjusted for age, sex and prior severe bleeds

After adjustments there were no significant differences between NOAC and warfarin treatment in high risk patients aged 80 and above for TIA/Ischemic or unspecified stroke/death (HR 0.99; CI 95 0.86-1.14) or any severe bleed (HR 1.14; CI 95 0.89-1.47). The risks were also similar between treatments in patients with a prior severe bleed: TIA/Ischemic or unspecified stroke/death (HR 1.00 ; CI 95 0.75-1.34), new severe bleed (HR 1.11; CI 95 0.75-1.64).

Explorative analyses of the influence of dosages on outcomes suggested that standard dose NOAC treatment was associated with fewer deaths and similar risks of severe bleeding compared to warfarin treatment in patients < 80 years, but there were increased risks of dying or suffering a gastrointestinal bleed among dose reduced younger patients. In patients aged 80 and above dose reduction of NOAC treatment was associated with a marked risk reduction for hemorrhagic stroke without any increase in gastrointestinal bleeds compared to warfarin treatment.

There were no significant differences between rivaroxaban or apixaban and warfarin treatment in exploratory analyses. Dabigatran treatment was associated with lower risks of suffering death and intracranial bleeds, but a higher risk for gastrointestinal bleeding compared to warfarin. There were no trends suggesting that warfarin treatment would have better effectiveness or safety than any of the individual NOACs.

In summary this population based cohort study of routine care indicated similar or better effectiveness and safety with NOAC compared to warfarin treatment. NOACs were associated with fewer intracranial bleeds, but more gastrointestinal bleeds.

## 5 DISCUSSION

### 5.1 METHODOLOGICAL CONSIDERATIONS

#### 5.1.1 Study design and generalizability

Registry based observational studies provide the possibility to investigate the introduction of new drugs in representative populations and from different angles compared to randomized trials. Also, the appropriateness of prescriptions in routine care can be investigated. Independent comparative effectiveness studies provide additional validation of the benefit and risks of new drugs in routine care [15]. Treatment results can also be assessed in ways that differ from those commonly used in the randomized trials.

The studies in this thesis all had a non-excluding design. Studies I and II were descriptive with the aim of characterizing the AF population, treatment and outcomes prior to the introduction of NOACs. Studies III and IV were cohort studies comparing persistence, effectiveness and safety between treatments.

The studies comprised all eligible patients recorded in the administrative health care database (VAL) of the Stockholm County Council, which includes diagnoses from inpatient care, specialist ambulatory care, and primary care. VAL also contains individual level data on all prescription drugs dispensed anywhere in Sweden to inhabitants in the region. Such rather complete coverage increases the external validity and the generalizability of the findings.

But organization of health care, regional drug and therapeutic recommendations, and socioeconomic factors might limit the generalizability of studies based on regional data collection. Studies I and II investigated treatment and outcomes prior to the introduction of NOACs and might not be relevant in the post-NOAC era. Study III investigated persistence with warfarin and NOACs in a setting where warfarin was recommended as first line treatment in AF according to regional guidelines. The regional recommendations have changed since then and recommendations may differ in other health care settings. Study IV only included new initiators of OAC treatment. The results including switches between drugs were assessed in intention-to-treat analyses, but have not been closer evaluated. The outcomes of the large number of AF patients switching from warfarin to NOAC treatment were not evaluated. This should be considered when interpreting the results.

#### 5.1.2 Using health care registers in epidemiological research

There are several advantages of using administrative health care registers such as VAL when evaluating the effectiveness of drug therapies [20,107]. The data is already structured and covers large parts of or, preferably, the entire health care system over a long period of time. These registers are often representative of routine clinical care and include all patients,

not only those eligible for a clinical trial, or those treated at selected health care units participating in observational registers. The data are prospectively recorded for all patients [20,107].

However, there are also limitations. A record is generated only at encounters with the health care system or a claim of prescription drugs. Diagnoses are only considered when registered as ICD-10 codes and reported into the administrative register. The diagnoses might be inaccurate, and information might be missing. ICD-10 codes might be repeated at follow-up visits or transfers between clinics which complicates the assessment of new events. Death is an accurate end-point in the registers, but causes of death are not which might lead to underestimations of other outcomes. Systematic lack of information might lead to misclassification and more residual confounding [20]. One example is lack of registered diagnoses in untreated patients who might have sparse contact with health care due to mistrust, psychiatric conditions, alcoholism, or other reasons. This systematic lack of information might lead to false classification of these individual as low-risk and differential misclassification when comparing with active treatment.

