Stroke prevention in atrial fibrillation

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To Anders, Erik, Arvid and Elsa
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References
Abstract

**Background:** The Framingham Study from 1991 showed a clear correlation between atrial fibrillation (AF) and ischemic stroke, where patients with AF had an almost fivefold increase in risk of stroke compared with patients without AF. Since then, several trials have evaluated different antithrombotic treatments to reduce the risk of stroke in patients with AF. Other trials have investigated factors that increase the risk of stroke in patients with AF and risk score systems have been developed to categorize patients into low or increased risk of stroke to help clinicians to decide which patients benefit from antithrombotic treatment and in whom it can be abstained, not to expose patients with low stroke risk to an increased risk of bleeding conferred by antithrombotic treatment. The aims of this thesis were: [1] to evaluate if a warfarin dosing algorithm can increase hit rate and decrease mean error compared with manually changed doses; [2] to assess the prevalence and net clinical benefit of aspirin as monotherapy for stroke prevention in AF; [3] to investigate the risk of thromboembolic and haemorrhagic complications within 30 days after electrical cardioversion (ECV) of AF in patients with and without oral anticoagulation (OAC) pre-treatment; and [4] to assess the proportion of patients discontinuing OAC after pulmonary vein isolation (PVI), identify factors predicting stroke after PVI and to investigate risk of complications after PVI with and without OAC.

**Materials and methods:** All studies are retrospective and based on data from Swedish national quality registries. In paper I, data from Auricula was used to compare the resulting INR values after algorithmic warfarin dose suggestions and manually changed doses. In paper II data was extracted from the Swedish National Patient Register, the Dispensed Drugs Register and the Cause of Death Register. Patients with aspirin treatment were compared with patients without any antithrombotic treatment regarding risk of thromboembolic and haemorrhagic complications. In paper III data was collected from the Swedish National Patient Register and the Dispensed Drugs Register to examine risk of complications (thromboembolic and haemorrhagic events) within 30 days after cardioversion, comparing patients with and without oral anticoagulation pre-treatment. In paper IV data from six different Swedish national quality registries were used (Swedish Catheter Ablation Register, Auricula, Swedish National Patient Register, Dispensed Drugs Register, Cause of Death Register and Riksstroke). Patients undergoing pulmonary vein isolation (PVI) were investigated for adherence to guidelines regarding oral anticoagulation, predictors for stroke after PVI,
as well as risk of ischemic stroke or intracranial haemorrhage after PVI in patients with and without treatment.

**Results:** Paper I showed that a computerized dosing algorithm for warfarin in most cases perform as well or better compared with doses that have been changed manually, with a better hit-rate (0.72 vs. 0.67) and a lower mean error (0.44 vs. 0.48). Paper II showed that 32% of 182,678 patients with a diagnosis of AF were on monotherapy with aspirin for stroke prevention. A total of 115,185 patients were included, 58,671 with aspirin treatment and 56,514 without antithrombotic treatment at baseline. After stratification after CHA2DS2-VASc score and after multivariable adjustment, aspirin treatment did not confer a decrease in thromboembolic events. After propensity score matching, rate of ischemic stroke was 7.4%/year (95% CI 7.1-7.6) in aspirin treated patients and 6.6%/year (95% CI 6.4-6.9) in patients without antithrombotic treatment. In paper III 22,874 patients undergoing electrical cardioversion were included, 10,722 with and 12,152 without OAC pre-treatment. In patients with low stroke risk (CHA2DS2-VASc 0-1), no thromboembolic complication was seen within 30 days after cardioversion. In patients with CHA2DS2-VASc ≥2, the risk of thromboembolic complications was increased when no oral anticoagulation pre-treatment was used, results that remained after propensity score matching. No difference regarding haemorrhagic complications was seen. Paper IV included a total of 1,585 patients undergoing PVI with a mean follow up of 2.6 years. Adherence to current guidelines regarding oral anticoagulation was good in patients with CHA2DS2-VASc ≥2. Previous ischemic stroke was a predictor for a new stroke after PVI. In patients with CHA2DS2-VASc ≥2 stroke risk was increased in patients discontinuing OAC compared to those continuing OAC (1.60%/year vs. 0.34%/year).

