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- Studies on Overanticoagulation and Risk Scores

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University of Turku

Faculty of Medicine
Department of Cardiology and Cardiovascular Medicine
Doctoral Programme in Clinical Research
Heart Center, Turku University Hospital, Finland

Supervised by

Professor K.E. Juhani Airaksinen, MD, PhD
University of Turku
Heart Center, Turku University Hospital
Turku, Finland

Docent Tuomas O. Kiviniemi MD, PhD
University of Turku
Heart Center, Turku University Hospital
Turku, Finland

Reviewed by

Professor Raimo Kettunen, MD, PhD
University of Eastern Finland
Kuopio, Finland

Docent Olli Anttonen, MD, PhD
University of Oulu
Päijät-Häme Central Hospital
Lahti, Finland

Opponent

Professor Juha Sinisalo, MD, PhD
University of Helsinki
Helsinki, Finland

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To my family

ABSTRACT

Samuli Jaakkola, MD

CLINICAL CHALLENGES IN THE MANAGEMENT OF ATRIAL FIBRILLATION – STUDIES ON OVERANTICOAGULATION AND RISK SCORES

University of Turku, Faculty of Medicine, Department of Cardiology and Cardiovascular Medicine, University of Turku Doctoral Programme in Clinical Research

Annales Universitatis Turkuensis Painosalama Oy – Turku, Finland 2018

Background: In addition to stroke prevention with oral anticoagulation (OAC), comprehensive management of atrial fibrillation (AF) involves several important aspects. The aim of this thesis is to bring new and practical information on AF management to guide clinicians in challenging situations. Unsuccessful electrical cardioversion (ECV), excessive warfarin anticoagulation (EWA) during warfarin treatment and the limitations of CHA_2DS_2-VASc and HAS-BLED scores in risk stratification are the specific clinical challenges addressed in this thesis. **Methods**: The studies are based on three distinct datasets, all collected retrospectively by reviewing patient records. The FinCV (study I) data included 5,713 ECVs in 2,868 patients from two university hospitals and one central hospital in Finland during 2003-2010. The EWA Study data (studies II and III) included all patients on warfarin for AF, from 2003 to 2015 in the Turku University Hospital region, who suffered an EWA episode (defined as INR ≥9). The FibStroke data (study IV) was collected at four hospitals in Finland. All patients with a diagnosis of AF / Atrial flutter and either an ischemic stroke or an intracranial bleed between the years 2003–2012 were included. **Results**: 1) A scoring system was created to predict unsuccessful ECV. The predictive score parameters were Age, not the First AF, Cardiac failure, Vascular disease, and Short interval from previous AF episode (AF-CVS). 2) A total of 412 patients with EWA were identified, of whom 25.5% suffered a bleed. Of the many observed predictors of EWA, the strongest were alcohol abuse and impaired renal function. 3) Of the 412 EWA episodes, non-bleeding symptoms were recorded in 40.0% of patients and in 34.5% the EWA was a coincidental finding without symptoms. The 30-day mortality rate was high (9.2% to 32.7%). 4) Ischemic strokes occurred more often than intracranial bleedings in patients on OAC in each (CHA_2DS_2-VASc and HAS-BLED) score category, except HAS-BLED score >4. **Conclusions**: The risk of ECV failure and early recurrence of AF can be predicted with simple clinical characteristics. EWA can be predicted with several risk factors, many of which are modifiable. Bleeds are not the major determinant of the poor prognosis of EWA, as coincidental INR ≥9 findings also associate with high mortality. In patients with AF, ischemic strokes are more common than intracranial bleedings irrespective of CHA_2DS_2-VASc score, HAS-BLED score ≤4, or use of oral anticoagulation.

Keywords: Atrial fibrillation, overanticoagulation, warfarin, risk score

TIIVISTELMÄ

Samuli Jaakkola, LL

ETEISVÄRINÄN HOIDON KLIINISIÄ HAASTEITA –

Liiallinen antikoagulaatio ja riskilaskureiden käyttö

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja kardiovaskulaarilääketiede, Turun kliininen tohtoriohjelma

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Tausta: Antikoagulaatiohoidolla toteutetun aivohalvausriskin pienentämisen lisäksi eteisvärinän kokonaisvaltaiseen hoitoon liittyy useita tärkeitä seikkoja. Tämän väitöskirjatyön tarkoituksena on saada uutta tietoa eteisvärinän hoidon käytännön ongelmakohdista ja tuottaa uusia keinoja niiden hoitamiseksi. Väitöskirjatyössä käsiteltäviin ongelmakohtiin lukeutuvat sähköisen kardioversion epäonnistuminen, liiallinen antikoagulaatiotaso, sekä CHA_2DS_2-VASc ja HAS-BLED –riskilaskureiden käyttöön liittyvät rajoitukset. **Metodit:** Osatutkimukset perustuvat kolmeen takautuvasti potilastietojärjestelmistä kerättyyn tietokantaan. FinCV-aineistoon (osatyö I) lukeutuu 5713 sähköistä kardioversiota 2868 potilaalla kahdesta yliopistosairaalasta ja yhdestä keskussairaalasta vuosina 2003-2010. EWA-aineistossa (osatyöt II ja III) sisältää kaikki varfariinia käyttävät eteisvärinäpotilaat vuosilta 2003-2015 Turun yliopistollisen keskussairaalan vaikutusalueelta, joilla todettiin korkea INR taso (≥9). FibStroke-aineisto (osatyö IV) sisältää kaikki aivohalvauksen tai kallonsisäisen vuodon sairastaneet eteisvärinä- ja eteislepatuspotilaat neljästä suomalaisesta sairaalasta vuosilta 2003-2012. **Tulokset**: Ensimmäisessä työssä kehitettiin eteisvärinän sähköisen kardioversion epäonnistumista ennakoiva riskilaskuri. Laskurin riskitekijöihin lukeutuvat ikä, aiempi eteisvärinä, sydämen vajaatoiminta, verisuonisairaus, sekä eteisvärinän lyhyt uusiutumisviive. Toisessa työssä tunnistettiin 412 INR≥9 episodin kokenutta potilasta, joista 25.5%:lla tilaan liittyi verenvuoto. Useista tunnistetuista riskitekijöistä voimakkaimmiksi todettiin runsas alkoholin käyttö ja munuaisten vajaatoiminta. Kolmannessa työssä INR≥9 episodien kliiniseksi ilmenemismuodoksi todettiin muu oire kuin verenvuoto 40.0%:lla ja 34.5%:lla se ilmeni oireettomana sattumalöydöksenä. Lisäksi 30 päivän kuolleisuus todettiin korkeaksi (9.2% - 32.7%). Neljännessä työssä antikoaguloiduilla eteisvärinäpotilailla iskeemisen aivohalvauksen todettiin olevan yleisempi komplikaatio kuin kallonsisäinen vuoto riippumatta CHA_2DS_2-VASc ja HAS-BLED riskipisteistä, pois lukien HAS-BLED > 4 pistestatus. **Päätelmät**: Sähköisen kardioversion epäonnistumista ja eteisvärinän uusiutumista voidaan ennakoida. Samoin INR≥9 tapahtumalle on useita riskitekijöitä, joista osaan voidaan vaikuttaa. Näihin tapahtumiin liittyvä kuolleisuus ei selity verenvuodoilla, sillä myös oireettomina niihin liittyy korkea kuolleisuus. Eteisvärinäpotilailla iskeemiset aivohalvaukset ovat kallonsisäisiä vuotoja yleisempiä riippumatta antikoagulaatiohoidosta, CHA_2DS_2-VASc, sekä HAS-BLED ≤4 pistestatuksesta

Avainsanat: Eteisvärinä, antikoagulaatio, varfariini, riskilaskuri

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ABBREVIATIONS

AAD	Antiarrhythmic drugs
AF	Atrial fibrillation
AF-CVS	Age, First episode of AF, Cardiac failure, Vascular disease, Short interval from previous AF episode
AFI	Atrial fibrillation investigators
BMI	Body mass index
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category female
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CYP	Cytochrome P450
ECG	Electrocardiograph
ECV	Electrical cardioversion
ESC	European Society of Cardiology
EWA	Excessive warfarin anticoagulation
HAS-BLED	Hypertension abnormal liver or renal function, history of stroke, bleeding history or predisposition to bleeding, labile INR, >65 years of age and the concomitant use of drugs or alcohol.
ISI	International sensitivity index
IS/IB-ratio	ischemic stroke/intracranial bleeding -ratio
INR	International normalized ratio
ISTH/SCC	the International Society on Thrombosis and Haemostasis / Scientific and Standardization Committee
LAA	Left atrial appendage
LMWH	Low molecular weight heparin
NOAC	Non-vitamin K antagonist oral anticoagulant
OAC	Oral anticoagulant
OR	Odds ratio
OSA	Obstructive sleep apnea
RR	Relative risk
SD	Standard deviation
SPAF	Stroke prevention and atrial fibrillation
TIA	Transient ischemic attack
VKA	Vitamin K antagonist anticoagulant
VKORC1	Vitamin K epoxide reductase complex subunit 1 gene

LIST OF ORIGINAL PUBLICATIONS

I. Jaakkola S, Lip GYH, Biancari F, Nuotio I, Hartikainen JEK, Ylitalo A, Airaksinen KEJ. Predicting Unsuccessful Electrical Cardioversion for Acute Atrial Fibrillation (from the AF-CVS Score). Am J Cardiol. 2017; 119(5):749-752.

II. Jaakkola S, Nuotio I, Kiviniemi T, Virtanen R, Issakoff M, Airaksinen KEJ. Incidence and predictors of excessive warfarin anticoagulation in patients with atrial fibrillation – The EWA study. PLoS One. 2017; 12(4): e0175975.

III. Jaakkola S, Nuotio I, Kiviniemi T, Virtanen R, Virta A, Airaksinen KEJ. Clinical Manifestations and Outcomes Of Severe Warfarin Overanticoagulation – from the EWA Study. Ann Med. 2018 Mar; 50(2):164-171.

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1 INTRODUCTION

Atrial fibrillation (AF) – the most common sustained heart arrhythmia – constitutes a global health problem with far reaching economical implications. In addition to increased mortality, AF associates with increases morbidity especially through higher risk of ischemic stroke. In clinical practice, stroke prevention with oral anticoagulation (OAC) is the most important element in AF management. However, the clinical management of AF also involves other important aspects, such as symptom management and the decision between pursuing sinus rhythm (rhythm control) and settling for ventricular rate control (rate control).

In rhythm control strategy, conversion to sinus rhythm with cardioversion often relieves unpleasant symptoms related to erratic ventricular rate. Nevertheless, cardioversion does not benefit patients in terms of prognosis, entails a risk of thromboembolic complications and is not always successful. For these reasons, evaluating the risk of unsuccessful electrical cardioversion (ECV) is of utmost importance. If the risk of unsuccessful ECV is very high, pursuing rhythm control might expose patients to possible procedure related complications without a realistic chance of achieving the desired outcome, not to mention the consequential economic impacts of both the procedures and the possible complications. To optimize the patient selection for ECV, we set to investigate the possibility of predicting unsuccessful ECV result in the large retrospective FinCV-study data.

For decades, warfarin was the only OAC available for stroke prevention. It still plays an essential role in stroke prevention for patients with AF. As opposed to non vitamin K antagonist oral anticoagulants (NOAC), warfarin anticoagulation intensity is regularly controlled using international normalized ratio (INR) tests. While these tests require laboratory and health care system resources, they also allow the monitoring of warfarin treatment quality and enable physicians to adjust warfarin dosing in an attempt to avoid excessive- and inadequate anticoagulation intensities. The multiple drug and food interactions of warfarin, as well as the influence of comorbidities, account for the common phenomenon of fluctuating INR level. There is little information on the factors predicting very high warfarin anticoagulation intensity and on the clinical consequences of the event. To gain more data on the etiology, manifestations and the outcome of these patients, we conducted a retrospective study (the EWA Study) including all INR ≥9 events in patients living the Southwestern part of Finland, receiving warfarin for AF. New information gained from this study can be used to improve the safety of stroke prevention with warfarin therapy.

As the risk of stroke is not equal throughout the whole patient spectrum suffering from AF, a risk stratification process has to be undertaken with each individual

considered for stroke prevention. This individual risk stratification process should consist of comprehensive evaluation of the net benefit of OAC therapy, i.e. weighing the OAC associated bleeding risks against the stroke risks without OAC. This is usually done by means of risk assessment scores, of which the most widely used are the CHA_2DS_2-VASc score for stroke risk stratification and the HAS-BLED score for evaluating OAC related bleeding risk. To achieve a realistic grasp on the actual risks for each individual patient, we need to explore the performance of both scores in different settings and throughout the whole spectrum of the score levels. We evaluated these scores in the large FibStroke-dataset (study IV) including all patients from a region of 1.2 million inhabitants, suffering either an ischemic stroke or an intracranial bleeding. By studying these scores thoroughly, we can learn to utilize them more efficiently and gain more information on the actual risks associated with AF associated stroke prevention.

2 REVIEW OF LITERATURE

2.1 Atrial fibrillation

2.1.1 Epidemiology and clinical significance

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. In 2010, the number of people suffering from AF globally was over 33 million (Chugh et al., 2014). The prevalence of this common arrhythmia is approximately 3% in people of 20 years of age or older, and after 40 years of age, one person in four is estimated to develop AF during their lifetime (Lloyd-Jones et al., 2004; Bjorck et al., 2013). Higher prevalence of AF associates with increasing age, as well as with different comorbidities, such as renal failure, hypertension, coronary artery disease, obesity, diabetes mellitus, heart failure and valvular heart disease (Kannel et al., 1998; McManus et al., 2012; Chugh et al., 2014; Zoni-Berisso et al., 2014). The prevalence of AF has been projected to double in the United States and Europe within the next 40 to 50 years for different reasons, such as increasing life expectancies and more sensitive modalities for AF detection (Go et al., 2001; Miyasaka et al., 2006; Engdahl et al., 2013; Krijthe et al., 2013). As the number of AF patients continues to increase, the already high economic burden of AF increases in the large scale. The considerable clinical and economic implications of AF are explained by the increased risk of cardioembolic stroke, heart failure and mortality that associate with AF (Benjamin et al., 1998; Kannel et al., 1998; Stewart et al., 2004; McManus et al., 2012). In a study of the renowned Framingham Heart Study cohort, the association between mortality and AF was 1.5-fold (95% CI 1.2-1.8) in men and 1.9-fold (95% CI 1.5-2.2) in women (Benjamin et al., 1998). Moreover, a meta-analysis on 104 studies including 587,867 patients with AF found an association of similar magnitude between AF and all-cause mortality (relative risk [RR] 1.46 (95% CI 1.39-1.54) (Odutayo et al., 2016). The causative role of AF in cardioembolic strokes has been firmly established in numerous studies over the past decades (Hinton et al., 1977; Wolf et al., 1991; Stewart et al., 2002). The pathophysiology of thrombus formation in AF consists of several mechanisms fulfilling the Virchows triad of thrombogenesis (Watson et al., 2009). Abnormal flow conditions in the left atrium and particularly in the left atrial appendage (LAA), anatomical and structural defects of the atrial tissue, abnormalities in the blood constituents and the activation of inflammatory responses are among the complex process of thrombus promotion during AF (Watson et al., 2009).