### **5.1.3 Validity of diagnoses, and treatments**

The coverage of healthcare records in the VAL database is almost complete, with almost 100% of discharges and consultations having at least one registered ICD-10 diagnosis, but some visits and diagnoses from private care and nursing homes might be missing. The validity of hospital diagnoses in Sweden is well documented [107,108,111], but diagnoses in primary care records are less validated [35,46,47]. In the CHA<sub>2</sub>DS<sub>2</sub>VASc-score only heart failure with an ejection fraction below 40% is a proven risk factor for stroke, but the ejection fraction cannot be identified in health care registers [52]. The information regarding prescription claims is accurate [109], but we do not know if patients actually took their prescribed and claimed treatments.

### **5.1.4 Validity of outcomes**

In study II we included patients based on a recorded diagnosis of AF during a five year time span but used the same index date for follow-up. The outcomes were then assessed during the relatively short time span of one year, in order to avoid misclassification. By including patients diagnosed during a large time span and then commencing follow-up at a common point in time (unrelated to the occurrence of a diagnostic code or a prescription claim) we reduce selective misclassification due to the associations of ICD-10 codes of AF, treatment and ICD-10 codes for outcomes (particularly for stroke). The method used in study II thus leads to reduced bias when evaluating outcomes of treatment for the entire AF population.

In study III we wanted to evaluate true discontinuation of antithrombotic treatments and therefore used prescription claims with a generous time-window as the primary outcome. Several papers about adherence and/or persistence with NOACs treatment in AF patients have been published, but both the settings, the definitions of adherence and/or persistence and the results are highly variable [112]. Prescription claims are reliable and valid measures of continued treatment, but sensitive to definitions such as time window and other methodological definitions. Prescription claims are often irregular and patients on treatment might wrongly be classified as discontinued if the time-windows are too short [113], but the

sensitivity might differ from one country to another [112]. It is especially important to avoid selective misclassification when evaluating warfarin treatment where one claim lasts 6 months for many patients in Sweden, in comparison to other treatments where the claim usually lasts only 3 months. The availability of new treatments might in some settings have driven switches from warfarin to NOACs due to financial or practical reasons unrelated to tolerability. In study III we made efforts to avoid bias due to short time windows when assessing prescription claims, variable follow-up time, mortality, changes in regional guidelines, or temporary indications among patients with CHA<sub>2</sub>DS<sub>2</sub>VASc scores 0-1.

In study IV the outcomes were carefully defined to avoid counting events registered during follow-up visits or transfers between inpatient clinics as new outcomes. Patients were included at an index date, i.e. the initiation of OAC treatment, and we found signs of misclassification due to transfer between clinics or follow-up visits after TIA/ischemic stroke. We therefore included TIA, ischemic and unspecified stroke only if they occurred as the main or first secondary diagnosis in inpatient hospital based acute somatic care [54]. Severe bleeds were included when occurring in hospital based acute somatic care as main or secondary diagnoses, and hospitalized bleeds were analyzed as a secondary endpoint [114]. With these conservative definitions the absolute risks for stroke and bleeding with OAC treatment might be slightly underestimated, but the accuracy is improved.

### **5.1.5 Confounding by indication**

Confounding by the indication for therapy is the major limitation of observational comparative effectiveness studies [15]. This is due to the fact that the prescription of drugs by physicians is influenced by many factors. Drugs are often systematically channeled to certain types of patients, based on their indications and contraindications. Residual confounding is the inability to compensate for differences in patient characteristics between treatment groups when comparing outcomes. There are always unmeasured factors such as biological age (fitness), severity of the co-morbidities, and lifestyle factors influencing the outcomes. If these factors differ systematically between the compared groups they might mislead the researcher into drawing the wrong conclusions. Thus, observational studies should not be used to draw conclusions about causal effects and efficacy, only to assess and discuss the effectiveness in routine care and indicate possible causal effects. The main aims of observational comparative effectiveness studies are to confirm results from randomized trials or to seek evidence when results from randomized trials are lacking. Unexpected differences between treatment groups should be interpreted as indications warranting either confirmation in randomized trials or support by consistent findings in other observational trials from other populations and settings.

Unmeasurable baseline factors might affect both the choice of treatment and the outcomes, leading to confounding by indication. But unexpected differences in outcomes between treatment groups might also be due to different utilization of the treatments in the studied populations, or different management of the treatments in health care, compared to the randomized trials [15]. Routine care patients are often older and have more co-morbidities than trial patients. They might also be less motivated and their follow-up is usually less thorough leading to higher discontinuation and lower adherence which may also differ between treatments. Run-in periods in clinical trials might lead to underestimation of side-

effects which are of importance when using drugs in a routine setting. Finding and exploring these differences are other reasons to conduct observational comparative effectiveness studies. Results from observational studies can be used to fine tune recommendations and improve the use of drugs in routine care.