**Conclusion:** Oral anticoagulation is still underutilized for prevention of stroke and systemic embolism in patients with atrial fibrillation. Patients with risk factors for stroke (CHA2DS2-VASc ≥2) benefit from continuous oral anticoagulation treatment to prevent stroke, also in conjunction with electrical cardioversion and after pulmonary vein isolation. If warfarin is chosen, a computerised dosing algorithm can facilitate and standardize warfarin dosing and lead to better resulting INR values than manually changed doses. Aspirin should not be used for stroke prevention in patients with atrial fibrillation.
Abbreviations

AF = atrial fibrillation

ATC = anatomical therapeutic chemical (drug classification)

BID = bis in die (Latin, twice a day)

BSA = body surface area

CHADS$_2$ = stroke risk score (congestive heart failure/left ventricular dysfunction, hypertension, age $\geq$65, diabetes, stroke (doubled))

CHA$_2$DS$_2$-VASc = stroke risk score (congestive heart failure/left ventricular dysfunction, hypertension, age $\geq$75 (doubled), diabetes, stroke (doubled) – vascular disease, age 65–74, and sex category (female))

CHF = congestive heart failure

CI = confidence interval

CKD-EPI = chronic kidney disease epidemiology collaboration

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

ESC = European Society of Cardiology

GDF-15 = growth differentiation factor 15

HAS-BLED = bleeding risk score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (e.g. age $> 65$, frailty, etc.), drugs/alcohol concomitantly)

HR = hazard ratio

ICD10 = international classification of disease, 10th edition

INR = international normalized ratio

LAA = left atrial appendage
LMWH = low molecular weight heparin
NOAC = new oral anticoagulant
NPR = National Patient Register
NSAID = non steroidal anti-inflammatory drugs
OAC = oral anticoagulation
OR = odds ratio
PPV = positive predictive value
PT = prothrombin time
PVI = pulmonary vein isolation
RCT = randomized controlled trial
ROC = receiver operating characteristic
RRR = relative risk reduction
SD = standard deviation
TEE = transesophageal echocardiography
TIA = transient ischemic attack
TTR = time in therapeutic range
cTTR = center time in therapeutic range
iTTR = individual time in therapeutic range
UFH = unfractionated heparin
WHO = World Health Organisation
Original publications

The thesis is based on the following manuscripts, hereafter referred to by their Roman numerals.


Sammanfattning (Summary in Swedish)

**Bakgrund:** Förmaksflimmer är den vanligaste hjärtarytmin och finns hos åtminstone 3% av den vuxna befolkningen i Sverige. En betydande andel av populationen har dock oupptäckt, symptomfritt förmaksflimmer, varför prevalensen sannolikt är betydligt högre. Förmaksflimmer innebär att hjärtns elektriska signal inte längre startar i den normala pacemakern, sinusknutan, utan att andra områden, vanligen belägna vid lungvenernas mynnning i vänster förmak, tagit över impulsstyrningen. Detta leder till snabba och oregelbundna sammandragningar i hjärtns förmak och oregelbunden rytm i hjärtns kammare. Blodet från förmaken pumpas inte ut i kamarna på samma sätt som vid normal sinusrytm, vilket leder till blodstas i förmaken och en ökad risk för bildande av blodproppar i framför allt förmaksörenen. En fruktad komplikation till förmaksflimmer är att en sådan blodpropp lossnar och följer med blodströmmen upp till hjärnan och orsakar en hjärninfarkt, stroke.

Flera olika faktorer har visat sig öka risken för blodpropbildning, som hjärtsvikt, högt blodtryck, stigande ålder, diabetes mellitus, tidigare stroke, kärlsjukdom och kvinnligt kön. För personer med förmaksflimmer och minst en ytterligare riskfaktor för stroke rekommenderas idag blodförtrunnande behandling för att minska risken för stroke. Behandling med blodförtrunnande läkemedel ökar dock risken för allvarliga blödningar, där hjärnblödning är den mest fruktade. Även risken för allvarlig blödning påverkas av flera olika faktorer såsom högt blodtryck, nedsatt njur- eller leverfunktion, tidigare stroke, tidigare blödning eller anemi, stigande ålder, användande av trombocythämmande läkemedel samt riskbruk av alkohol. Nyttan med blodförtrunnande behandling för att förebygga stroke måste därför noggrant vägas mot risken att drabbas av en allvarlig blödning.

Upprepade studier har visat att blodförtrunnande behandling med vitamin K-antagonist (warfarin), trombinhämmare (dabigatran) och faktor Xa-hämmare (rivaroxaban, apixaban, edoxaban) minskar risken för patienter med förmaksflimmer att drabbas av stroke jämfört med att inte behandla. Behandling med acetylsalicylsyra har i de flesta studier inte kunnat visa någon förebyggande effekt mot stroke. Behandling med warfarin kräver regelbundna blodprovskontroller (INR) för att kontrollera intensiteten på blodförtrunnningen. Normalt eftersträvas ett värde mellan 2-3, där ett värde på 2.5 är optimalt. Ett lägre värde än 2 ger en sämre blodförtrunnande effekt och ökar risken för blodproppar medan ett högre värde än 3 istället ökar risken för blödningar. Sverige har i upprepade studier visats ha hög kvalitet på warfarinbehandling. Kvaliteten på warfarinbehandlingen kan mätas på olika sätt, dels genom att undersöka frekvensen stroke och blödningar, men
också genom hur väl doseringen leder till ett INR-värde inom önskat intervall. Hur stor andel av tiden som en patient ligger i önskat INR-intervall kallas TTR. Ett högt värde på TTR (dvs. stor andel av tiden i rätt INR-intervall) leder till minskad risk för stroke och blödningar. "Hit rate" (träffsäkerhet) och "mean error" (medelfel) är två andra sätt att mäta kvaliteten på warfarinbehandlingen, vilka innebär hur stor andel av doseringarna som träffar inom rätt INR-intervall, respektive hur långt en dosering hamnar från den optimala nivån 2.5.