Approximately 20-30% of patients with an ischemic stroke are diagnosed with AF before, during or after the stroke event (Henriksson et al., 2012; Grond et al., 2013; Kishore et al., 2014). Furthermore, AF-associated cardioembolic strokes are the most disabling and entail the highest mortality rate of all ischemic strokes (Kolominsky-Rabas et al., 2001; Hannon et al. 2010). The risk of ischemic stroke in AF patients varies considerably according to certain patient characteristics. Several risk stratification tools have been developed for assessing the individual stroke risk (Lip et al., 2010; Singer et al., 2013; Hijazi et al., 2016a). Identifying the at-risk patients and preventing cardioembolic strokes is the primary objective of AF management. More evidence is warranted on the effect of paroxysmal versus chronic AF on the risk of thromboembolism and consequently on the indication of OAC (for example in patients with CHA_2DS_2-VASc 0 and chronic AF) (Kirchhof et al., 2016).

2.2 Management of atrial fibrillation – stroke prevention

2.2.1 Oral anticoagulation

2.2.1.1 Coagulation and vitamin K

A constant balance is maintained in the human body between clot formation and dissolution. Both systems are under careful regulation and highly interconnected. Under normal circumstances the balance favors anticoagulation and spontaneous thrombus formation is prevented (Dahlbäck, 2000). Clot formation is a complex process utilizing coagulation cascade, fibrinolytic system, vascular wall endothelium and platelets. The coagulation cascade consists of two separate pathways (the contact activation pathway and the tissue factor pathway) both leading to the final common pathway, which begins with the activation of the factor X. Activated factor X (Xa) converts prothrombin to thrombin and thrombin in turn induces fibrin formation from fibrinogen. Activated and aggregated platelets are stabilized by fibrin resulting in a stable blood clot (Dahlbäck, 2000). The fibrinolytic system is also simultaneously activated to counteract the coagulation system, to maintain the equilibrium between the two states. Plasminogen is activated (by tissue plasminogen activator or urokinase) to form plasmin on the surface of the formed fibrin clot. This proteolytic protein degrades fibrin and fibrinogen to form fibrin degradation products, and a stable clot is dissolved (Rijken et al., 2009). The proper function of these complex cascades requires several additional substances, such as calcium, phospholipids, vitamin K, protein C and protein S.

The important role of vitamin K in the coagulation cascade is to act as a cofactor of the enzyme (vitamin K-dependent epoxide reductase), which is responsible for the post-translational formation of γ-carboxyglutamyl residues. These residues are vital for certain coagulation factors (prothrombin, factor VII, factor IX and X) and also for proteins (protein S and protein C) that downregulate certain clotting factors (Dahlbäck, 2000; Rijken et al., 2009). Considering the complexity and delicacy of the above-described process, small changes in the availability of cofactors and other vital substances may cause severe disturbances that result in clinical thrombotic- or hemorrhagic complications.

2.2.1.2 Measuring anticoagulation intensity: INR

Prothrombin time (PT) measures the activity of three clotting factors (II, VII and X), which constitute ¾ of vitamin K-dependent factors. PT is measured by adding calcium and thromboplastin to citrated plasma. Vitamin K-dependent clotting factor activity is reflected by the reactivity of thromboplastins, which in turn produces prolongation of the PT according to the reactivity level of thromboplastins (Ageno et al., 2012). Factor VII has the shortest half-life (6h) and thus during the first days of warfarin therapy, PT reflects the activity of factor VII. Later, the reduced activity of factors II and X contribute to the prolonged PT. In Finland, all PT results have been reported as INR since 1.1.2000 according to a national agreement. This calibration model standardizes the reporting of PT (Kirkwood, 1983). INR is calculated as follows:

$$INR = (\text{patient PT}/\text{mean normal PT})^{ISI}$$

ISI stands for international sensitivity index, which reflects the responsiveness of a certain thromboplastin to clotting factor activity changes as compared to World Health Organization reference preparations. The standardization of values makes INR results comparable worldwide. In clinical practice, patients on warfarin treatment have regular INR controls to detect anticoagulation intensity variations and consequently dose adjustments can be made. The median INR control frequency was 16.6 days in a recent large study assessing the quality of warfarin treatment in AF patients in Finland (Lehto et al., 2017). Considering this, and the high number of patients on warfarin (66% of anticoagulated patients in Finland during 2016), INR measurements are among most common blood samples for now.

2.2.1.3 Vitamin K antagonist anticoagulants

The hemorrhagic effect of coumarins (derived from sweet clover) and the significance of vitamin K were discovered in Northern America in the 1920s after an outbreak of a disease causing fatal bleedings in cattle. Karl Link and Harold Cambell showed that 3,3′-methylenebis (4-hydroxycoumarin) was the anticoagulant occurring in sweet clover and consequently synthesized vitamin K antagonist warfarin in 1948 (Cambell et al., 1941; Stahmann et al., 1941). Warfarin (WARF for Wisconsin Alumni Research Foundation, and –ARIN for coumarin) is a derivate of 4-hydroxycoumarin, which is 99% bound to plasma proteins in the blood. It is a racemic mixture of S- and R-enantiomers, the former being 2.7-3.8 times more potent than the latter (et al., 2012). They both inhibit the γ-carboxylation reaction (by inhibiting vitamin K-dependent epoxide reductase) resulting in a loss of ability to form interactions with the phospholipid membrane, which is an essential part of coagulation cascade. As a result, the vitamin K-dependent coagulation factors (II, VII, IX, and X) have decreased activity and consequently the thrombus formation is decreased. In addition, proteins that have anticoagulant effects (proteins S, C and Z) are also inhibited, although to a lesser extent (Ageno et al., 2012; Becker, 2005). This inhibition explains the transient procoagulant effects of vitamin K antagonist anticoagulants (VKA) occasionally observed during the initiation of VKA treatment, before full inhibition of clotting factors is achieved.

Warfarin is metabolized by cytochrome P450 (CYP) 2C9, CYP1A2 and CYP3A4 enzymes in the liver. These highly unspecific enzymes catalyze the metabolism of a wide variety of different chemicals. The low specificity explains the numerous significant pharmacokinetic drug- and food interactions of warfarin, as different drug molecules are used as substrates by the same CYP enzymes (Wells et al., 1994; Holbrook et al., 2005). Furthermore, warfarin associated food and drug interactions have several other mechanisms, such as reduced absorption of warfarin in the gastrointestinal tract, changes in the dietary vitamin K intake and several pharmacodynamic mechanisms (for example inhibition or increased clearance of vitamin K–dependent coagulation factors, interference of non-vitamin K dependent coagulation pathways) (Hirsh et al., 2003). The above-described pharmacokinetic and –dynamic mechanisms are under genetic variability, and the abnormal response to warfarin may manifest as increased sensitivity or increased tolerability (O'Reilly et al., 1968). The most important gene in the pharmacodynamics of warfarin is VKORC1 (vitamin K epoxide reductase complex subunit 1 gene) (Wadelius et al., 2007). CYP2C9 and VKORC1 polymorphisms associate with significant differences in warfarin dosage requirements to achieve therapeutic anticoagulation level, as well as with increased risk of

overanticoagulation (Aithal et al., 1999; Higashi et al., 2002; Wadelius et al., 2007).

Warfarin was approved as a rodenticide in 1952 and two years later for human use (Pirmohamed, 2006). Vitamin K-antagonists were the only oral anticoagulants available for decades, until NOACs emerged in the recent years. According to the Finnish Statistics on Medicines 2016, warfarin was the most used anticoagulant in Finland with 167,662 patients receiving reimbursed prescriptions for it in 2016. As expected, the rate decreased 9% from 2015, but still 66% of the prescribed OACs in 2016 were warfarin.

Comprehensive meta-analyses have shown that dose adjusted warfarin reduces ischemic strokes in patients with AF by ~60% as compared to placebo and by 40% as compared to antiplatelets (Lip et al., 2006; Hart et al., 2007). All cause mortality was also reduced by 26% (confidence interval (CI) 4% to 43%) in patients receiving warfarin (Hart et al., 2007). The obvious downside of OAC treatment is the increased risk of severe bleeding complications. In large randomized studies on anticoagulation for AF, the annual risk of major bleeds and intracranial bleeds during warfarin therapy have ranged from 3.09% to 3.43% and 0.70% to 0.85% respectively (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). However, in majority of AF patients, the benefits of OAC treatment (stroke prevention) are considered to outweigh the risk (bleeding complications) (Aguilar et al., 2005; Friberg et al. 2012a).

2.2.1.4 Non-vitamin K antagonist oral anticoagulants

Non-vitamin K antagonist oral anticoagulants (also known as direct oral anticoagulants or NOACs) are increasingly prescribed as the first choice for oral anticoagulation in patients with AF. This policy is in accordance with the European Society of Cardiology (ESC) 2016 Guideline on the management of AF, which states that NOACs should be the primary choice in patients with AF when initiating oral anticoagulation (Kirchhof et al. 2016). NOACs provide fast and stable anticoagulation, with less dietary precautions, drug interactions, laboratory test measurements and dose adjustments in comparison to warfarin. The ESC guideline recommendation is based on the fewer intracranial bleeding events with NOACs as compared to warfarin, while the efficacy was non-inferior (dabigatran 150mg dose and apixaban 5mg dose were superior) to warfarin in the large randomized trials (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013; Kirchhof et al., 2016). There are no randomized trials comparing different NOACs head-to-head in terms of efficacy and safety and the comparative data is derived indirectly from studies comparing NOACs to warfa-

rin (Lopez-Lopez et al., 2017). Four NOACs (rivaroxaban, apixaban, edoxaban and dabigatran) have been introduced and approved for clinical use for AF associated stroke prevention. As compared to warfarin, the pharmacodynamic target of NOACs is "downstream" in the coagulation cascade and thus they have also been called target-specific oral anticoagulants. Rivaroxaban, apixaban and edoxaban provide anticoagulation through clotting factor Xa inhibition, while dabigatran directly inhibits thrombin (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). A meta-analysis of the four major NOAC trials (RE-LY, ARISTOTLE, ENGAGE-AF and ROCKET AF) showed a significant reduction of all-cause mortality (risk reduction [RR] 0.90 [CI 0.85-0.95]) and intracranial bleeding events (RR 0.48 [CI 0.39-0.59]) as compared to warfarin (Ruff et al., 2014). A more recent meta-analysis of 28 studies on rivaroxaban, dabigatran or apixaban compared with VKA, also confirmed the large reduction of intracranial bleeding events with all studied NOACs, while the rate of ischemic strokes were similar to warfarin (Ntaios et al., 2017).

2.2.2 Left atrial appendage closure

During AF the blood flow is often particularly slow in the left atrial appendage (LAA), which consequently is the most common origin of thromboembolisms in AF patients. As oral anticoagulation aims at interfering the process of thrombus formation, a different approach in stroke prevention is to occlude the potential site of thrombus formation. The LAA closure procedure can be done percutaneously or surgically.

Percutaneous LAA closure has been studied in two large randomized trials (PROTECT AF and PREVAIL) and found to be non-inferior to warfarin in preventing ischemic strokes in patients with AF (Holmes et al., 2009; Holmes et al., 2014; Reddy et al., 2014). A meta-analysis on these two major studies supported these findings in addition to showing significantly lower rates of hemorrhagic strokes, nonprocedural bleedings and cardiovascular- or unexplained deaths in patients with LAA closure as compared to warfarin treatment (Holmes et al., 2015). As with all percutaneous heart procedures, LAA closure bears the risk of major complications. The most common severe procedure-related complications reported are pericardial effusion, device embolization and stroke (Holmes et al., 2014; Holmes et al., 2015). ESC guideline recommendation on AF management suggests that LAA closure may be considered for patients at stroke risk, who are unsuited for OAC, such as those with previous severe bleed (Kirchhof et al., 2016). However, these patients are often excluded from randomized trials, which require eligibility for both OAC treatment and LAA closure for all randomized

patients. A small study of 65 high stroke risk patients classified as unsuited for long-term warfarin treatment found a 3.8% annual reduction in stroke/transient ischemic attack (TIA) as compared to the anticipated stroke/TIA rate according to the stroke risk factors (Block et al., 2009). In a recent retrospective study, 151 patients with AF and a history of intracerebral hemorrhage receiving a LAA closure device (AMPLAZER Cardiac Plug or AMPLAZER AMULET) were compared to a propensity score-matched control group of 151 patients on medical therapy. The results suggested a major clinical benefit in favor of the device group (Nielsen-Kudsk et al., 2017). Similar result were found among the 1005 patients in the prospective non-randomized EWOLUTION-trial, reporting a 1.1% stroke rate at 12 months after implantation even though the mean CHA_2DS_2-VASc score was 4.5 ± 1.6 and 73% of patients were not anticoagulated (Boersma et al., 2017). A randomized study on LAA closure versus medical therapy for stroke prevention in patients with AF who suffered an intracerebral hemorrhage is ongoing (STROKECLOSE –study, ClinicalTrials.gov Identifier: NCT02830152).

There are several techniques for surgical LAA occlusion, which is performed usually during other open-heart surgery. There are only limited number of controlled studies on surgical LAA occlusion available, and a study of 72 patients showed that an incomplete occlusion can even increase the risk of stroke (Aryana et al., 2015). Consequently, the current ESC guideline on AF management recommends that OAC should be continued for stroke prevention after surgical LAA occlusion (Kirchhof et al., 2016). An ongoing LAA-CLOSURE trial (ClinicalTrials.gov Identifier: NCT02321137) will bring important information on the efficacy and safety of surgical closure of LAA

2.3 Management of atrial fibrillation – symptom management

2.3.1 Rhythm control strategy

2.3.1.1 Electrical cardioversion

An ECV is performed by delivering an external direct current energy shock to the patient during short general anesthesia. It was first performed in the 1950s for terminating ventricular fibrillation, and introduced for converting AF to sinus rhythm in 1963 (Zoll et al., 1956; Lown et al., 1963). Since then, ECV has become a routine procedure in rhythm control strategy for AF (Mittal el al., 2000;

Kirchhof et al., 2002). Acute symptomatic episodes of AF (duration of < 48 hours) are typically terminated with ECV in the emergency department. The procedure can also be applied to AF episodes of > 48 hours of duration as long as the use of adequate anticoagulation (preceding 3 weeks) is ensured (Kirchhof et al., 2016).

The overall success of ECV is evaluated by taking into account both the initial result of the cardioversion (i.e. patient is discharged in sinus rhythm) and the longevity of the result (i.e. time to recurrence of AF). Initial success of ECV has been reported to vary between 66%-99% (Burton et al., 2004; Kuppahally et al., 2009; Xavier Scheuermeyer et al., 2010; Bellone et al., 2012; Toso et al., 2012; Grönberg et al., 2015). Logically, the overall success rate of ECV (i.e. composite of conversion to sinus rhythm and no recurrence during follow-up period) is of course lower than the initial success rate. In two retrospective studies, the overall success rates were 54.7% (Hellman et al., 2017) and 47% (Kuppahally et al., 2009) with 30 days and 365 days follow-up periods respectively.