There are several methods that can be used to reduce, if not completely suppress, confounding by indication [15]. The analysis can be restricted to certain types of patients, for example only new users, only patients with standard dose, patients without contraindications, or patients on treatment. The major objection to such restrictions is that if the main aim of observational studies is to assess the effectiveness and safety in all patients in routine care then restriction inevitably reduces generalizability and representativeness.

Stratification of populations based on age, sex and major risk factors leads to improved accuracy in comparisons while still allowing for inclusion of all patients. There are many techniques for modeling and analyzing several variables. Regression analyses use statistical modeling to estimate the relationships among variables. It is assumed that parametric statistical distributions fit the data. Regressions can adjust for several confounders in the same model, but large scale administrative registers might contain hundreds of possible confounders. In these cases propensity score stratification is often used to adjust for a large number of possible confounders.

A combination of the above-mentioned strategies is often used in order to reduce confounding. A combination of several strategies can also be used to confirm the models and/or to explore possible differences in subgroups of interest.

In study II we had obvious confounding when comparing treatment groups with mortality rates being approximately 2-3 times higher in AF-patients with aspirin or no treatment compared to warfarin, even after stratification. We therefore refrained from comparing treatments and concentrated on exploring the treated populations separately. We focused on understanding possible contraindications or complicating co-morbidities in the population on aspirin treatment since these patients could be foreseen to become candidates for anticoagulant treatment in an era of more aggressive treatment with new treatment alternatives.

In study III a combination of restriction and regression was used, with adjustments for possible confounders. We restricted the analysis to AF patients with a definite indication for OAC treatment. We also restricted the analysis in time in order to reduce influences from changes in regional AF-guidelines since apixaban and dabigatran were recommended in the Stockholm region from 2015 onwards. The results were consistent in unadjusted and adjusted models. The CHA<sub>2</sub>DS<sub>2</sub>VASc-score did not affect treatment persistence. The number of drugs claimed 6 months prior to inclusion was used as a measure of frailty and morbidity; and was significantly associated with lower persistence.

In study IV a combination of restriction, stratification and regression was used, with adjustments for possible confounders. The results obtained in multiple regression analyses were confirmed using two different types of propensity score models. The results were consistent in all analyses performed.

## 5.2 MAIN FINDINGS AND INTERPRETATION

### 5.2.1 Anticoagulant treatment of AF before the introduction of NOACs

AF is a chronic disease which to a large extent affects elderly patients with many concomitant and sometimes complicating diseases. Primary care plays an important role in the antithrombotic treatment of AF; but also in treating hypertension and diabetes which are relevant both in the development of AF and included in the CHA<sub>2</sub>DS<sub>2</sub>VASc-criteria as risk factors for stroke. Lack of diagnoses registered in primary care leads to underestimation of CHA<sub>2</sub>DS<sub>2</sub>VASc scores and possible overestimation of treatment benefits in low-risk patients.

Anticoagulants were underused prior to the introduction of NOACs and aspirin was clearly overused as stroke prophylaxis. Thus, half of the high-risk AF patients treated with aspirin were obvious candidates for OAC treatment with no identified contraindications, a high risk for ischemic stroke, a low bleeding risk, and a moderate mortality rate. However, the other half of the patients had a high risk for ischemic stroke, but also possible contraindications, a high risk for bleeding and a poor prognosis. Conversely, a substantial proportion of AF patients with a doubtful indication (i.e. CHA<sub>2</sub>DS<sub>2</sub>VASc scores 0-1) received OAC treatment. Thus, there were signs of both under- and overuse of effective OAC treatment among AF patients in Stockholm before the introduction of NOACs.

### 5.2.2 Anticoagulant treatment of AF after the introduction of NOACs

During the introduction of NOACs the number of patients with a registered diagnosis of AF increased considerably in the Stockholm health care region, as did the proportion of OAC-treated patients. The largest increases of OAC treatment were found in patients with complicating co-morbidities and in patients aged 80 years and above. Since 2010 the initiations of OAC treatment have increased markedly; from 2012 onwards initiations with NOACs have increased steadily while initiations with warfarin have decreased. With the possibility to switch between OAC treatments the overall persistence with any OAC was high in AF patients. Warfarin and apixaban had higher persistence than dabigatran and rivaroxaban. There were indications of better adherence with the once daily regimen of rivaroxaban, in contrast to the twice daily regimens of apixaban and dabigatran, when measured as proportion of days covered. However, with twice daily regimens (and drugs with longer half-lives than rivaroxaban) the therapeutic coverage may be better if patients only miss one of the two daily doses. Estimation of adherence with warfarin was not possible due to the individual dosing and lack of PT-INR results in the databases.