**Avhandlingens syfte:** Att undersöka om ett datoriserat doseringsprogram för warfarin kan leda till lika bra eller bättre kvalitet på warfarinbehandlingen jämfört med manuellt ändrade doser. Att ta reda på om trombocythämning med acetylsalicylsyra leder till minskad risk för stroke hos patienter med förmaksflimmer i ett stort svenskt material. Vidare är avhandlingens syfte att undersöka antikoagulationsbehandling med warfarin hos patienter med förmaksflimmer vid speciella tillfällen i form av akut elkonvertering av förmaksflimmer samt efter lungvensablation. Frågeställningarna är om akut elkonvertering på ett säkert sätt kan utföras utan föregående blodförortunnande behandling samt om patienter som genomgått lungvensablation på grund av förmaksflimmer fortsatt har nytta av blodförortunnande behandling eller om risken för stroke hos dessa patienter är så låg att behandlingen kan avslutas.

**Resultat:** Delarbete I jämförde träffsäkerhet och medelfel på INR-värden efter warfarindoseringar som är föreslagna av ett datoriserat ordinationsprogram respektive doseringar som ändrats manuellt. Det visade sig att en datoriserad doseringsalgoritm för warfarin ledde till både bättre träffsäkerhet och mindre medelfel än om warfarindosen hade ändrats manuellt.

Delarbete II visade att det fortfarande förskrivs en hel del acetylsalicylsyra som enda strokeförebyggande behandling till patienter med förmaksflimmer. Jämfört med patienter helt utan antitrombotisk behandling hade inte patienterna som behandlades med acetylsalicylsyra någon strokeförebyggande effekt, inte heller efter olika statistiska justeringar för ålder, kön och övrig sjuklighet.

Delarbete IV studerade följsamhet till riktlinjer gällande antikoagulation hos patienter med förmaksflimmer som genomgått lungvensablation och hur det påverkade risken för stroke och hjärnblödning. Resultaten visade att följsamheten till riktlinjer, dvs. att fortsätta med warfarinbehandling till de patienter som har en ökad risk för stroke även efter lungvensablation är god i Sverige. De patienter med riskfaktorer för stroke som trots allt avslutade warfarinbehandlingen hade en ökad förekomst av stroke jämfört med de som kvarstod på behandlingen.

**Slutsatser:** Det finns fortfarande en underanvändning av oral antikoagulation för att förebygga stroke hos patienter med förmaksflimmer. Patienter med riskfaktorer för stroke (CHA₂DS₂-VASc ≥2p) har nytta av kontinuerlig antikoagulationsbehandling för att minska risken för stroke, även i samband med elkonvertering och efter lungvensisolering. Om man väljer warfarin som strokeförebyggande behandling kan ett datoriserat doseringsstöd leda till bättre behandlingskvalitet än manuellt ändrade doser. Acetylsalicylsyra bör inte användas för att förebygga stroke hos patienter med förmaksflimmer.
Introduction

Atrial fibrillation

Historical background
The earliest description of atrial fibrillation may be in The Yellow Emperor's Classic of Internal Medicine; “When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small.” (Huang Ti Nei Ching Su Wen.) (1). The document is believed to have guided China for many years (2598-1696 BC.).

William Harvey (1578-1657) was probably the first to describe “fibrillation of the auricles” in animals in 1628 (1, 2). In those times it was generally believed that the arterial pulse and the heartbeat were two different mechanisms, occurring independent of each other. Harvey concluded that the contraction of the left ventricle caused the arterial pulsation, but his contemporaries were not of the same opinion.

A French pathologist, Jean Baptist de Sénac (1693-1770), established the concept irritability of the heart and assumed an association with stenosis of the mitral valve and palpitations (2). De Sénac stated that “the causes of palpitation are not the causes of the natural heartbeat”, thereby suggesting an ectopic origin of palpitations. He also described that quinine could relieve palpitations of the heart.

The Scottish general practitioner MacKenzie followed a woman with mitral stenosis between 1880-1887. He observed that the jugular A wave was lost when the patient went from normal regular rhythm to an irregular rapid rhythm. In 1902 Mackenzie published this observation, concluding that the irregular heart rhythm was due to “paralysis of the auricle” (3).

In 1887, MacWilliam wrote about his experiments in animal hearts, calling the phenomenon delirium cordis (4). Hering used the term “pulsus irregularis perpetuus” in 1903, and separated it from other types of irregular heart rhythms. Cushny reported in 1899 that the arterial pulse in dogs with directly (open-chested) observed “auricular delirium” or “fibrillary contractions” was the same as the radial pulse from a patient with “delirium cordis”, suggesting that the two conditions were actually the same (3).