Many predictors of successful cardioversion have been identified in numerous studies on patients with non-acute (>48 hours) AF. A retrospective study on 370 consecutive patients (AF duration was <4 days in 25%) undergoing ECV found that the duration of AF was inversely associated with the initial ECV success (Kuppahally et al., 2009). A similar finding has been reported in several studies, including mostly elective ECVs (Frick et al., 2001; Fumagalli et al., 2002; Kirchhof et al., 2002; Pisters et al., 2012). However, by definition, the significance of this risk factor is diminished when the success of ECV in acute AF is evaluated. Obesity is a known risk factor for AF progression and it also predicts unsuccessful ECV result according to several studies (Frick et al., 2001; Kirchhof et al., 2002; Blich et al., 2006; Lavie et al., 2017). Furthermore, overall adiposity and high body mass index (BMI) as well as more site-specific fat accumulation (e.g. the biologically active epicardial adipose tissue) have been suggested to increase the risk AF progression and recurrence after catheter ablation (Lavie et al., 2017). Obstructive sleep apnea (OSA) has also been shown to associate with increased risk of AF recurrences after cardioversion (Kanagala et al., 2003). This finding may in part be explained with higher BMI in patients with OSA. However, the treatment of OSA (with continuous positive airway pressure mask) reduces AF recurrences in comparison to untreated patients with OSA, independent of BMI (Kanagala et al., 2003).

In clinical practice, left atrial diameter is often measured to assess the probability of achieving and maintaining sinus rhythm. However, there are multiple studies showing no association between left atrial diameter and ECV success or short-term recurrence of AF (Botto et al., 1999; Frick et al., 2001; Fumagalli et al.,

2002; Pisters et al., 2012; Blich et al., 2006; Hellman et al 2017), while some studies found left atrial enlargement to predict unsuccessful ECV (Kirchhof et al., 2002; Toso et al., 2012). Successful ECV can be predicted also with certain procedure-related technical factors, such as antero-posteriorly positioned electrodes (Botto et al., 1999; Kirchhof et al., 2012) and the use of biphasic defibrillation waveform (Mittal et al., 2000).

Cardioversion entails a risk of thromboembolic complications (Airaksinen et al., 2013). As mentioned earlier, AF predisposes to thrombus formation in the left atrium and the gradually improving flow circumstances after conversion to sinus rhythm may cause embolization of the previously formed thrombus. Therefore, if ECV is to be performed in patients without the required 3 week anticoagulation and an AF episode duration over 48h, a transesophageal echocardiography should be performed to rule out thrombus in the LAA (Klein et al., 2001; Calkins et al., 2012; Cappato et al., 2014; Kirchhof et al., 2016). Rhythm conversion from AF to sinus rhythm has been shown to temporarily reduce the blood flow velocity in the LAA, which is the most common source of AF-related cardiogenic embolisms (Grimm et al., 1993). This generally accepted concept of atrial stunning acting as a catalyst for thrombus formation offers a logical explanation to the post-cardioversion risk of thromboembolic complications.

In large retrospective analysis of 7,660 cardioversions for acute (<48 hours) AF in patients with no anticoagulation, the 30-day risk of thromboembolic complications was 0.7% (95% CI 0.5%-1.0%) (Airaksinen et al., 2013). The study also showed that the risk of post-cardioversion thromboembolism can be stratified by using the conventional risk factors for AF related stroke. The risk of stroke after elective ECV in adequately anticoagulated (>3 weeks prior to ECV) patients has been reported to range between 0.5% and 0.8% (Klein et al., 2001). Furthermore, a recent retrospective study including 1424 elective ECVs showed an association between 30-day thromboembolism risk and anticoagulation intensity, as the risk was 0.1% in patients with INR≥2.5 and 0.9% in patients with INR 2.0-2.4 (Hellman et al., 2017).

2.3.1.2 Pharmacological cardioversion

Certain antiarrhythmic drugs (AAD) can be used to restore sinus rhythm in patients with recent onset AF. The obvious benefit of pharmacological cardioversion is that no general anesthesia or fasting is needed. However, the success rate is markedly lower than with ECV, approximately 50% (Dankner et al., 2009; Chen et al., 2013; Gitt et al., 2013). Commonly used agents for pharmacological cardioversion include flecainide, propafenone, vernakalant and amiodarone

(Camm et al., 2011; Savelieva et al., 2014; Kirchhof et al., 2016). Certain comorbidities and patient characteristics restrict the use of these drugs, such as structural heart diseases (flecainide and propafenone), severe aortic stenosis, severe left ventricular dysfunction or hypotension (vernakalant) (Camm et al., 2011; Kirchhof et al., 2016). The use of ECV is often preferred over pharmacological cardioversion due to the better efficacy and shorter procedure duration of ECV. Also, the availability of doctors with expertise in anesthesiology is increasing in emergency departments.

2.3.1.3 Maintaining sinus rhythm – antiarrhythmic drugs

Maintaining sinus rhythm is equally as important as the rhythm conversion itself. As the pathophysiology of AF is becoming better understood, the treatment targets are shifted more towards upstream therapies in an effort to reduce the likelihood of AF (Savelieva et al., 2011). The concept of atrial cardiomyopathy has been recently introduced and the structural and electrical remodeling of the atrial tissue is becoming more understood (Maan et al., 2014; Ferrari et al., 2016; Goette et al., 2016). These findings have promoted the role of renin-angiotensin inhibitors and mineralocorticoid receptor antagonists, polyunsaturated fatty acids and statins in AF management (Savelieva et al., 2011). Furthermore, novel drug therapies to reduce AF burden are actively being developed. Target mechanisms include for instance the reduction of atrial fibrosis and ion channel remodeling (Fragakis et al., 2016).

Long-term AAD therapy should be aimed at reducing the symptoms of AF and reducing AF episodes instead of preventing AF recurrences altogether (Kirchhof et al., 2016). According to a Cochrane Review, AADs reduce AF recurrences by 20-50% compared to patient without AADs (Lafuente-Lafuente et al., 2015). Most commonly used AADs in long-term AF treatment are flecainide, amiodarone, sotalol and dronedarone (Kirchhof et al., 2016). The use of these drugs necessitates regular electrocardiograph (ECG) and laboratory controls to detect potential proarrhythmic and extracardiac adverse effects. The 2016 ESC guideline on management of AF suggests a strategy where the safety of the AAD (rather than the efficacy) should be the primary determinant in selecting the drug (Kirchhof et al. 2016). In addition to medication, underlying and concomitant cardiovascular conditions should be managed to reduce AF recurrences and symptoms (Abed et al., 2013; Pathak et al., 2014).

2.3.1.4 Maintaining sinus rhythm – caheter ablation

Spontaneous paroxysms of AF are commonly triggered by ectopic electrical waves originating from the pulmonary veins, which then propagate to the atrial tissue causing re-entrant wavelets (Haïssaguerre et al., 1998). Electrical isolation of the pulmonary veins and the consequential interruption of the wave propagation to atrial tissue is the main target of modern AF ablation therapy (Calkins et al., 2012; Kirchhof et al., 2016; Kuck et al., 2016a).

Several randomized controlled trials have shown that especially in patients with paroxysmal or persistent (probably also longstanding persistent) symptomatic AF episodes during AAD, catheter ablation reduces AF recurrences compared to AADs (Calkins et al., 2009; Wilber et al., 2010; Ganesan et al., 2013). The efficacy of catheter ablation as the first-line treatment option for paroxysmal AF is considered to be only moderate (Cosedis Nielsten et al., 2012; Morillo et al., 2014; Hakalahti et al., 2015). According to large randomized trials, sinus rhythm without symptomatic AF recurrence is achieved in 50-70%, after which the disease progression commonly results in recurrence of AF episodes in the following years (Ganesan et al., 2013; Verma et al., 2015; Kirchhof et al., 2016; Kuck et al., 2016b)

The recently published CASTLE-AF –study results suggest that hospitalizations and adverse outcomes could be prevented with catheter ablation therapy in patients with heart failure, although no other studies assessing these outcomes have yet been published (Marrouche et al., 2009; Kirchhof et al., 2013; Marrouche et al., 2018). Furthermore, current guidelines suggest that anticoagulation for stroke prevention should be continued regardless of the ablation result in at-risk patients (January et al., 2014; Kirchoff et al. 2016). Ablation as a procedure is not risk-free, as the risk of severe intra- or postprocedural complications is 2-3%, including cardiac tamponade, stroke/TIA, pulmonary vein stenosis and oesophageal injury (Kirchhof et al., 2016).

2.3.2 Rate control strategy

2.3.2.1 Pharmacological rate control

Ventricular rate control strategy in AF is usually implemented in patients who have either unsuccessful rhythm control strategy or in patients with little or no symptoms. In patients with acutely elevated ventricular rate, secondary reasons (such as anemia, infections, hyperthyroidism or pulmonary embolism) have to be

considered before initiating rate control medication. The optimal target heart rate has been investigated in a randomized study (the RACE II Study) concluding that a simple target of <110 beats/minute was adequate in terms of the composite clinical end-point (death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events) (Van Gelder et al., 2010).

There is no solid evidence as to which rate control medication is more efficient or safe than others in the long-term rate control (Al-Khatib et al., 2014). Among the most commonly used medications are beta-blockers, digitalis, diltiazem, verapamil and sometimes amiodarone (Kirchhof et al., 2016). The clinical circumstances and patient characteristics dictate the selection of medication, as for instance in patients with reduced left ventricular ejection fraction (LVEF), negatively inotropic verapamil and diltiazem should be avoided (Elkayam, 1998; Ponikowski et al., 2016). The first-line treatment option for long-term rate control is typically beta-blocker monotherapy, which does not appear to improve prognosis in patients with AF and heart failure as opposed to patient with sinus rhythm and heart failure (Kotecha et al., 2014; Kotecha et al., 2017). Verapamil and diltiazem also provide effective rate control and relieve AF related symptoms, with the limitation of negative inotropy (Nikolaidou et al., 2009; Ulimoen et al., 2013). Digitalis has been in clinical use for over two hundred years and still has a role in AF treatment. An association between digitalis use and increased mortality in AF patients has been suggested, but different study results are inconsistent as many studies found no evidence of the connection (Rathore et al., 2003; Gheorghiade et al., 2013; January et al., 2014; Turakhia et al., 2014; Kirchhof et al., 2016). Amiodarone is an efficient rate control drug, which can be administered intravenously in acutely decompensated patients with very high ventricular rate (Kirchhof et al., 2016). However, long-term amiodarone use is often complicated by the multiple extracardiac side effects.

2.3.2.2 AV-nodal ablation and pacemaker implantation

Pharmacological rate control strategy does not always adequately lower ventricular rate and relieve symptoms. In these situations, av-nodal ablation and a single lead ventricular pacemaker implantation can be performed to permanently limit the ventricular rate in a safe and fairly simple procedure (Queiroga et al., 2003; January et al., 2014 Kirchhof et al., 2016). Usually the pacemaker implantation takes place several weeks before the ablation to ensure lead stability and proper function of the pacemaker. Av-nodal ablation should not be considered as a first-line treatment for rate control, as patients are left permanently pacemaker de-

pendent (January et al., 2014; Kirchhof et al., 2106). In patients with cardiac resynchronization therapy (CRT) pacemaker, the rate control is of particular importance. Generally patients in sinus rhythm gain better prognosis improvement than patients in AF and a lower heart rate maximizes the amount of biventricular pacing. Furthermore, an observational prospective study of 7,384 CRT patients found that the mortality rate of patients in AF was equal to patients in sinus rhythm only if the rate control in AF was achieved through av-nodal ablation as opposed to rate-lowering drugs (Gasparini et al., 2013).

2.4 Clinical challenges in management of atrial fibrillation

2.4.1 Selecting the management strategy – rate control vs. rhythm control

The choice between rate control and rhythm control should be assessed individually by considering the risks and benefits of both strategies as well as the chances of maintaining sinus rhythm control in the long run. Long-lasting AF episodes induce electrical and structural remodeling of the atrial tissue rendering it more prone to further AF episodes – "AF begets AF" (Wijffels et al., 1995; Koebe et al., 2008). However, there are no data showing that rhythm control strategy could improve prognosis or prevent disease progression even in young patients (Van Gelder et al., 2002; Wyse et al., 2002; Wasmer et al., 2014; Lafuente-Lafuente et al., 2015). Even in patients suffering from congestive heart failure, rhythm control strategy does not seem to reduce the rate of cardiovascular death (Roy et al., 2008). Especially the AFFIRM (Wyse et al., 2002) and RACE-trials (Van Gelder et al., 2002) had an important impact on clinical practice by reducing the number of cardioversions and increasing the number of av-nodal ablations (Mason et al., 2005).

The most common reason for resiliently pursuing sinus rhythm is symptom improvement, while other justified reasons include for example tachycardia related cardiomyopathy, AF provoked by acute temporary illness and ineffective rate control (January et al., 2014). If rhythm control strategy turns out to be unsuccessful (i.e. failed cardioversion or frequent AF recurrences despite AAD and/or ablation), rate control remains as the only viable strategy. As discussed previously, the risk of unsuccessful ECV and the early recurrence of AF can be evaluated with certain risk factors (Grönberg et al., 2015). Furthermore, repetitive cardioversions predispose patients to treatment related thromboembolisms, especially if the rhythm converts back and forth between sinus rhythm and AF (Airaksinen et

al., 2013). Taking these findings into consideration, clinical tools for evaluating the pros and cons associated with each management strategy are warranted.

2.4.2 Stroke risk assessment using CHA_2DS_2-VASc score

The risk of AF-related thromboembolic complications varies significantly according to patient characteristics and comorbidities. Several risk scores have been developed over the past two decades for individual stroke risk stratification (Gage et al., 2001; Fang et al., 2008; Lip et al., 2010; Singer et al., 2013; Hijazi et al., 2016a). In 2001, earlier risk evaluation schemes from the Stroke Prevention and Atrial Fibrillation (SPAF) investigators and Atrial Fibrillation Investigators (AFI) were merged to form the $CHADS_2$-scheme (Atrial fibrillation investigators, 1994; Stroke Prevention in Atrial Fibrillation Investigators, 1995; Gage et al., 2001).

In the $CHADS_2$-scheme, one point is assigned to prior cerebral ischemia, history of hypertension, diabetes mellitus and chronic heart failure, while two points are assigned to patients 75 years of age or older. This scheme was further developed to more effectively characterize patients as "truly low" risk of thromboembolic complication, by introducing the CHA_2DS_2-VASc –scheme in 2010 (Lip et al., 2010; Olesen et al., 2011a; Olesen et al., 2012; Coppens et al., 2013; Potpara et al., 2013). The stroke rate in low risk category according to $CHADS_2$ score 0, was 1.9% (95% CI, 1.2%-3.0%) per year and 0% according to CHA_2DS_2-VASc score 0, although there were only 103 patients with low stroke-risk in the original CHA_2DS_2-VASc publication (Gage et al., 2001; Lip et al., 2010).

The CHA_2DS_2-VASc stratifies the risk of thromboembolic complication in patients without anticoagulation. Risk points are assigned for congestive heart failure, hypertension, Age ≥ 75 (two points), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (two points), vascular disease, Age 65 to 74, sex category (female) (Lip et al., 2010). This risk stratification scheme is based on the Euro Heart Survey data of 1084 patients with no anticoagulation, where it reached a modest c-statistic of 0.61 (95% CI 0.51-0.70) (Lip et al., 2010). It has since been further validated in several studies in which the c-statistics have ranged from 0.59 to 0.89, while the annual stroke risk for low-risk patients was between 0% and 1.67% (Olesen et al., 2011a; Friberg et al., 2012b; Potpara et al., 2012; Coppens et al., 2013; Okumura et al., 2014; Chao et al., 2016). Currently, the most used stroke risk assessment tool in clinical practice is the guideline-recommended CHA_2DS_2-VASc score (Lip et al., 2010; January et al., 2014; Kirchhof et al., 2016).