NOAC treatment seemed to result in similar or better effectiveness and safety compared to warfarin treatment in routine care. NOACs were associated with fewer intracranial bleeds, but more gastrointestinal bleeds. The outcomes were similar between NOAC and warfarin treatment in high risk patients aged 80 and above and in patients with a prior severe bleed. The advantages with NOAC treatment were most pronounced with standard dosing in patients under the age of 80, and with dose reductions in patients aged 80 and above.

There were no significant differences between rivaroxaban or apixaban and warfarin treatment. Dabigatran treatment was associated with lower risks of suffering death and intracranial bleeds, but a higher risk for gastrointestinal bleeding compared to warfarin.

Importantly there were no trends in any of the analyses suggesting that warfarin treatment would be better than any of the individual NOACs, either in total or in frail and/or elderly patients.

Taken together these results indicate large improvements in the management of AF in the Stockholm Health care region during the introduction of NOACs. NOACs seem to be attractive treatments in routine care, but warfarin still plays an important role with over 20 000 AF patients remaining under treatment in 2015.

## 6 CONCLUSIONS

In this thesis AF patients and their use of antithrombotic treatments in the Stockholm health care region were studied before and after the introduction of NOACs. From the analyses we concluded that:

- Primary care plays an important part in the management of AF in the Stockholm health care region
- Warfarin appeared to be underused and aspirin overused prior to the introduction of NOACs, but there were also indications of overuse of anticoagulants in low-risk AF patients.
- Many of the patients without anticoagulant treatment were old, with complicating co-morbidities, high bleeding risk and a poor prognosis in addition to a high risk of ischemic stroke.
- With the introduction of NOACs the number of patients with an AF diagnosis and the proportion of OAC-treated AF patients have increased. The largest increases in treatment were found in patients with complicating co-morbidities and in patients aged 80 years and above.
- The overall treatment persistence with any OAC was high after the introduction of NOACs. The persistence with warfarin and apixaban was higher than with dabigatran and rivaroxaban.
- NOAC treatment was associated with similar or better effectiveness and safety compared to warfarin treatment in routine care. NOACs were associated with fewer intracranial bleeds, but more gastrointestinal bleeds.

## 7 PERSPECTIVES

As illustrated in this thesis there have been considerable changes and most likely also improvements regarding stroke prophylaxis in patients with AF after the introduction of NOACs. There has been an increased focus on AF and the patients are more often treated with anticoagulants. There is now a choice between several OAC treatments facilitating individualized treatment. The NOACs are gradually adopted as first line antithrombotic treatment in AF patients in specialist care, but also in primary care.

But the largest increase of OAC treatment can be seen in patients with high risk for both stroke and bleeding, leading to increasing demands in the management of these frail patients throughout the health care system. The high persistence to OAC treatment is probably in part due to active management of bleeding complications and restarting of OAC therapy; which might implicate switching of OAC treatment, dose adjustments and other qualified considerations. Thus, the availability of the new and apparently easier to use NOACs might paradoxically increase the complexity of OAC treatment in AF and raise numerous questions that need to be addressed in a specialist setting, possibly by multidisciplinary teams. Another possible issue will be the need to centralize warfarin treatment, when fewer and more complex patients will be using this demanding treatment.

Several questions remain for further research. The predictive value of CHA<sub>2</sub>DS<sub>2</sub>VASc can be discussed and the optimal cut-off level for OAC treatment is still debated. How should patients who experience bleeding problems be managed? How should OAC treatment be continued after bleeding events? There is limited knowledge on the consequences when switching between OACs. Further research is needed to compare outcomes with the different treatment alternatives, as well as the outcomes of treatment in relation to persistence and adherence in regular health care. Can monitoring of NOACs and individual dose adjustments improve results further? How well do the NOACs perform in AF patients with ischemic heart disease, in combination with antiplatelet agents, or for patients needing cardioversion? What are the bleeding rates of patients interrupting NOACs before surgery or other invasive procedures? What are the risks for thromboembolism in these patients? How should NOAC treatment best be managed in connection with invasive procedures? Are there other patient subgroups in addition to those with mechanical valves in whom warfarin is preferable and should be used? Further studies comparing the effectiveness and safety of the individual NOACs in routine care are needed. The consequences of the dosing regimens with frequent dose reductions of the NOACs should be explored in larger materials. Comparisons of outcomes with warfarin and NOAC treatment should also be repeated when NOAC treatment is more firmly established and widespread in routine care. Also, it is of interest to perform detailed analyses of over- or undertreatment of specific patient categories with OACs.



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