The famous Swedish poet Carl Michael Bellman (1740-1795) may have written an early Swedish description of atrial fibrillation; “in brandy’s anxiety my heart is shaking” (“brännvins ångest mitt hjärta skakar”, Fredmans epistel n:o 24).
In the end of the 19th century, Einthoven tried to develop a device with the intention to record the electrical signals emitted by the heart (3). A diagnostic breakthrough of atrial fibrillation came after Einthoven invented the string galvanometer in 1901 (3, 4). For the development of the string galvanometer to record electrocardiograms, Einthoven was awarded with the Nobel Prize in 1924. Lewis was then the first to record an electrocardiogram in a patient with atrial fibrillation in 1909, thereby demonstrating the irregular waves resulting from the fibrillary movements of the auricles (Figure 2) (1, 3).

In 1975, William Withering discovered the therapeutic capacity of Digitalis purpurea (1). He recorded a patient whose pulse went from weak and irregular to “more full and more regular” after treatment with digitalis and suggested digitalis to be “a sort of opium for the heart”.

Figure 1: Carl Michael Bellman, 1740-1795.
The mechanisms of atrial fibrillation were controversial. In 1895 Engelmann presented the “multiple heterotopous centers theory”, in which it was believed that each heart fiber becomes rhythmic independent of the other fibers, causing multiple foci circuits (4). The theory was further developed by Winterberg and Lewis. Later, Rothenberg and Winterberg proposed that accelerating rate from a single focus accounted for atrial fibrillation. Both these theories were soon replaced by another, called “circus movement”. This theory was valid for 30 years and originated from the jellyfish, suggesting the contraction going around a circuit in one direction. Then Moe presented his multiwavelet theory, suggesting that atrial fibrillation could persist and spread through any part of the wave front around sites with refractory tissue and that atrial fibrillation therefore was not dependent of specific foci (5). In 1997, Jais et al. presented an electrophysiological study which demonstrated...
that paroxysmal AF was due to one focus with irregular activity (6), and in 1998 Haissaguerre et al. presented observations of a focus of impulses at the entrance of the pulmonary veins in the left atrium (7).

Figure 3: Triggering foci in 45 patients with atrial fibrillation, mainly located at the entrance of the pulmonary veins. Reproduced with permission from the New England Journal of Medicine, Copyright Massachusetts Medical Society.

Treatment options for atrial fibrillation were initially only digitalis and quinidine (8, 9). In 1962-63 Lown et al. published their results regarding cardioversion of cardiac arrhythmias (10, 11). Continuously new antiarrhythmic drugs developed, all with expectations of restoring and/or retaining sinus rhythm (12). It soon became evident that even after successful cardioversion, an antiarrhythmic agent was often needed to retain sinus rhythm and prevent relapse into AF (13). Thereafter, repeated studies showed that a strategy promoting rate control was not inferior to rhythm control (14-17), probably because of disadvantages of antiarrhythmic drugs. In 1998 Haissaguerre et al. discovered that the origin of electrical activation in atrial fibrillation in 94% is found at the entrance of the pulmonary veins in the left atrium, and invented pulmonary vein isolation by radiofrequency ablation to prevent the electrical signals from reaching the atrium (7).
**Definition and classification**

According to the 2010 European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation, the definition of AF is a cardiac arrhythmia with the following three characteristics (18):

1. **On a surface electrocardiogram (ECG) there are ‘absolutely’ irregular RR-intervals, i.e. the RR-intervals do not follow a repetitive pattern. Therefore, AF is sometimes called arrhythmia absoluta.**

2. **A surface ECG does not show distinct P waves, but some apparently regular atrial electrical activity may be seen in some ECG leads, usually in lead V1.**

3. **When visible, the length of the atrial cycle (i.e. the interval between two atrial activations), is variable and less than 200 milliseconds (>300 beats per minute).**

A cardiac arrhythmia with the criteria mentioned above, that lasts at least 30 seconds or sufficiently long for an ECG to be recorded, must be considered to be AF (19).

A patient who has had two or more events of atrial fibrillation is considered to have recurrent AF. AF that terminates spontaneously is defined as paroxysmal AF. If AF has sustained for more than seven days or requires cardioversion it is defined as persistent AF. Long-standing AF is included in the category of persistent AF and implies AF that has persisted for more than one year. Permanent AF is when cardioversion is abstained or has failed (20). Termination of AF pharmacologically or by electrical cardioversion does not alter the definition. Lone AF refers to AF in a young patient (<60 years) free of cardiopulmonary disease. The natural course of AF is a progress from short, rare episodes to more frequent and more sustaining attacks and eventually permanent AF (Figure 4).
Figure 4: Classification and natural course of atrial fibrillation. After first diagnosed episode of AF, the arrhythmia most often occurs intermittent and self-terminating, with a progress to more sustaining attacks possibly requiring cardioversion and finally the arrhythmia is usually permanent.