2.4.3 Bleeding risk assessment using HAS-BLED score

The reduction of thromboembolic complications has to be weighted against the inherent risk of major bleeding complications associated with OAC. Similarly to stroke risk scores for predicting thromboembolic complications in AF patients, numerous bleeding risk assessment tools have been developed to aid clinical decision making when considering AF patients for long-term OAC therapy (Gage et al., 2006; Pisters et al., 2010; Fang et al., 2011; O'Brien et al., 2015). The first bleeding risk score for AF patients was the complex $HEMORR_2HAGES$ (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke) score introduced in 2006 (Gage et al., 2006). In 10 years, the scores have evolved to a simpler structure and to include biomarkers in addition to clinical history, as the most recent published bleeding score, the ABC (age, biomarkers and clinical history) bleeding score demonstrates (Hijazi et al., 2016a; Hijazi et al., 2016b).

Currently the most used bleeding risk stratification tool is the HAS-BLED score, which is based on the Euro Heart Survey data of 2,242 patients on OAC experiencing a moderately low number (n=53) of major bleeds during a 12 months follow-up period (Pisters et al., 2010). Score points are assigned for hypertension (systolic blood pressure > 160mmHg), abnormal liver function or renal insufficiency, history of stroke, bleeding history or predisposition to bleeding, labile INR, >65 years of age and the concomitant use of drugs or alcohol (1 point each). There are several validation studies on HAS-BLED, which has reached c-statistics of 0.61 – 0.80 in predicting bleeding complications (Lip et al., 2011; Olesen et al., 2011b; Apostolakis et al., 2012; Friberg et al., 2012b; Gallego et al., 2012; Lip et al., 2013; Roldan et al., 2013). At HAS-BLED score ≥3, the bleeding risk is considered to be high, intermediate at 1-2 and low risk at HAS-BLED score 0. There are variable bleeding rates reported at each HAS-BLED score level, because the reported bleeding severity and the use of OAC varies considerably between studies. Recognizing these differences between studies, the annual bleeding risk in the low risk category (HAS-BLED 0) is between 0 and 1.1%. (Lip et al., 2011; Olesen et al., 2011b; Apostolakis et al., 2012; Friberg et al., 2012b; Gallego et al., 2012; Roldan et al., 2013) In the high bleeding risk category, the original HAS-BLED study reports a 3.74%-12.0% annual bleeding risk at HAS-BLED scores 3 – 5 respectively (Pisters et al., 2010). In a large prospective cohort study (48,599 patients with AF and OAC), the risk of major bleeding was 2.4%-15.5% annually at score levels 3-6 respectively (Friberg et al., 2012b). The risk of intracranial bleedings has been reported to vary between 0.2% and 10.9% per year in patients with HAS-BLED score 0 and 4 respectively (Lip et al., 2013).

2.4.4 Clinical implementation of risk scores

The evaluation of AF related stroke risk using the CHA_2DS_2-VASc score is given a class I, level B recommendation in the American and a class I, level A recommendation in the European guidelines (January et al., 2014; Kirchhof et al., 2016). The quideline recommendations and the simplicity of the score have led to its widespread use in clinical practice. The score performs optimally in selecting low stroke risk patients, who do not benefit from OAC (Lip et al., 2010; Potpara et al., 2012; Kirchhof et al., 2016). It should be noted that most AF patients require OAC according to the CHA_2DS_2-VASc score, as only less than 10% of patients with AF are categorized as low stroke risk (Lip et al., 2010; Olesen et al., 2011a). The aforementioned guidelines also suggest that a high bleeding risk score should result in correcting modifiable bleeding risk factors, closer observation of INR (warfarin users) and more frequent controls, whereas withholding OAC based on bleeding risk scores only is not recommended (January et al., 2014; Kirchhof et al., 2016).

To identify patients who could benefit most from OAC therapy, Friberg et al. analyzed the net clinical benefit (ischemic strokes versus intracranial bleeds) of OAC therapy in different CHA_2DS_2-VASc and HAS-BLED score classes from a large Swedish hospital discharge register (Friberg et al., 2012a). They found that patients with CHA_2DS_2-VASc score 0 and HAS-BLED score 2 benefited the least and CHA_2DS_2-VASc score 6 and HAS-BLED score 4 the most from OAC therapy. Some risk factors (hypertension, prior stroke and age) are included in both CHA_2DS_2-VASc and HAS-BLED scores, which means that both scores are often high in patients with multiple comorbidities. However, the use of CHA_2DS_2-VASc score for predicting bleeding complications and HAS-BLED for stroke predicting is discouraged because of inadequate predicting performance (Roldan et al., 2013).

2.4.5 Warfarin overanticoagulation

2.4.5.1 Definition and epidemiology

The time spent in the therapeutic anticoagulation range in different studies varies between 56.7% and 66.4% according to study setting (van Walraven et al., 2006). The incidence of excessive warfarin anticoagulation intensity (i.e. overanticoagulation) varies significantly between publications due to differences in the definition of overanticoagulation and study patient populations. In a retrospective anal-

ysis of 1020 patients on warfarin (of whom 39.4% had AF), attending an outpatient anticoagulation clinic, 603 (4.7%) INR samples out of 12 897 were ≥4 (Wittkowsky et al., 2004). In a prospective cohort study of 1077 patients on VKA with heart failure, up to 396 (37%) patients had INR >6 (Visser et al., 2004). A prospective analysis of 3090 patients acutely hospitalized and referred to internal medicine department included 412 patients on VKA, 40 (9.7%) of whom suffered overanticoagulation defined as INR >6 (Marie et al., 2012). A retrospective study of 2379 patients receiving warfarin, found INR ≥5 in 507 (21.3%) patients, and an increasing incidence of overanticoagulation with increasing age (Froom et al., 2003). In the randomized, prospective and double-blinded COAG-trial (Clarification of Optimal Anticoagulation through Genetics), comparing genotype-guided versus clinically based warfarin dosing, 1015 patients received warfarin and the overall incidence of INR ≥4 was 18,9% within the first 4 weeks of warfarin (Kimmel et al., 2013).

Several studies utilized the Rosendaal linear interpolation method for calculating the "time spent in INR category" (Rosendaal et al., 1993). In a large retrospective study including 13,559 AF patients from an integrated health care system (Kaiser Permanente of North California), the person years spent in INR ≥4 was 2.1% and in a prospective study of 472 AF patients, the person years spent in INR ≥4 was 2.0% (Hylek et al., 2003; Hylek et al., 2007). In a large retrospective cohort study of 10,020 patients on OACs, patients spent 14.2% of time in INR >3 (van Walraven et al., 2007).

2.4.5.2 Mechanisms

Overanticoagulation is a complex process in which several constituting factors have been identified. Intuitively, the clinical scenario in which the INR sample was taken plays a vital role. In heart failure, the liver congestion results in impairment of liver function (i.e. decreased clotting factor synthesis) (Visser et al., 2004). The resulting pharmacodynamic changes manifest as increased responsiveness to warfarin and thus predispose to overanticoagulation (Penning-van Beest et al., 2001; Self et al., 2006). Similarly, the impaired protein synthesis in different hepatic diseases causes the amount of most coagulation factors to decline (Mammen, 1992; Visser et al., 2004). In advanced renal disease, the activity of CYP enzymes is decreased and the response to warfarin is increased (Elston et al., 1993; Dreisbach et al., 2003). Fever and other hypermetabolic conditions have also been shown to increase warfarin response through increased clotting factor catabolism (Richards, 1943; Owens et al., 1962). Dietary causes for overanticoagulation are most commonly caused by changes in the intake of vita-

min K (Harris et al., 1995; Holbrook et al., 2005). However, garlic and herbal derived products, such as danshen and dong quai interact with warfarin by enzyme induction and amplification of the anticoagulant effect of warfarin (Zhou et al., 2007). Alcohol consumption increases the amount of warfarin through several mechanisms: protein-binding interactions of warfarin, CYP interactions (1A2 and 3A4) and deteriorating liver function (Havrda et al., 2005; Reddy et al., 2015). Cigarettes have been reported to include compounds that induce CYP1A2 increasing the sensitivity to warfarin, after smoking cessation (Zevin et al., 1999; Evans et al., 2005). Previous studies have shown that advancing age increases sensitivity to warfarin through low vitamin K stores and low concentrations of vitamin K dependent factors (Shepherd et al., 1977; Gurwitz et al., 1992). Logically, excessive warfarin dosage and low INR test frequency offer simple explanations for INR elevations in some cases (Samsa et al., 2000; Berg et al., 2013). Polymorphism of CYP2C9 and VKORC1 naturally accounts for higher rates of overanticoagulation in patients with these genotypes (Higashi et al., 2002; Limdi et al., 2008).

The numerous interactions with concomitant medication (e.g. amiodarone, paracatamol, many antifungals and antibiotics) play an essential role in the clinical management of patients on warfarin. Several mechanisms of drug interactions that lead to warfarin overanticoagulation have been proposed, such as inhibition of clearance, inhibition of vitamin K, increased metabolism of clotting factors and inhibition of VKOR, while many mechanisms of interactions remain unknown (Owens et al., 1962; Bechtold et al., 1984; Heimark et al., 1992; Cropp et al., 1997; Thijssen et al., 2004; Ageno et al., 2012). Similar mechanisms have been described to explain interactions between chemotherapeutic agents and warfarin (Pangilinan et al., 2007).

2.4.5.3 Clinical significance

As described above, regardless of stable dosing of warfarin the intensity of anticoagulation may vary considerably in different clinical situations. The time in treatment range (TTR) during warfarin treatment varies considerably between countries in the large randomized NOAC-trials, ranging from 44% to 80% (Wallentin et al., 2010; Wallentin et al., 2013; Piccini et al., 2014). In a large Finnish retrospective register study, better describing the actual real world scenario, the median TTR was 67% (Lehto et al., 2017).

Considering that even a pharmacists-managed dosing of warfarin could not prevent INR elevations from occurring, the risk of overanticoagulation can be considered to concern virtually all patients on warfarin treatment (Berg et al., 2013).

Labile INR is considered to be a risk factor for bleeding complications, according to the widely used HAS-BLED score (Pisters et al., 2010). Overanticoagulation carries high risk for intracranial bleeding complications when INR reaches ≥4.5 (Hylek et al., 2003). In a study of patients initiating warfarin treatment (first year of treatment), INR≥4 significantly increased the risk of major bleeds (Hylek et al., 2007). In an older retrospective cohort study including 1950 patient-years, the first 3 months of warfarin therapy were found to associate with increased risk for major bleedings (Fihn et al., 1993). Furthermore, excessive anticoagulation intensity is a significant predictor of 60-day mortality and an increasing INR has been shown to increase mortality rate after INR reaches ≥2.5 (Oden et al., 2002; Koo et al., 2004). Low warfarin treatment quality in AF patients, measured utilizing the TTR, associates with bleeding events and mortality (Lehto et al., 2017). These severe consequences of overanticoagulation and the high number of patients at risk confirm the clinical significance of the phenomenon of excessive warfarin anticoagulation.

3 AIMS OF THE STUDY

The aim of this dissertation is to gain new information on common clinical problems complicating the management of AF.

1. To develop a simple tool for stratifying the risk of unsuccessful ECV of acute AF (I)

2. To describe the incidence and predictors of and to investigate the clinical manifestations and consequences of severe warfarin overanticoagulation (II and III)

3. To assess the CHA_2DS_2-VASc and HAS-BLED scores in patients experiencing either an intracranial bleeding or an ischemic stroke (IV)

4 MATERIALS AND METHODS

4.1 Study designs and patient populations

4.1.1 Study I

The FinCV study (ClinicalTrials.gov Identifier: NCT01380574) is an observational retrospective multicenter study on cardioversion for acute AF. The study population consisted of 3134 patients undergoing 7660 cardioversions for acute AF in two university hospitals (Turku University Hospital, Turku, Finland and Kuopio University Hospital, Kuopio, Finland) and one central hospital (Satakunta Central Hospital, Pori, Finland) between 2003 and 2010. The study data included all patients with ≥18 years of age, admitted to emergency departments of the participating hospitals for acute AF. In total, 5,713 ECVs in 2,868 patients were included in the analysis.

Patients from Turku University Hospital region and Satakunta Central hospital region were assigned to the derivation cohort and patients from Kuopio University Hospital region to the validation cohort in accordance with the geographic location of the participating centers. The derivation cohort included two thirds of the total amount of ECVs (3,716) and the validation cohort one third (1,997).

Patients were identified from emergency room admission registries as well as hospital discharge registries. The study data, including type and duration of AF and details on patient characteristics, and information on the cardioversion were collected from electronic patient records retrospectively, to an electronic case report form. In patients with multiple ECVs, only the first one was included. To ensure adequate and reliable follow-up data, only patients living within the catchment area of the participating hospital were included. A follow-up period of 30 days was recorded to register AF recurrence.

ECV was performed under general anesthesia, and pre- and post-cardioversion electrocardiograph (ECG) recordings were recorded. If sinus rhythm was not achieved or patient was discharged in AF, the ECV outcome was defined as initial failure. The composite of initial failure and recurrence of AF within 30 days of ECV was considered as a short-term failure of ECV

4.1.2 Studies II and III

Studies II and III (ClinicalTrials.gov Identifier: NCT02761941) are based on the Excessive warfarin anticoagulation (EWA) Study data. The EWA study is a retrospective observational study on patients with severe warfarin overanticoagulation. The patient population was identified with computer searches from the la-

boratory database of Turku University Hospital district by screening all INR samples between 2003-2015. In total, 961431 INR samples were screened to find 13,618 patients living in the aforementioned region with one or more INR ≥ 2. Within this group, electronic patient records and discharge registries were reviewed. All patients (age ≥18) fulfilling the following criteria were included in the study and allocated to either the excessive warfarin anticoagulation (EWA) group or control group:

EWA group (412 patients)	**Control group (405 patients)**
warfarin anticoagulation	long term warfarin anticoagulation
prior diagnosis of AF	prior diagnosis of AF
INR ≥9 at least once	regular INR controls
	all INR values ≤ 4

EWA was defined as INR ≥9, which is the highest numerical INR value of the laboratory results scale. Long-term warfarin anticoagulation in the control group patients was defined as >730 days since the initiation of warfarin treatment. The definition of regular controls was that the maximum INR interval in days was 60, and the mean interval in days was 32. The index date for data collection in the EWA group was obviously the date of INR ≥9 and in the control group it was the date of the first occurrence of the highest INR value (2.7-4.0) for each patient. In the case of multiple EWAs in one patient, only the first one was included in the analysis. All patient records from Turku University Hospital and Turku City hospital were reviewed and the data was collected using an electronic case report form. Data on patient characteristics, medication, as well as events prior to, during and after the INR ≥9 event were recorded. Short and long-term mortality data was acquired from the Statistics Finland (National Statistical Service in Finland). A 90-day follow up on thromboembolic and bleeding complications was recorded. Bleeding complications were scored according to the International Society on Thrombosis and Haemostasis (ISTH) / Scientific and Standardization Committee (SCC) score (Rodeghiero *et al.*, 2010).