Epidemiology

Atrial fibrillation is a very common cardiac arrhythmia, and has been shown to affect 2.9% of the adult population (≥20 years) in Sweden (21). The prevalence of atrial fibrillation increases with age, from about 1% in persons aged 50 years to 14% in persons aged 85 years. These prevalence figures are deducted from the National Patient Register, covering all diagnoses set in the specialized care. Though, these numbers do not include patients who have been treated in primary care only. Also, these numbers are only valid for patients with known AF. In a systematic review of 30 studies of AF screening there was a substantial number of silent, previous undiagnosed AF, that amount to an additional 1% in the general population and 1.4% in persons aged ≥65 years (22). In the Swedish Strokestop study, AF screening was performed in 75- and 76-year-old individuals (23). Total AF prevalence in the screened population was 12.3% and 3.0% of those had a previously unknown AF. Because of the missing data from primary health care in Swedish registers and because of the unknown prevalence of silent AF, the real prevalence of AF is unknown and would require large-scale population screening to be determined. Because of the ageing population, AF is believed...
to become even more common in the future (24, 25). In the most newly presented data from the Framingham study, both age-adjusted incidence and prevalence are increasing, and age-adjusted mortality and stroke rate decreasing (26).

The prevalence of AF is probably different in different populations. In the ATRIA study, AF was more common in white than in black patients ≥50 years old (25). Prevalence of AF in Indo-Asians ≥50 years of age has been shown to be only 0.6% (27). In Europe and the USA, however, similar rates have been reported of 5.1 in women and 6.0 in men aged ≥55 years in the Rotterdam study (28), as well as 4.9 in women and 9.6 in men aged 50-89 years in the Framingham study (26).

AF is more common in men than in women, this holds for all age groups (21, 28, 29). AF is very common in individuals suffering from ischemic stroke. A Swedish register based study has shown that 33.4% of patients with ischemic stroke have a previously known or newly diagnosed AF (30). Data from Riksstroke has shown AF in 20% of stroke patients <80 years, increasing to 44% in patients aged ≥80 years (31). In a register-based study from France, 25.6% of 65,807 patients admitted with stroke had a known AF, and additional 7.3% were diagnosed with AF within 15 months after the stroke admission (32). Another study found silent AF in 10% of patients who had suffered from TIA or ischemic stroke (33).

**Stroke risk in atrial fibrillation**

Atrial fibrillation confers an independent risk of stroke, a risk that is increased about five-fold compared with a person without AF (34). A stroke caused by AF is associated with greater disability, higher rate of stroke recurrence and a higher mortality compared with stroke in patients without AF (35). There is no difference in stroke risk in patients with paroxysmal or persistent AF (36) and asymptomatic patients have as high risk of stroke as patients with symptoms, after adjustment for baseline differences (37).

**Patophysiology**

The thrombogenic tendency in atrial fibrillation is dependent on several pathophysiological mechanisms, still probably only partly understood. Abnormal changes in blood flow, vessel wall changes and changes in blood constituents are referred to as Virchow’s triad (38) and has been shown to contribute to the prothrombotic state in patients with AF:
• Atrial fibrillation causes changes in blood flow, resulting in stasis in the left atrium. The left atrial appendage (LAA) is a blind-ended passage, which is long and has a narrow inlet predisposing to blood stasis (38). The phenomenon dense spontaneous echo contrast, which can be seen in echocardiography, is independently associated with thromboembolic risk in patients with AF, as well as LAA thrombi and LAA peak flow velocities ≤ 20 cm/second (39). Thrombus formation has been shown to be associated with both decreased LAA contraction and LAA dilatation (40).

• AF is associated with endocardial fibrosis (41), an excessive deposition of extracellular matrix which can occur as a result of mechanical overload of the tissue or as a result of tissue damage. An autopsy study found “rough endocardium” macroscopically in patients who had suffered from AF and cerebral embolism (42). The rough endocardium was associated with oedematous and fibrous thickening. In the microscope mural thrombi and oedema with neutrophil infiltration could be seen in the subendocardium.

• Patients with AF had 2.4 times higher concentrations of a type of circulating procoagulant microparticle (annexin V-positive procoagulant microparticle) than patients without AF (43), which could contribute to an increased risk of thromboembolism in AF patients. Patients with AF also had increased levels of platelet microparticles (procoagulant membrane vesicles derived from activated platelets), but increased levels were also found in patients with cardiovascular disease without AF, why it may be due to underlying cardiovascular disease rather than AF (44). A Japanese study from 1990 showed that plasma D-dimer (a fibrin degradation product) levels were increased in patients with AF compared to patients without AF (45).