4.1.3 Study IV

The study IV (ClinicalTrials.gov Identifier: NCT02146040) data (the FibStroke Study) were retrospectively collected from the electronic patient records of two university hospitals (Turku University Hospital and Kuopio University Hospital) and two central hospitals (Satakunta Central Hospital and Central Finland Cen-

tral Hospital) covering a population of over 1.2 million people. The patient population was identified from hospital discharge records with computer searches. The comprehensive data included all patients with a diagnosis of AF or atrial flutter who suffered an ischemic stroke, a transient ischemic attack (TIA) or an intracranial bleeding (traumatic or non-traumatic) during 2003-2012 (2006-2012 in Central Finland Central Hospital). The patient characteristics, neurological event details, laboratory results, operations and procedures, preceding cardioversions (within 30 days) as well as comprehensive medication data were recorded to an electronic case report form. In addition, the 30-day mortality data was collected. For the current analysis, patients who suffered a TIA and patients with AF diagnosis after the index event were excluded. Two study groups were created: the Intracranial bleeding group and the Ischemic stroke group. The CHA_2DS_2-VASc and HAS-BLED scores were calculated for all patients in both study groups. All patients were given 0 points for labile-INR risk factor in the HAS-BLED score. To evaluate the relative risk of ischemic stroke and intracranial bleeding, an ischemic stroke/intracranial bleeding (IS/IB)-ratio was calculated by dividing the absolute number of ischemic strokes with the absolute number of intracranial bleedings within each score category. For the supplementary analysis of patients with HAS-BLED score > CHA_2DS_2-VASc score, all bleeding complications were reviewed from the patient records. These bleeding events were classified according to ISTH/SCC classification as major, clinically significant minor or minor (Schulman et al., 2005).

4.2 Ethical considerations and funding

4.2.1 Study I

The study I complies with the Declaration of Helsinki as revised in 2002. The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland, and the ethics committee of the National Institute for Health and Welfare. Informed consent was not acquired because of the retrospective study design.

The study was funded by the Finnish Foundation for Cardiovascular Research, Helsinki, Finland and State Clinical Research Fund (EVO) of Turku University Hospital, Turku, Finland and the Finnish Medical Foundation, Helsinki, Finland.

4.2.2 Studies II and III

The study protocols of studies II and III were approved by the Medical Ethics Committee of the Hospital District of Southwest Finland. Informed consent was not acquired because of the retrospective study design. The study complies with the Declaration of Helsinki, as revised in 2002.

The study was funded by the Finnish Foundation for Cardiovascular Research, Helsinki, Finland and State Clinical Research Fund (EVO) of Turku University Hospital, Turku, Finland and the Finnish Medical Foundation, Helsinki, Finland.

4.2.3 Study IV

The study IV protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. Informed consent was not acquired because of the retrospective study design. The study complies with the Declaration of Helsinki, as revised in 2002.

The study was funded by the Finnish Foundation for Cardiovascular Research, Helsinki, Finland and State Clinical Research Fund (EVO) of Turku University Hospital, Turku, Finland.

4.3 Statistical analysis

4.3.1 Study I

In study I, the statistical analyses were performed using SAS 9.4 statistical software (SAS Institute Inc, Cary, North Carolina). For comparisons between groups, chi-square and Wilcoxon nonparametric test were used for bivariate comparisons. Logistic regression was used for score point creation, utilizing a repeated-measures model for the derivation data set. Known predictors of unsuccessful cardioversion (age, gender, AF duration, AF episode within the preceding 30 days, previous episode of AF, increasing number of ECVs, atherosclerotic vascular disease, heart failure, diabetes mellitus, renal failure and a history of thromboembolism) were included in the model. Covariates with <0.05 significance were accepted in the final model. Regression coefficients were divided by the smallest coefficient, and rounded to the nearest integer. Hosmer-Lemeshow

goodness-of-fit test value >0.1 was considered acceptable. Model discrimination was evaluated with C-statistics. Finally, the predictive ability of the score was tested in the validation dataset. All tests were 2 sided and the significance level at $p < 0.05$.

4.3.2 Study II

In study II, the statistical analyses were performed with SPSS software (version 23.0, SPSS, Inc., Chicago, Illinois) and SAS software (version 9.4, SAS Institute, Inc., Cary, North Carolina). Normally distributed variables were reported as mean ± standard deviation and as median [inter-quartile range (IQR)] if they were skewed unless stated otherwise. Chi-square test and Fisher's exact test were used for categorical variables, which were presented as absolute and relative frequencies an. Mann-Whitney U test was used for subgroup comparison. A binary stepwise logistic regression analysis (backward Wald) was performed to identify independent predictors of excessive warfarin anticoagulation. Predictors with p value <0.05 in the univariate analysis were included in the multivariate analysis. All tests were two-sided, and statistical significance was set at 5%. The manuscript of study II was written following STROBE guidelines for the reporting of observational studies (von Elm et al., 2007)

4.3.3 Study III

In study III, the statistical analyses were performed with SPSS software (version 23.0, SPSS, Inc., Chicago, Illinois) and SAS software (version 9.4, SAS Institute, Inc., Cary, North Carolina). Normally distributed were reported as mean ± standard deviation and as median [inter-quartile range (IQR)] if they were skewed unless stated otherwise. Chi-square test and Fisher's exact test were used for categorical variables, which were presented as absolute and relative frequencies an. Mann-Whitney U test was used for subgroup comparison. A binary stepwise logistic regression analysis (backward Wald) was performed to identify independent predictors of 30-day mortality and bleeding complications in patients with very high INR values. Predictors with a strong association (<0.1) with the dependent variable in the univariate analysis were included in the multivariate analysis. All tests were two-sided, and statistical significance was set at 5%. Coronary artery disease and not-independent living were excluded from the multivariate model due to significant intercorrelations with other variables. Kaplan– Meier survival curves were constructed to display the time-to-event re-

lationship for the occurrence of death. Study III was written following STROBE guidelines for the reporting of observational studies (von Elm et al., 2007)

4.3.4 Study IV

In study IV, the CHA_2DS_2-VASc and HAS-BLED scores were analyzed in both study groups (Ischemic stroke and Intracranial bleeding) with two-sample t-test. Equality of variances was tested with Levene's test, and equal variance for the CHA_2DS_2-VASc score was assumed. For the HAS-BLED risk score, the equality of variances was not assumed according to Levene's test result. The ratio of ischemic strokes to intracranial bleeds was calculated by dividing the absolute number of ischemic strokes with the absolute number of intracranial bleedings. This manuscript of study IV was written following STROBE guidelines for the reporting of observational studies (von Elm et al., 2007). Statistical analyses were performed with SPSS software (version 23.0, SPSS, Inc., Chicago, Illinois).

5 RESULTS

5.1 Predicting Unsuccessful ECV for Acute Atrial Fibrillation (I)

In study I, the ECV failed (initial failure or AF recurrence within 30 days) in 20.5% and 17.8% of patients in the derivation and validation cohorts respectively. Clinical characteristics of patients in both study groups are presented in Table 1. A multivariate analysis for predicting the combination of initial cardioversion failure and AF recurrence within 30 days (i.e. overall failure of ECV), identified 5 clinical parameters describing the increased risk: age, not the first AF, heart failure, vascular disease and an AF episode within 30 days prior to the ECV. Table 2 shows the results of the multivariate analysis for predictors of unsuccessful ECV, forming the score acronym AF-CVS score. The AF-CVS score reached a c-statistic of 0.67 (95% CI 0.65-0.69). The Hosmer-Lemeshow goodness of fit test p value was 0.84.

Table 1. Patient characteristics. Modified from the original publication I.

Variable	Derivation Cohort (n = 3716)	Validation Cohort (n = 1997)	P-value
Event rate	763 (20.5%)	355 (17.8%)	0.01
Failure of cardioversion	246 (6.6%)	90 (4.5%)	0.001
AF recurrence	517 (13.9%)	265 (13.3%)	0.5
Age (years)			0.044
≤45	311 (8.4%)	153 (7.7%)	
45 - 65	1653 (44.5%)	957 (47.9%)	
≥65	1752 (47.2%)	887 (44.4%)	
First AF episode	588 (15.8%)	823 (41.2%)	<0.001
Heart failure	217 (5.8%)	63 (3.2%)	<0.001
Vascular disease[a]	876 (23.6%)	759 (38.1%)	<0.001
AF within last 30 days	555 (15.0%)	237 (11.9%)	0.001
Additive AF-CVS score	3.9±1.8	3.3±1.9	<0.001
Women	1423 (38.3%)	626 (31.4%)	<0.001
Hypertension	1746 (47.0%)	1067 (53.4%)	<0.001
Diabetes mellitus	372 (10.0%)	181 (9.1%)	0.2
Antiarrhythmic medication	477 (12.8%)	356 (17.8%)	<0.001

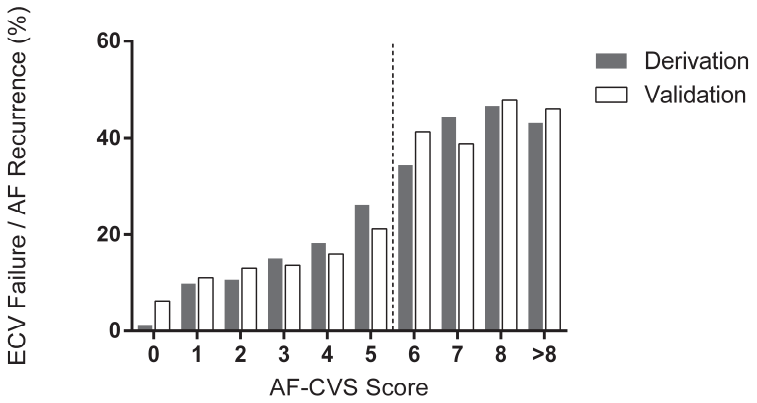
AF = Atrial fibrillation; AF-CVS = Age, First episode of AF, Cardiac failure, Vascular disease, Short interval from previous AF episode. [a]Vascular disease = previous myocardial infarction, peripheral arterial disease or aortic plaque.

Table 2. Multivariate analysis for the predictors of unsuccessful EVC. Modified from the original publication I.

Variable	B-Coefficient	Multivariate Analysis OR (95% CI)	Score Points
Age group[a]	0.27	1.31 (1.13 to 1.52)	1 to 2
Not the **F**irst AF episode	0.44	1.55 (1.19 to 2.02)	2
Congestive heart failure	0.42	1.52 (1.08 to 2.13)	2
Vascular disease[b]	0.32	1.38 (1.11 to 1.71)	1
Short interval (<1 month) from previous AF episode	0.84	2.31 (1.83 to 2.91)	3

AF = atrial fibrillation; CI = confidence interval; OR = odds ratio. [a]Age group: <45 years. 0 points, 45 - 65 years .1 points, >65 years. 2 points. [b]Vascular disease = previous myocardial infarction, peripheral arterial disease or aortic plaque.

Low AF-CVS scores (< 3) showed low failure rates (1.3% to 13.0%), and high scores (> 5) showed high failure rates (34.4% to 66.7%) as presented in Figure 1. Of all patients in our study, the lowest short-term failure rates were seen in men under 45 years of age having their first AF episode (0% to 6% in both derivation and validation datasets). Antiarrhythmic drugs did not influence the predictive performance of the score.



ECV = electrical cardioversion; AF = atrial fibrillation. AF-CVS score points: Age (years): <45 = 0 points; 45 to 65 = 1 point; >65 = 2 points; Not the First AF episode = 2 points; Cardiac failure = 2 points. Vascular disease = 1 point; Short interval (another AF episode within 30 days) = 3 points.

Figure 1. Incidence of ECV failure and AF recurrence in the derivation and validation datasets. From the original publication I.

5.2 Incidence and predictors of excessive warfarin anticoagulation in patients with atrial fibrillation (II)

In study II, we found that 4.1% (n = 564) of patients with INR ≥ 2 at least once, experienced EWA (INR ≥9). Of these patients, we created the study group (EWA Group) by selecting all patients with an AF diagnosis (412 patients). The patient characteristics of the EWA Group and the Control Group patients are presented in

Table 3. A total of 92 patients suffered multiple (2 to 5) EWA events. A total of 105 patients (25.5%) suffered a significant bleed during the very high INR event.

Table 3. Clinical characteristics of patients in studies II and III. Modified from the original publication II.

Patient characteristic	EWA Group (n=412)	Control Group (n=405)	P-value
Age (years)	77.7±10.5	76.6±8.5	0.05
Female	217 (52.7)	223 (55.1)	0.493
CHA_2DS_2-VASc	4.0 ±1.8	3.7 ± 1.5	0.0007
Chronic heart failure	155 (37.6)	55 (13.6)	<0.0001
Treatment for hypertension	235 (57.0)	283 (70.0)	<0.0001
Diabetes	111 (26.9)	99 (24.4)	0.414
History of ischemic stroke	82 (19.9)	57 (14.1)	0.027
Coronary artery disease	130 (31.6)	89 (22.0)	0.002
History of AMI	80 (19.4)	41 (10.1)	0.0002
Peripheral artery disease	34 (8.3)	9 (2.2)	<0.0001
eGFR[a]			
<15	28 (6.9)	0 (0.0)	<0.0001
15-30	58 (14.2)	5 (1.3)	<0.0001
30-60	148 (36.3)	132 (34.6)	0.614
60-90	114 (27.9)	211 (55.2)	<0.0001
>90	60 (14.7)	34 (8.9)	0.012
Independent living[b]	248 (60.2)	338 (83.7)	<0.0001
Psychiatric disorder	21 (5.1)	11 (2.7)	0.103
Dementia	57 (13.8)	23 (5.7)	<0.0001
History of malignancy	104 (25.2)	53 (13.1)	<0.0001
Active malignancy	48 (11.7)	15 (3.7)	<0.0001
Liver disease	12 (2.9)	1 (0.2)	0.003
Mechanical heart valve	16 (3.9)	1 (0.3)	0.0002
Active smoker	35 (8.5)	7 (1.7)	<0.0001
Alcohol abuse[c]	73 (17.7)	6 (1.5)	<0.0001
Recent bleed[d]	15 (3.6)	4 (1.0)	0.018
Recent surgical operation[e]	30 (7.3)	14 (3.5)	0.016
Recent medical treatment[f]	155 (37.6)	67 (16.5)	<0.0001
Concomitant medication			
Cholesterol-lowering drugs	81 (19.7)	161 (39.8)	<0.0001
NSAID	11 (2.7)	3 (0.7)	0.055
Aspirin	18 (4.4)	9 (2.2)	0.116
SSRI/SNRI	38 (9.2)	11 (2.7)	<0.0001
Tramadol	16 (3.9)	4 (1.0)	0.011
Dronedarone	3 (0.7)	3 (0.7)	1.000
Amiodarone	8 (1.9)	2 (0.5)	0.107
Paracetamole	170 (41.3)	146 (36.0)	0.109
Carbamatzepine	5 (1.2)	2 (0.5)	0.451
Antifungal medication	17 (4.1)	0 (0.0)	<0.0001
Recent antibiotic therapy[g]	107 (26.0)	22 (5.4)	<0.0001
Chemotherapeutic agents	12 (2.9)	3 (0.7)	0.034

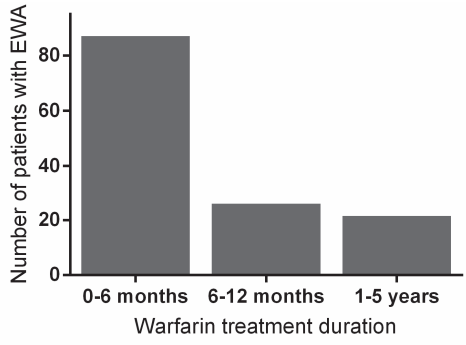
Values are mean ± SD, n (%). AMI = acute myocardial infarction; $CHA_2DS_2$2-VASc = Congestive heart failure, Hypertension, Age 75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); eGFR = estimated glomerular filtration rate (ml/min/1.73 m2); EWA = excessive warfarin anticoagulation; NSAID = non steroidal anti-inflammatory drug; SSRI/SNRI = selective serotonin/norepinephrine reuptake inhibitor [a]Data missing on 27 patients (3.3%); [b]Living at home independently without outside help in daily routines; [c]Alcohol related diagnosis or a hospital/health care center visit due to alcohol use; [d]Bleeding event in the preceding 1 month; [e]Operation in the preceding 1 month; [f]Hospitalization or outpatient visit in the preceding 1 month; [g]Antibiotic therapy in the preceding 14 days.