**Stroke risk stratification**

The risk of stroke conferred by AF is not homogeneous, but differs considerably among different groups of patients, and several clinical and echocardiographic characteristics have been identified to stratify AF patients into low-, intermediate-, and high-risk of thromboembolism (46).

In a systematic review of stroke risk factors and risk stratification schema, Hughes et al. included 18 studies regarding stroke risk factors (47). In this systematic review all studies including previous stroke, TIA or systemic
embolism showed an association between previous thromboembolism and increased risk of a new stroke. Most of the studies found congestive heart failure/left ventricular dysfunction, hypertension and increasing age to be independent risk factors for stroke. About half of the studies including female gender found a correlation between female gender and increased stroke risk and less than half of the studies evaluating diabetes mellitus found an association with diabetes mellitus and increased risk of stroke. No association was found between AF subtypes and risk of stroke.

Risk stratification systems

In clinical medicine, procedures for predicting risk of an outcome are important tools in selecting prevention- and treatment strategies (48). The Framingham study was the pioneer study for the development of risk score systems and since then multiple risk score systems have been developed, based on evaluation of individual risk factors for a certain outcome. To evaluate the adequacy of a risk score system, C-statistic is routinely used. The C-statistic includes logistic regression models, where a pair of one subject with and one subject without an outcome is used to estimate the probability for developing the outcome. The probability is plotted in a receiver operating characteristic (ROC) curve against the outcome measure as the dependent variable. The area under the ROC curve represents the ability for a risk score system to accurately classify risk for the outcome and is also referred to as the C-statistic. The C-statistic express how well a risk score system can discriminate between subjects developing an outcome and subjects who will not. Values for C-statistic range from 0.5-1.0, where 0.5 indicates that the risk score system is no better than chance, and a value of 1.0 indicates a perfect prediction of which individuals in a group will develop the outcome. Risk score systems are considered reasonable when C-statistic is above 0.7, and good with a C-statistic higher than 0.8.

In recent years, four different risk score systems regarding stroke risk in patients with AF have mainly been discussed, the CHADS$_2$ score, the CHA$_2$DS$_2$-VASc score, the R$_2$CHADS$_2$ score and the ATRIA score.

The CHADS$_2$ score was introduced in 2001 and is a combination of two at that time existing risk score systems (AFI scheme and SPAF scheme) (49). In CHADS$_2$, one point each is earned for the presence of congestive heart failure, hypertension, age $\geq$75 years and diabetes mellitus, and two points for previous stroke or TIA. CHADS$_2$ was evaluated with data from 1,733 patients with AF without warfarin treatment. Analysis showed a C-statistic of 0.82, which was significantly better than the two original risk score systems CHADS$_2$ was compared with.
In 2010 the CHADS\textsubscript{2} score was further developed into the CHA\textsubscript{2}DS\textsubscript{2}-VASc score (50). Except for risk factors included in the CHADS\textsubscript{2} score, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score also includes vascular disease, female gender, age $\geq 65$ years, as well as a doubling of score points for age $\geq 75$ years (2p). The CHA\textsubscript{2}DS\textsubscript{2}-VASc score was compared with the CHADS\textsubscript{2} score and other existing stroke risk stratification systems in a cohort consisting of 1,084 AF patients. The results showed that all risk score systems had a modest predictive value for thromboembolic events, with C-statistic of 0.61 for the CHA\textsubscript{2}DS\textsubscript{2}-VASc score and 0.56 for the CHADS\textsubscript{2} score. Compared with other existing risk scores, CHA\textsubscript{2}DS\textsubscript{2}-VASc defined the lowest proportion of patients as low risk. Those patients classified as low risk by CHA\textsubscript{2}DS\textsubscript{2}-VASc were truly low risk with no thromboembolic events recorded.

Data on the R\textsubscript{2}CHADS\textsubscript{2} score was published in 2012 (51). The study showed that renal dysfunction was a strong independent risk factor for stroke in AF patients, second only to previous TIA or stroke. R\textsubscript{2}CHADS\textsubscript{2} score (which gives the same score points as CHADS\textsubscript{2} score except for adding two score points for creatinine clearance $<60$ ml/min) had a C-statistic of 0.59 compared with 0.58 for both CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc.

The ATRIA score was presented in 2013 (52). In the ATRIA cohort, 10,927 patients with AF contributed to 32,609 years at risk without warfarin treatment. In the final model, significant predictors for stroke were female gender, diabetes mellitus, congestive heart failure, hypertension, proteinuria, estimated glomerular filtration rate (eGFR) $<45$ ml/min or end-stage renal disease (requiring dialysis) and increasing age, which contributed differently in patients with and without previous stroke. The ATRIA score was also externally validated in 25,306 patients with a diagnosis of AF or atrial flutter, and was found to have a C-statistic of 0.7, compared with 0.66 for CHADS\textsubscript{2} score and 0.68 for CHA\textsubscript{2}DS\textsubscript{2}-VASc score. When only severe outcome events were considered (high level of disability or death), the C-statistic rose to 0.76 for the ATRIA score, 0.72 for the CHADS\textsubscript{2} score and 0.73 for the CHA\textsubscript{2}DS\textsubscript{2}-VASc score.
Table 1: Diagnoses and risk factors with score points in different stroke risk score systems.

<table>
<thead>
<tr>
<th></th>
<th>CHADS&lt;sup&gt;2&lt;/sup&gt;</th>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;CHADS&lt;sub&gt;2&lt;/sub&gt;</th>
<th>ATRIA, patients without prior stroke</th>
<th>ATRIA, patients with prior stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>75-84</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>65-74</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>&lt;65</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>eGFR &lt;45 or end-stage renal disease</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine clearance &lt;60ml/min</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Score sum</strong></td>
<td>0-6</td>
<td>0-9</td>
<td>0-8</td>
<td>0-12</td>
<td>7-15</td>
</tr>
</tbody>
</table>
The different risk score systems are continuously being validated in different patient cohorts.

Two studies validating the R2CHADS2 score found that chronic kidney disease in AF patients confers increased rates of thromboembolic events, but that adding chronic kidney disease to the CHADS2 score or the CHA2DS2-VASc score did not add predictive information (53, 54).

A validation study of the ATRIA score showed that the event rate in patients classified as low risk (ATRIA 0-5) was 1.1-36.9/100 person-years when subdivided by CHA2DS2-VASc scores, and that the CHA2DS2-VASc score more accurately identified truly low risk patients without indication for OAC (55). On the opposite, a study from the United Kingdom showed that the ATRIA score was more accurate in identifying low risk patients than the CHA2DS2-VASc score, and therefore could prevent overuse of anticoagulants in patients with very low stroke risk (56). A newly published Swedish study also showed that the ATRIA score had a significantly higher C-statistic (0.71) than CHADS2 and CHA2DS2-VASc (both 0.69), and was consequently better at predicting risk of stroke (57).

Recently, a new risk score system called the ABC score has been developed, focusing more on biomarkers than other existing risk scores (58). In the ABC score, previous stroke or TIA, age and the biomarkers troponin I or T, and NT-proBNP are taken into account in risk stratification. The results have shown higher values on C statistics than the CHA2DS2-VASc score, even if C-statistics were generally low in these cohorts (both derivation and validation cohorts), ranging from 0.50 to 0.62 for the CHA2DS2-VASc score and from 0.66 to 0.68 for the ABC score when troponin I was used and from 0.63 to 0.67 when troponin T was used.

According to current European guidelines, CHA2DS2-VASc is recommended for stroke risk stratification (59), where patients with CHA2DS2-VASc score 0 (including women with no other risk factors for stroke) are recommended no antithrombotic treatment and patients with CHA2DS2-VASc ≥2 are recommended OAC. In patients with CHA2DS2-VASc 1 it is still optional to use OAC or not, even though OAC treatment is considered favourable. The risk of stroke has been shown to range from 0%/year in patients with AF and CHA2DS2-VASc score 0 to 15.2%/year in patients with CHA2DS2-VASc score 9, adjusted for warfarin use (60), where warfarin is assumed to provide a 64% reduction in the risk of thromboembolic events (61).
OAC treatment in patients with a CHA$_2$DS$_2$-VASc score of 1 is still debated. In a register based study by Friberg et al., women with CHA$_2$DS$_2$-VASc score 1 (no other risk factors beyond female gender) were truly low risk with an annual stroke rate of 0.1-0.2% depending on what definition of stroke that was used (62). For men, the annual stroke rate ranged from 0.5-0.7%, increasing to 1.3% when also diagnoses of TIA, systemic embolism, unspecified stroke and pulmonary embolism were considered. Friberg et al. concluded that patients with CHA$_2$DS$_2$-VASc score 1 are unlikely to benefit from OAC treatment due to low stroke risk. In contrast, in a register based Taiwanese study by Chao et al., the annual stroke rate for men with CHA$_2$DS$_2$-VASc score 1 was 2.8%/year (ranging from 2.0-3.5% depending on what risk factor composed the score point) (63). In this study, women with one additional risk factor beyond gender were considered (e.g. CHA$_2$DS$_2$-VASc score 2) showing an annual stroke rate of 2.6% (ranging from 1.9-3.3% depending on what risk factor composed the score point beyond gender). Since Friberg et al. considered women with CHA$_2$DS$_2$-VASc score 1 (e.g. female gender only), the studies can not be compared regarding women. The registries used in both studies have been validated previously (64, 65) with, in general, high positive predictive values (PPVs) for most diagnoses. Both registries have, however, diagnoses with lower validity, e.g. the Taiwanese National Health Insurance Research Database (NHIRD) where a diagnosis of myocardial infarction has a PPV of 50% (65), compared to 98-100% in the Swedish NPR (64). This could lead to a lower CHA$_2$DS$_2$-VASc score in the study by Chao et al. than was actually present. On the other hand, in a letter Lip et al. suggested that excluding patients who received OAC during follow-up (as in the study by Friberg et al.) would introduce bias away from the null hypothesis (that patients with AF and one additional risk factor for stroke would benefit from OAC treatment) (66). Also previous studies have shown very divergent results regarding thromboembolic rates in patients with CHA$_2$DS$_2$-VASc score 1, from 0.6%/year (50) to 2.0%/year (67).