Logistic regression analyses found multiple independent predictors of EWA, which were assigned to different risk factor categories (permanent, temporary or lifestyle related risk factors) according to the type of the risk factor. Of all significant risk factors for EWA, the strongest were alcohol consumption (OR 24.4, 95% CI 9.85-50.4), severe renal dysfunction (OR 15.2, 95% CI 5.70-40.7) and mechanical heart valve (OR 15.0, 95% CI 1.74-129). The independent predictors of EWA according to the multivariate logistic regression analysis are presented in Table 4. In addition, EWA occurred during the first 6 months of warfarin treatment in 21.2% of patients in the EWA group. The number of patients with EWA per 6 months of warfarin treatment after the initiation of warfarin is presented in Figure 2. The patient distribution to different risk factor categories is illustrated in Figure 3.

Table 4. Independent predictors of excessive warfarin anticoagulation (INR ≥9). Modified from the original publication II.

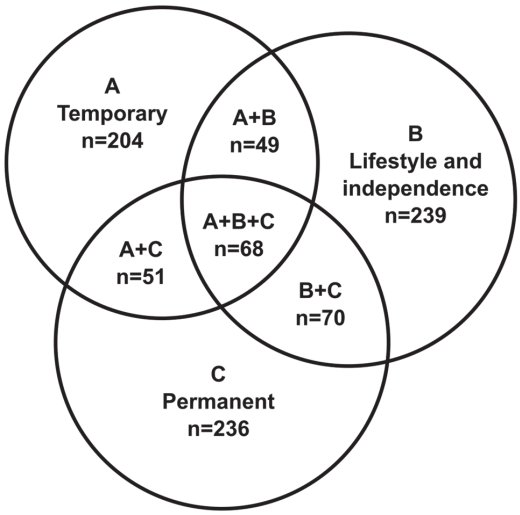
Predictor	Multivariate Analysis OR (95% CI)	P-value
Temporary		
Chemotherapeutic agents	5.61 (1.31-24.1)	0.020
Antibiotic or antifungal therapy[a]	4.57 (2.56-8.16)	<0.0001
Recent medical treatment[b]	2.42 (1.56-3.75)	<0.0001
Lifestyle and independence		
Alcohol abuse[c]	24.4(9.85-50.4)	<0.0001
Active smoking	3.23 (1.19-8.77)	0.021
Not independent[d]	2.63 (1.73-4.00)	<0.0001
Permanent		
Severe renal dysfunction[e]	15.2 (5.70-40.7)	<0.0001
Mechanical heart valve	15.0 (1.74-129)	0.014
Active malignancy	7.07 (3.46-14.4)	<0.0001
Chronic heart failure	2.78 (1.80-4.31)	<0.0001
Treatment for hypertension	0.62 (0.43-0.92)	0.016
Cholesterol-lowering drugs	0.45 (0.30-0.67)	0.001

CI = confidence interval; INR = international normalized ratio; OR = odds ratio. [a]Antibiotic or antifungal medication in the preceding 14 days; [b]Hospitalization or outpatient visit in the preceding 1 month; [c]Alcohol related diagnosis or a hospital/health care center visit due to alcohol use; [d]Patient requiring outside help in daily routines; [e]eGFR < 30 ml/min/1.73 m^2, data missing on 27 patients (3.3%)



Data on patients with warfarin treatment duration >5 years not show.
EWA = excessive warfarin anticoagulation.

Figure 2. Number of patients with EWA per 6-month episodes from the initiation of warfarin treatment. From the original publication II.



EWA = excessive warfarin anticoagulation. (A) Temporary risk factors = Antibiotic or antifungal therapy, Recent medical treatment (Hospitalization or outpatient visit in the preceding 1 month) or Chemotherapy; (B) Lifestyle and independence related risk factors = Alcohol abuse, Active smoking or non-independence in everyday living; (C) Permanent risk factors = Severe renal dysfunction (eGFR<30), Mechanical heart valve prosthesis, Active malignancy or Chronic heart failure.

Figure 3. Number of patients with EWA in each risk factor category. Modified from the original publication II.

Of the permanent risk factors of EWA, a chronic medical condition (heart failure, active cancer, severe renal dysfunction and mechanical heart valve prosthesis) was present in 236 patients (57.3%) with EWA and in 72 control group patients (17.8%). Normal renal function was recorded in only 11.5% (n=94) of all study patients, eGFR was between 60 and 30 in 45.4% (n=371). Impairment of renal

function was found to be a significant risk factor for EWA. All patients with eGFR < 15 suffered an EWA event.

A temporary risk factor was found in 204 patients (49.5%) with EWA and 76 (18.8%) control patients. In 37.6% (n = 155), a recent medical treatment (an outpatient visit to emergency clinic or health center, or hospitalization for a treatment of a medical condition) preceded EWA (within 30 days prior), resulting in a 2.4 fold increase in the risk of EWA. Antibiotic or antifungal treatment was also a significant risk factor (4.6-fold risk) of EWA, as were chemotherapeutics (5.6-fold risk). There was no statistical significance between groups in the use of paracetamol, amiodarone, dronedarone, carbamatzepine, or aspirin. The use of selective serotonin reuptake inhibitors (SSRI)/ selective noradrenalin reuptake inhibitors (SNRI) reached borderline statistical significance in predicting EWA. Lifestyle related risk factors were present in 58.0% (n = 239) patients with EWA and in 2.7% (n =11) of the control group patients.

5.3 Clinical manifestations and outcomes of severe warfarin overanticoagulation (III)

In study III, we analyzed the clinical manifestations of INR ≥9 episodes and the effect on patient outcomes. In total, 4.1% (n=564) of all patients (n=13,618) in the catchment area of Turku University Hospital with an INR ≥2 at least once, suffered an EWA (INR ≥9). All patients in this group with AF (n=412) were included in the study. We identified three different manifestation categories during EWA. A total of 142 patients (34.5%) experienced EWA as a coincidental finding without any symptoms, whereas bleeding symptoms were recorded in 105 patients (25.5%). Other symptoms –group consists of 165 patients (40.0%) who experienced symptoms other than bleeding, such as nausea, fever or shortness of breath. The patient characteristics of both study groups are presented in Table 1 and the characteristics of patients according to clinical manifestation type in Table 5.

The previous INR (before the index event) was higher in the EWA group (3.04±1.44) as compared to the Control group (2.27±0.37). The previous INR was > 3 in 29.6% of the patients (n =42, mean INR 2.91, 95% CI 2.69– 3.14) in the No symptoms group, in 24.8% (n = 26, mean INR 2.67, 95% CI 2.46– 2.89) of the Bleeding symptoms group and in 38.8% (n = 64, mean INR 3.38, 95% CI 3.13– 3.62) of the Other symptoms group. The median intervals between the previous INR and EWA were 15 days (IQR 19), 16 days (IQR 26) and 9 days (IQR 15) in the No symptoms, Bleeding symptoms and Other symptoms groups respectively.

There were 112 bleeding events in 105 during the overanticoagulation event. Nearly half (49.1%) of the bleedings were severe (ISTH class 3-4). A third of the bleeds were from the gastrointestinal tract. Cutaneous, urinary tract and nosebleeds comprised a total of 41.1% of all bleeds during EWA, but most of them were minor (ISTH class 1-2). Five patients in total suffered an intracranial bleeding event. The bleeding types and severity classification are listed in Table 6.

Table 5. Characteristics of patients with EWA according to manifestation. Modified from the original publication III.

Clinical parameter	No symptoms (n=142)	Bleeding symptoms (n=105)	Other symptoms (n=165)
Age, y ± SD	77.6±10.6	76.2±11.4	78.8±9.8
Female, n (%)	71 (50.0)	45 (42.9)	101 (61.2)
CHA_2DS_2-VASc, mean ± SD	4.0±1.8	3.6±1.9	4.5±1.6
Chronic heart failure	47 (33.1)	25 (23.8)	83 (50.3)
Treatment for hypertension	86 (60.6)	59 (56.2)	90 (54.5)
Diabetes	39 (27.5)	22 (21.0)	50 (30.3)
History of ischaemic stroke	25 (17.6)	22 (21.0)	35 (21.2)
Coronary artery disease	48 (33.8)	22 (21.0)	60 (36.4)
History of myocardial infarction	24 (16.9)	15 (14.3)	41 (24.8)
Peripheral artery disease	9 (6.3)	7 (6.7)	18 (11.0)
eGFR< 30[a]	16 (11.6)	20 (19.0)	50 (30.3)
Independent living[b]	85 (59.9)	73 (69.5)	90 (54.5)
History of malignancy	32 (22.5)	37 (35.2)	35 (21.2)
Active malignancy	15 (10.6)	18 (17.1)	15 (9.1)
Recent medical treatment[c]	52 (36.6)	31 (29.5)	72 (46.5)
Alcohol abuse[d]	29 (20.4)	27 (25.7)	17 (10.3)
Recent bleed[e]	0 (0.0)	10 (9.5)	5 (3.0)
Concomitant medication			
Tramadol	1 (0.7)	9 (8.6)	6 (3.6)
Paracetamole	57 (40.4)	39 (37.1)	74 (44.8)
Antifungal medication[f]	9 (6.4)	4 (3.8)	4 (2.4)
Antibiotic therapy[g]	20 (14.1)	18 (17.1)	69 (41.8)

$CHA_2DS_2$2-VASc = Congestive heart failure, Hypertension, Age 75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); eGFR, estimated glomerular filtration rate (ml/min/1.73 m2); EWA = excessive warfarin anticoagulation; SD, standard deviation. [a]Data missing on 27 patients (3.3%); [b]Living at home independently without outside help in daily routines; [c]Hospitalization or outpatient visit during the preceding 30 days; [d]Alcohol related diagnosis or a hospital/health care center visit due to alcohol use; [e]Bleeding event during the preceding 30 days; [f]Antifungal therapy during the preceding 7 days; [g]Antibiotic therapy during the preceding 14 days.

Table 6. Number of observed bleeds and severity classifications during EWA. Modified from the original publication III.

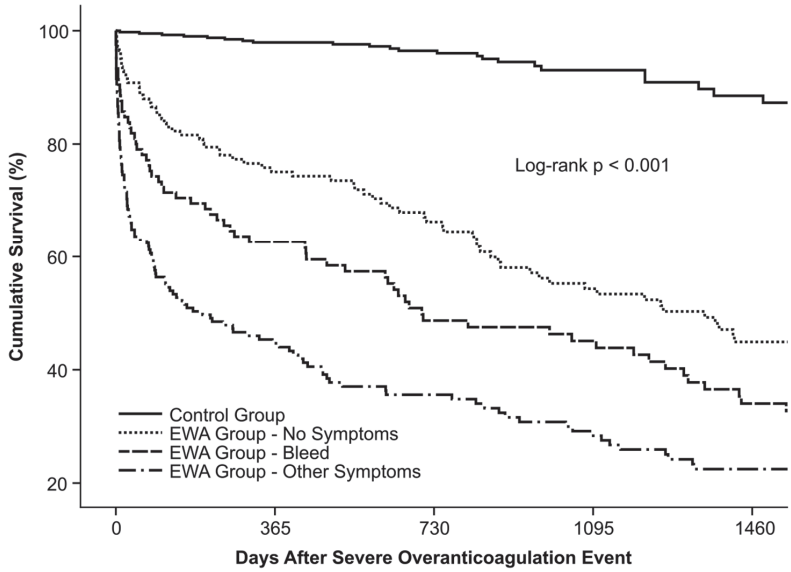
Bleed	ISTH 1	ISTH 2	ISTH 3	ISTH 4	Total
Gastrointestinal, n (%)	10	6	2	19	37 (33.0)
Cutaneous	6	3	6	2	17 (15.2)
Hematuria	5	8	0	2	15 (13.4)
Epistaxis	6	1	4	3	14 (12.5)
Oral cavity	1	2	3	1	7 (6.3)
Other bleed[a]	2	2	0	3	7 (6.3)
Minor wounds	3	0	1	2	6 (5.4)
Intracranial bleed[b]	0	0	3	2	5 (4.5)
Menorrhagia	1	0	0	1	2 (1.6)
Muscle hematoma	0	1	0	0	1 (0.9)
Hemarthrosis	0	0	0	1	1 (0.9)
Total	**34 (30.4)**	**23 (20.5)**	**19 (17.0)**	**36 (32.1)**	**112**

[a]Hemoptysis, retroperitoneal bleed, outer ear bleed; [b]Subdural bleed or intracerebral bleed. EWA, excessive warfarin anticoagulation; ISTH, International Society on Thrombosis and Haemostasis.

According to the multivariate analysis, significant independent predictors of bleeding events during EWA were use of tramadol (OR 3.63, 95% CI 1.28– 10.3, p = 0.015) and a bleeding event within 30 days before EWA episode (OR 5.87, 95% CI 1.93– 17.9, p = 0.002).

Warfarin was discontinued in all patients experiencing the severe overanticoagulation event. Vitamin K was used in 85.7% (n = 353) of patients without difference between the manifestation groups. The effect of warfarin was reversed with medications (prothrombin complex concentrate, solvent detergent (S/D) treated human plasma or tranexamic acid) in 41.9% (n = 44) of patients with a bleed, in 5.9% (n = 4) without symptoms and in 29.4% (n = 20) patients with non-bleeding symptoms. There were only 5 patients with a bleed who did not receive any medications to counteract warfarin.

The short-term (30-day) mortality rate was 20.4% (n = 84) and 0.2% (n = 1) in the EWA group and in the Control group respectively. The manifestation of EWA had a significant impact on mortality as 9.2% (n = 13) of asymptomatic patients, 16.2% (n = 17) of patients with bleeding symptoms and 32.7% (n = 54) of patients with symptoms other than bleeding died within 30 days of EWA. Only 1.7% (n = 7) of patients in the Control group died within 12 months, while the mortality rate was as high as 40.5% (n = 167) in the EWA group. At 4 years, the rates were 4.9% (n = 20) and 62.4% (n = 257) respectively. Kaplan-Meier representation of the cumulative survival in all study groups is illustrated in Figure 4.



No. at risk					
Control Group	405	327	227	98	72
EWA Group - No Symptoms	142	100	78	58	41
EWA Group - Bleed	105	60	41	35	25
EWA Group - Other Symptoms	165	66	44	33	24

EWA = excessive warfarin anticoagulation. Other symptoms = patients suffering from other symptoms than bleeding-related symptoms.

Figure 4. Cumulative survival analysis (Kaplan-Meier) of study patients. Modified from the original publication III

Several predictors of short-term mortality were identified in a multivariate analysis (Table 7). The only bleed to predict short-term mortality was intracranial bleed, but there were only 5 patients in this group. The use of vitamin-K or other drugs used for warfarin reversal did not influence the short-term mortality, thromboembolic complications or the duration of hospital stay.

Table 7. Multivariate predictors of 30-day mortality in patients with EWA. Modified from the original publication III.

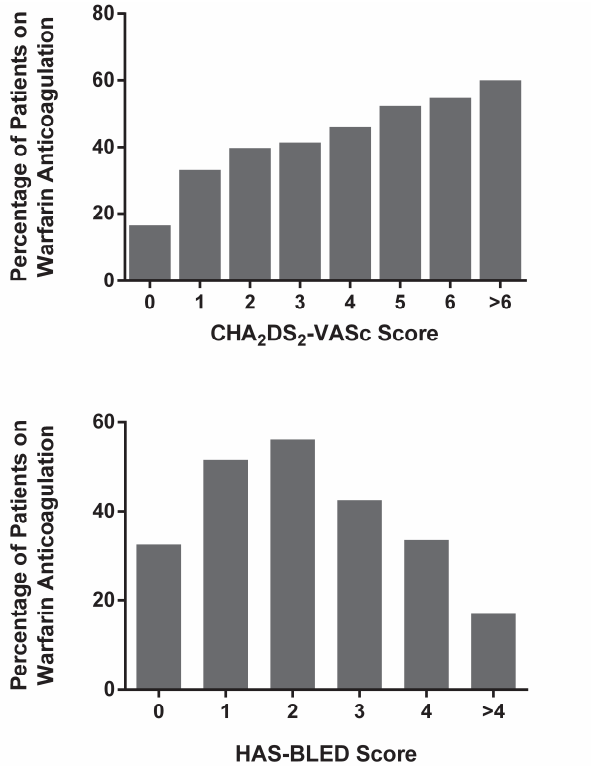
Clinical risk factor	OR (95% CI)	P-value
Intracranial bleed	69.2 (6.60-725)	<0.001
Active malignancy	4.21 (1.95-9.11)	<0.001
Non-bleeding symptoms	4.08 (2.27-7.32)	<0.001
Recent bleed[a]	3.38 (1.04-11.0)	0.043
History of myocardial infarction	2.99 (1.64-5.43)	<0.001
Age ≥ 75 years	2.42 (1.26-4.67)	0.008
eGFR < 30	2.00 (1.08-3.70)	0.028
Recent medical treatment[b]	1.86 (1.06-3-25)	0.030

eGFR = estimated glomerular filtration rate (ml/min/1.73 m2); EWA = excessive warfarin anticoagulation; MI = myocardial infarction. [a]Bleeding event in the preceding 30 days before excessive warfarin anticoagulation. [b]Hospitalization or outpatient visit during the preceding 30 days.

5.4 CHA_2DS_2-VASc and HAS-BLED scores in predicting the risk of stroke versus intracranial bleed (IV)

In study IV, there were 3816 (82.7%) ischemic strokes and 798 (17.3%) intracranial bleedings in 3909 patients with AF. In Figure 5, a clear association between both scores (CHA_2DS_2-VASc and HAS-BLED) and the use of OAC is shown: the higher the HAS-BLED the less patients used OAC, and the higher the CHA_2DS_2-VASc the more patients were on OAC therapy. We recorded 1545 ischemic strokes and 604 intracranial bleeds in patients on warfarin treatment at the time of the event. INR was <2.0 in half of the ischemic strokes (n = 772, 50.5%) and 41.0% (n = 628) of ischemic strokes occurred while INR was between 2-3. Of all intracranial bleeds, 32.8% (n = 192) occurred with INR above the target range, whereas 50.5% (n = 297) of intracranial bleeds occurred during INR within target range.

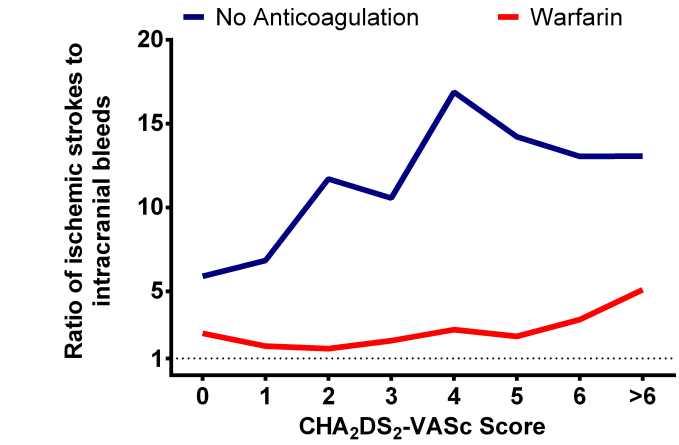
The CHA_2DS_2-VASc score was higher in patients with ischemic stroke (mean 4.16; 95%CI 4.10-4.21) as compared to in patients with intracranial bleeding (mean 3.95; 95%CI 3.83-4.07, p=0.002). There was no significant difference in the mean HAS-BLED scores between groups (2.50; 95%CI 2.46-2.53 vs. 2.44; 95%CI 2.37-2.51, p=0.18).



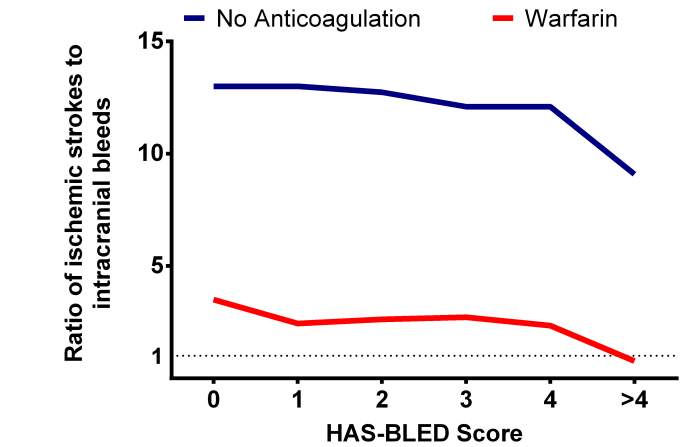
CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); HAS-BLED (modified) = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; OAC = oral anticoagulation. All patients were assigned 0 points for labile INR.

Figure 5. Rate of OAC use according to CHA_2DS_2-VASc and HAS-BLED scores. Modified from the study IV manuscript.

In all CHA_2DS_2-VASc score categories, the absolute number of ischemic strokes outweighed the number of intracranial bleedings, also in patients on warfarin. In patients without anticoagulation, the ischemic stroke/intracranial bleeding (IS/IB)-ratio increased as CHA_2DS_2-VASc score increased. The IS/IB-ratio was reduced with warfarin anticoagulation, and the IS/IB-ratio increased only after CHA_2DS_2-VASc score reached level >5 (Figure 6).



No. of strokes/ intracranial bleeds								
No anticoagulation	81/14	130/19	281/24	444/42	591/35	384/27	261/20	170/13
Warfarin	14/5	47/27	124/78	231/112	346/127	316/136	262/79	204/40



No. of strokes/ intracranial bleeds						
No anticoagulation	52/4	312/24	675/53	745/70	387/32	100/11
Warfarin	21/6	254/104	672/256	440/162	148/63	10/13

CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); HAS-BLED (modified) = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly. All patients were assigned 0 points for labile INR.

Figure 6. Ratio of ischemic strokes to intracranial bleedings in study IV patients. Modified from the study IV manuscript.

Ischemic strokes were the predominant intracranial event also in all HAS-BLED score levels in patients without anticoagulation (Figure 6). The IS/IB-ratio started to decrease only at very high (>4) HAS-BLED level, still remaining as high as 9.09. During warfarin therapy, the IS/IB-ratios were logically lower (2.4-3.5),

and at HAS-BLED >4, the IS/IB-ratio fell below 1 (i.e. the number of intracranial bleeds exceeded the number of ischemic strokes).

In the subgroup analysis of patients with HAS-BLED > CHA_2DS_2-VASc (n = 263, 6.7% of all study patients), we found 221 ischemic strokes and 100 major bleeding event (53 of which were intracranial bleeds). The mean HAS-BLED was 2.77 (95% CI 2.62-2.92) and CHA_2DS_2-VASc 1.55 (95% CI 1.41-1.69) in these patients. A total of 32 (14.5%) strokes occurred during warfarin, half (46.9%) of which during subtherapeutic INR level. There were 22 (41.5%) intracranial bleedings during warfarin, 10 (45.5%) of which during supratherapeutic INR level. Of the 100 major bleeds, 36 (36%) occurred during warfarin, 30 (30%) during aspirin and 5 (5.0%) during aspirin plus warfarin, while 3 (3.0%) during low molecular weight heparin (LMWH). Importantly, the IS/IB-ratio was high in this subgroup (6.10 in patients without anticoagulation and 1.45 with warfarin), showing that most intracranial events are ischemic strokes also in this subgroup, even during warfarin anticoagulation.

6 DISCUSSION

6.1 Predicting unsuccessful electrical cardioversion for acute atrial fibrillation (I)

In study I, we developed a novel risk assessment tool for stratifying the risk of unsuccessful ECV in acute AF. We found that the risk of unsuccessful ECV (composite of initial failure and AF recurrence in 30 days) can be predicted with 5 clinical parameters composing the score acronym AF-CVS. The c-statistic of our score (0.67) was at the same level as in studies on the CHA_2DS_2-VASc score in stroke risk stratification (Lip et al., 2010; Friberg et al., 2012b).The initial success rate of ECV in acute AF has been studied extensively and varies considerably between studies (Burton et al., 2004; Kuppahally et al., 2009; Xavier Scheuermeyer et al., 2010; Bellone et al., 2012; Toso et al., 2012; Grönberg et al., 2015), whereas information on recurrence of AF after initial ECV success and the factors predicting it is scarce (Grönberg et al., 2015). Our study demonstrates that recent AF episodes, reflecting the activity of AF, strongly predict the overall ECV failure (composite of initial ECV failure and AF recurrence in 30 days), as do older previous AF episodes but with a weaker negative effect. The use of AADs, which indirectly reflects the disease severity of AF, was also found to be predictive, but the indications for AADs in everyday clinical practice vary considerably and thus the use of AADs was excluded from the score model.

Older age, heart failure and vascular disease are known risk factors for AF related stroke and thromboembolic complications after ECV (Lip et al., 2010, Airaksinen et al., 2013). In our study, they were found to predict the overall ECV failure and were included in the AF-CVS score. Female gender did not quite reach statistical significance ($p = 0.065$) for predicting overall ECV failure, but it is a known risk factor for AF associated stroke, as well as for thromboembolism and bradyarrhythmic complications after ECV (Lip et al., 2010; Airaksinen et al., 2013; Grönberg et al., 2013; Nuotio et al., 2014).

The AF-CVS score utilizes simple clinical parameters for identifying patients in high risk for short-term ECV failure. This score can be used to help clinical decision making in selecting the optimal treatment strategy for patients with acute AF. Symptomatic patients with high AF-CVS score (>5) should be referred to more intensive rhythm control therapies when appropriate (i.e. catheter ablation or AADs). Considering that rhythm control offers no survival benefit as compared to rate control and that repetitive cardioversions may predispose to thromboembolic complications, asymptomatic patients with high AF-CVS score may be suitable for rate control strategy (Grimm et al., 1994; Van Gelder et al., 2002;

Wyse et al., 2002; Airaksinen et al., 2013). Conversely, AF-CVS score may also be used to identify patients at low risk for ECV failure or AF recurrence.

Study I has the inherent limitations of a retrospective study design, as the data was recorded by physicians performing the ECVs and collected afterwards by study personnel. An obvious limitation is the underestimation of AF recurrences as AF is asymptomatic in almost 40% of patients (Boriani et al., 2015). It should also be noted that AF-CVS score applies only patients with acute AF. In addition, the role of obesity in predicting ECV failure could not be evaluated in this study, because of the lack of data on BMI index or waist to hip ratio.

6.2 Incidence and predictors of excessive warfarin anticoagulation in patients with atrial fibrillation (II)

Study II showed that in AF patients, severe warfarin overanticoagulation (INR≥9) can be predicted with certain clinical characteristics and temporary predisposing factors. The multiplicity of predictors highlights the complexity of the phenomenon of excessive warfarin anticoagulation. While NOACs are currently the first choice in majority of new patients receiving anticoagulation for AF, warfarin is still widely used and remains to be the only option for patients with mechanical heart valve prosthesis (Vahanian et al., 2012; Eikelboom et al., 2013; Nishimura et al., 2014). By identifying the risk factors for severe warfarin overanticoagulation, we may improve the safety of warfarin treatment.

Considering that the initiation of warfarin therapy has been reported to carry risk for major bleeding complications, an important finding in our study was that the first months of warfarin therapy carry the highest risk for overanticoagulation (Fihn et al., 1993; Hylek et al., 2007). Warfarin is often initiated in an acute clinical situation, for example first occurrence of AF, exacerbation of chronic disease or decompensation of heart failure. Early dosing of warfarin may be affected by concomitant medications or patients may not be accustomed to nutritional precautions associated with warfarin.

Alcohol abuse was found to be the strongest risk factor (OR 24.4) predicting excessive warfarin anticoagulation. Direct inhibition of warfarin breakdown, liver impairment and poor drug compliance (such as overdosing while intoxicated) offer explanations for the high risk associated with alcohol (Havrda et al., 2005; Reddy et al., 2015). Because smokers and alcohol abusers are at risk of EWA, supporting abstinence and smoking cessation may stabilize INR levels. In theory, stable anticoagulation achieved with NOACs may be beneficial for some of these

patients (e.g. patients who fail to quit alcohol consumption), but there are no studies to support this hypothesis.

High INR episodes in patients suffering from chronic diseases, such as heart failure, malignancies and chronic kidney diseases, may be a sign of exacerbation of the disease or reflect high disease burden. Spontaneous very high INR values are sometimes observed in the final stages of critical illnesses, reflecting the failing homeostasis of the body rather than a problem with warfarin. Congestion in heart failure impairs liver function and reduces clotting factor synthesis promoting excessive anticoagulation (Visser et al., 2004). Once high INR event occurs, heart failure, advanced age and active malignancy have been shown to prolong the return of INR to therapeutic range, further complicating the clinical scenario (Hylek et al., 2001). Institutionalized and patients needing help in everyday activities were unsurprisingly at risk of EWA. This finding reflects the general disease burden of comorbidities and problems in drug adherence in these patients (Luzny et al., 2014). NOACs might offer stable anticoagulation with simple unvarying dosage, but the detection of overanticoagulation may be more difficult as compared to regularly controlled INR in patients on warfarin.

Considering the fact that renal impairment, a common finding among AF patients, increases the risk of bleedings, cardiovascular and all-cause mortality, it was expected that severe renal impairment strongly predicted EWA (Sarnak et al., 2003; Tonelli et al., 2006; Pavord et al., 2011; Lutz et al., 2014; Boriani et al., 2016). These findings underline the need for careful weighing of the risks and benefits of warfarin anticoagulation in patients suffering from renal impairment. Furthermore, patients on chronic hemodialysis are often withheld from OAC therapy because of the increased bleeding risk, which is in line with our findings as all study patients with eGFR<15 suffered the severe overanticoagulation event (Wizemann et al., 2010; Garg et al., 2016).

Active cancer is considered to be a prothrombotic state, but we found that in warfarin treated patients it predisposes to serious overanticoagulation. However, the number of patients with active malignancies in our study was low. This is because LMWH is usually preferred over warfarin in cancer patients, although there are no recommendations on its use among AF patients as opposed to patients with deep vein thrombosis or pulmonary embolism (Buller et al., 2004).

Mechanical heart valve prosthesis increased the risk of EWA considerably (15-fold risk), which may be the result of excessive dose adjustments in an attempt to avoid thromboembolic complications in subtherapeutic INR levels. Furthermore, the upper limit of the target range is set higher than in patients with AF. These findings are in agreement with an interesting report showing a higher rate of bleedings, death and total complications in mechanical heart valve patients with

higher INR level (2.8-3.2 vs 2.2-2.7) after adjusting for valve position, age and comorbidity (Grzymala-Lubanski et al., 2017). In line with previous reports, antibiotic or antifungal treatment was found to strongly predict EWA in our study (Wittkowsky et al., 2004; Holbrook et al., 2005). Taking this finding into account, frequently controlled INR and strict indications for antibiotic and antifungal prescriptions might prevent EWA events or enable earlier detection of high INR.

The low number of patients on concomitant interactive medications in our study was expected, as the national electronic database for interactive medication (Swedish, Finnish, Interaction X-referencing -database) is widely used in Finland. Interactive medications should be avoided if possible to optimize INR stability and reduce the risk of bleeding complications (Gasse et al., 2005; Pottegard et al., 2012). The interesting finding that long-term statin therapy reduced the likelihood of EWA by 50%, is supported by a previous small study that found statins to be protective against overanticoagulation in warfarin treated patients (Marie et al., 2012). This may be in part due to the fact that patients on long-term statin therapy often have regular clinical controls and thus more attention is paid to comorbidities and other factors affecting anticoagulation stability (such as nutritional factors) as compared to patients without statin therapy.

While various acute and chronic diseases cause hospitalizations/outpatient visits, they also may cause INR elevations as mentioned before. Warfarin dosage is often adjusted during these treatment episodes, sometimes without thorough knowledge of the long-term dose requirements or possible drug compliance issues. Furthermore, sometimes the reason for the contact to a clinic/hospital necessitates warfarin discontinuation and the following re-initiation of warfarin may predispose to overanticoagulation. Thus, it was logical that an outpatient clinic visit or a hospitalization predicted EWA. Frequent INR controls and better patient education may prove useful in preventing the adverse EWA event.

The exceptionally comprehensive coverage of the laboratory service provider of Turku University Hospital (TYKSLAB) enables reliable follow-up on all patients in the southwestern Finland. Even though the electronic patient records are comprehensive, we were reliant on the physicians assessment of the clinical situation and data documentation. Warfarin dosage data in patient records was inadequately documented and thus was not registered in the study data. Also, the duration of treatments was not included in the comparison between groups, as we excluded patients with short-term warfarin from the control group to ensure stable long-term anticoagulation.

6.3 Clinical manifestations and outcomes of severe warfarin overanticoagulation (III)

The study III showed that severe overanticoagulation (defined as INR≥9) during warfarin treatment for AF associates with high mortality also in patients with a coincidental finding of INR ≥9 in routine controls. Several significant clinical predictors for 30-day mortality and bleeding complications during severe overanticoagulation were identified.

Our results show that even though EWA predisposes to severe bleeds, intracranial bleeds were the only type of bleed to predict short-term mortality after EWA (Koo et al., 2004). These findings are in accordance with a recent meta-analysis on 71,683 patients enrolled in 4 randomized trials of NOAC versus warfarin for AF, reporting that only 6% of deaths in these patients are bleeding related (Gomez-Outes et al., 2016). Intracranial bleeding event was the strongest predictor of short-term mortality, although there were only 5 intracranial bleeds in our study.

Patients experiencing non-bleeding related symptoms during EWA had the worst prognosis (30-day mortality 35.1%) of all patient groups, with a 4-fold increase in the risk of death within 30 days. The prognosis in these patients is dictated mainly by the critical illnesses, which may cause INR elevations even spontaneously without warfarin (Oden et al., 2002). Asymptomatic coincidental finding of INR≥9, detected in routine INR controls, was expectedly associated with the best prognosis. These EWA events were detected before symptomatic complications occurred enabling timely interventions. Furthermore, asymptomatic INR≥9 is less frequently associated with acute illnesses, which might worsen the prognosis. Regardless of these facts, the 30-day mortality rate after asymptomatic EWA was as high as 9.2% - three times higher than for example in contemporary trials on ST-elevation myocardial infarction (0.9-3.1%) (Stone et al., 2007; Stone et al., 2008). This finding underlines the importance of recognizing the predictors of EWA presented in study II.

In addition to predicting the occurrence of EWA as shown in study II, hospital treatment episodes and outpatient clinic visits in the emergency room/health care center were found to also predict 30-day mortality after EWA. Several aspects of this clinical situation influence the worsened prognosis: the medical condition itself in addition to possible operations and concomitant medications used to manage the condition. Our findings suggest that systematic and frequent INR controls should be routinely programmed during and after these treatment episodes.

While bleeding during EWA did not influence the prognosis, prior (preceding 30 days) bleeding event increased the risk of death 3.4-fold. This finding is probably associated with the underlying comorbidities and acute diseases, which render patients prone to bleedings even during lower INR values. Recent treatment interventions for these conditions may also play role in the prognosis of these patients as INR reaches ≥9. Our findings highlight the significance of OAC stability in patients with bleeding history. Cancer, as expected, also predicted short-term mortality after severe overanticoagulation. Active cancer is a risk factor for the occurrence of EWA as we reported in study II. As expected, it also predicted short-term mortality after EWA, emphasizing the need for careful weighing of the risks and benefits of warfarin in cancer patients.

A history of myocardial infarction in patients with AF is a known risk factor for cardiovascular death and accordingly we found these patients to be at increased risk (2.9-fold) of EWA compared to patients without a history of myocardial infarction (Norgaard et al., 2010; Gomez-Outes et al., 2016). Renal insufficiency has been reported to increase the risk of all-cause mortality, bleeding and EWA (Pavord et al., 2011; Boriani et al., 2016). Taking this into account, a logical finding in our study was that severe renal impairment also predicted death in 30-days after EWA. As was presumable, elderly patients (≥75 years) were also at increased risk for short-term mortality. The diagnosis and treatment interventions of different illnesses/conditions, such as infections, malnutrition or dehydration may be delayed because of subtle and nonspecific symptoms in elderly patients (High et al., 2009). These delays may sometimes be crucial in terms of diseases progression and the consequential short-term prognosis.

The cause of death in study III (and II) patients is often multifactorial, as is the reason for overanticoagulation. Many of the study patients had serious comorbidities dictating the clinical course after the overanticoagulation. These diseases may be sometimes interpreted to be the cause of death and thus the role of overanticoagulation may be subsided, even though it may be a crucial factor in the rapidly deteriorating clinical course. Considering this, the reported acute cause of death is often a subjective interpretation of the causalities and associations in a complex process in which overanticoagulation plays a vital role. The fact that active bleeding is a prothrombotic condition may also have an impact on this interpretation by modifying the final circumstances prior to death. Sometimes it may be, that no distinct single factor can be named as the primary cause of death even after autopsy. If conclusions on the influence of individual factors are made based on reported causes of death in these situations, the reliability of these conclusions may be questionable. Taking the above-discussed reasoning in consideration, the causes of death in our study patients with overanticoagulation should be evaluated critically. For these reasons we concluded that the best way

to describe the process leading from overanticoagulation to death in different subgroups is the manifestation of overanticoagulation.

A recent bleed is a known risk factor for subsequent bleeds in patients on OAC therapy, which reflects the persons' susceptibility of bleedings (Pisters et al., 2010; Fang et al., 2011). At high anticoagulation intensity levels, patients are more prone to bleeds as the threshold for bleedings to manifest is lowered (Grzymala et al., 2017). In accordance, we found that a recent bleeding was a strong (5.9-fold) risk factor for bleeding complication during EWA. Despite the very high INR in our study, the majority of our study patients did not suffer a bleeding complication, although the rate of major bleeds was higher than for example in the four major NOAC studies (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). It has been reported that INR elevations seem to develop only shortly before a bleeding manifests, which hinders the yield of frequent INR controls in preventing bleeding complications (Kucher et al., 2004). Most bleeding events during OAC therapy occur already at low anticoagulation intensity from occult sites that are unmasked by therapeutic (or even subtherapeutic) anticoagulation intensity (Landefeld et al., 1989; Oden et al., 2002). This reasoning may be behind the finding that recently initiated warfarin therapy did not predict bleeding complications during EWA as the above-mentioned occult bleeding locations probably manifest in to bleedings before INR reaches ≥9. Of note, the bleeding sites were similar in our study as in several earlier OAC studies (Landefeld et al., 1989; Landefeld et al., 1993; Torn et al., 2005; Hylek et al., 2007; Connolly et al., 2009; Granger et al., 2011; Giugliano et al., 2013). As in previous reports, vitamin K did not offer obvious clinical benefit as the occurrence of death, thromboembolisms or length of hospital stay were not affected by vitamin K administration (Koo et al., 2004; Crowther et al., 2009).

However, the limitations of a retrospective study setting render the evaluation of the effects of vitamin K impossible as majority of patients received vitamin K. The study setting sets also other limitations, such as relying on the data documented by the physicians treating the study patients, as the study personnel collected the data retrospectively. Also, factors not included in the case report form may affect the results. Warfarin dosage prior to or after EWA, or the adherence to medication were not recorded.

6.4 Usefulness of the CHA_2DS_2-VASc and HAS-BLED scores in predicting the risk of stroke versus intracranial bleed in patients with atrial fibrillation (from the FibStroke study) (IV)

Study IV, shows that the predominant complication during AF treatment is ischemic stroke, regardless of the CHA_2DS_2-VASc and anticoagulation status. Also, in the subgroup of patients with bleeding risk score (HAS-BLED) higher than stroke risk score (CHA_2DS_2-VASc), ischemic strokes occurred 4 times more often than intracranial bleedings. In patients with HAS-BLED score >4, the intracranial bleeding rate exceeded that of ischemic strokes.

The aim of study IV was to assess the ability of these scores to distinguish the two major complications in a large cohort of patients with either one of the two complications. Ischemic strokes occurred more often than intracranial bleedings also in these low risk categories (CHA_2DS_2-VASc 0-1) in our study, as the IS/IB-ratio was 2.8 in patients on OAC and 5.8 in those without. This finding implies that, even though ischemic strokes are rare in this low risk category, theoretically these patients may benefit from OAC if other risk factors (not included in the CHA_2DS_2-VASc) are present, such as renal insufficiency, dyslipidemia or smoking.

At CHA_2DS_2-VASc scores 2-5, where OAC is indicated, IS/IB-ratio was stable and ischemic strokes were more common regardless of OAC status. IS/IB-ratio started to increase after reached CHA_2DS_2-VASc >5 reflecting a very high stroke risk burden. In the four major NOAC versus warfarin trials (ARISTOTLE, RELY, ROCKET-AF and ENGAGE-AF), the IS/IB-ratios range from 1.63 to 2.87 during oral anticoagulation, which is comparable to our data, even though only less than 100 intracranial bleeds were observed in each of the large randomized trials (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). Our data is not restricted by the strict exclusion criteria of randomized trials in patient selection and thus represents real-life setting in a large cohort including all strokes and intracranial bleeds within a population of 1.2 million people.

Even though there were 100 major bleeds in 263 patients with HAS-BLED > CHA_2DS_2-VASc, the IS/IB-ratio was still 1.45 (221 strokes / 53 intracranial bleedings) meaning that ischemic strokes (n = 221) were more common than intracranial bleedings (n = 53) and major bleeds even in this subgroup. Withdrawing or denying OAC therapy from all patients with HAS-BLED > CHA_2DS_2-VASc does not seem to be justified according to our results.

Patients with HAS-BLED > 4, were more prone to suffer an intracranial bleeding than an ischemic stroke (IS/IB-ratio 0.77) and consequently the net clinical benefit of OAC in this group was negative in our study. While the risk factors of CHA_2DS_2-VASc and HAS-BLED overlap (hypertension, age and history of stroke), patients with HAS-BLED >4 have risk factors unique to the bleeding score, which may in part explain the ability to distinguish between intracranial bleedings and ischemic strokes. In addition to the guideline-suggested correction of all modifiable risk factors and careful INR monitoring, OAC dose adjustment and even withdrawal OAC therapy may be justified in this patient group of patients with very high bleeding risk (January et al., 2014; Kirchhof et al., 2016). NOACs may offer a rational option for these patients, by providing a stable and predictable anticoagulation intensity as well as a lower risk of intracranial bleeds as compared to warfarin (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). Furthermore, left atrial appendage closure may also be considered as an alternative for OAC in this patient group.

As do studies I-III, also study IV has the typical limitations of a retrospective study setting, as the diagnosis and data documentation was done by the physicians treating the patients. All patients underwent head CT or MRI scan in addition to clinical assessment, to ensure appropriate stroke diagnosis. All major bleeds were analyzed only in the subgroup of HAS-BLED > CHA_2DS_2-VASc, which underestimates the clinically significant bleeds in our study patients. Nevertheless, intracranial bleedings are the most significant bleeds as they entail high mortality rate and cause even more severe and long-lasting disabilities than ischemic strokes.

7 CONCLUSIONS

The new information gained from studies I-IV offers more understanding and new perspectives on managing patients with AF. These studies address common challenges in clinical decision-making and the findings provide valuable information on specific situations, which are scarcely studied earlier:

The overall success of ECV can be predicted with simple clinical parameters, using the AF-CVS Score. The new information from this study may be used for individual treatment strategy optimization in AF patients (Study I).

The complex and multifactorial complication of excessive warfarin anticoagulation in AF patients can be predicted with multiple clinical factors. Identifying and recognizing these factors may help to prevent (or detect earlier) the severe overanticoagulation (Study II).

Severe overanticoagulation associates with poor short- and long-term prognosis. Bleeding does not seem to be the major determinant of poor outcome in these patients. Acknowledging the risk factors for excessive warfarin anticoagulation is essential in an attempt to improve the safety of warfarin anticoagulation (study III). Even though NOACs may resolve some of the issues underlying the phenomenon of overanticoagulation that exist during warfarin therapy, the multiple predictors of EWA suggest that the problem of overanticoagulation may still persist during NOAC therapy.

In real-world patients with AF, ischemic stroke was more common than intracranial bleed irrespective of OAC status, CHA_2DS_2-VASc score or HAS-BLED score ≤ 4, also in patients categorized as low risk for thromboembolic complications (CHA_2DS_2-VASc 0-1). The HAS-BLED score predicted the predominant complication only at high very high risk level (study IV).

The four studies included in this dissertation shed light on specific, but common problematic situations encountered in everyday clinical management of AF. The key to fundamental expertise in the context of AF management is the elaborate understanding of the many problems faced in clinical practice.

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