Bleeding risk scores

The risk of thromboembolic events in patients with AF must always be weighed against the risk of haemorrhagic complications with OAC treatment. In a systematic review, risk factors for anticoagulation-related haemorrhagic complications in AF patients were appraised based on the results of nine studies (68). Most of the studies evaluating hypertension, a history of bleeding or anaemia and use of antiplatelet agents or polypharmacy (defined as either at least three or more than three medications) found an association between these factors and an increased risk of OAC associated bleeding. Increasing age was associated with
increased risk of OAC associated bleeding in about half of the studies, and cerebrovascular disease in less than half of the studies. There was no association between OAC associated bleeding and diabetes mellitus or gender, although some studies found that female gender was of borderline significance for an increased bleeding risk.

In recent years, three different risk score schemes have mainly been discussed for predicting haemorrhage in AF patients on OAC:

• In 2006, Gage et al. investigated the risk of haemorrhage in elderly patients with AF (69). To guide clinicians through risks and benefits with antithrombotic treatment, the bleeding risk score HEMORR²HAGES was invented. In this risk classification scheme two score points are earned for the risk factor prior bleeding, and one point each for the following risk factors: hepatic or renal disease, ethanol abuse, malignancy, age >75 years, reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors (CYP 2C9 single-nucleotide polymorphisms), excessive fall risk (including neuropsychiatric disease) and previous stroke. The risk score scheme was tested among elderly (mean age 80.2 years) with AF, C-statistic was found to be 0.67.

• The HAS-BLED score for predicting bleeding events in AF patients on OAC was presented in 2010 (70). In the HAS-BLED scheme, 1 score point each is earned for the presence of hypertension (systolic blood pressure >160 mmHg), abnormal renal function (chronic dialysis, renal transplantation or serum creatinine ≥200 µmol/l), abnormal liver function (chronic hepatic disease or biochemical evidence of hepatic disease), previous stroke, history or predisposition of bleeding, labile INR values, age >65 years, excessive alcohol use and use of other drugs (antiplatelet agents or nonsteroidal anti-inflammatory drugs) concomitantly. C-statistic for the HAS-BLED scheme varied across different patient groups, from 0.72 in the entire cohort to 0.69 in OAC treated patients and 0.91 in patients with only antiplatelet therapy. A comparison was also made between HEMORR²HAGES and HAS-BLED, with similar bleeding predictive values, but HAS-BLED with the benefit of simplicity.

• The ATRIA risk score scheme was invented in 2011 and contains only 5 variables: anaemia (haemoglobin <13 g/dl in men and <12 g/dl in women, 3 points), severe renal disease (eGFR <30 ml/min or
dialysis dependent, 3 points), age ≥75 years (2 points), prior bleeding (any diagnosis of haemorrhage, 1 point) and a diagnosis of hypertension (1 point) (71). C-statistic was found to be 0.74 for the continuous risk score and 0.69 for the 3-category score, where 0-3 points was considered as low risk, 4 points as intermediate and 5-10 points as high risk of bleeding.

Table 2: Diagnoses and risk factors with score points in different bleeding risk score systems.

<table>
<thead>
<tr>
<th></th>
<th>HEMORR$_2$HAGES</th>
<th>HAS-BLED</th>
<th>ATRIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic or renal disease</td>
<td>1</td>
<td>1 or 2</td>
<td></td>
</tr>
<tr>
<td>Severe renal disease</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Ethanol abuse</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Reduced platelet count or function</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding history</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive fall risk</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Use of antiplatelet drugs or NSAID</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labile INR values</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum score</td>
<td>0-12</td>
<td>0-9</td>
<td>0-10</td>
</tr>
</tbody>
</table>
When all three bleeding risk scores were compared, Apostolakis et al. found that the HAS-BLED score performed best considering prediction of clinically relevant bleeding with a c-statistic of 0.6 compared with 0.55 for the HEMORR\textsubscript{2}HAGES score and 0.50 for the ATRIA score (72).

The risk factor excessive fall risk included in the HEMORR\textsubscript{2}HAGES score has been heavily debated and tested in several studies. One study found that the rate of intracranial haemorrhage per 100 patient-years rose from 1.1 in patients without excessive fall risk to 2.8 in patients with excessive fall risk, but the study concluded that if there are multiple stroke risk factors the patient will still benefit from OAC (73). In another study Donzé et al. investigated patients on OAC (not only AF patients) and concluded that patients with high risk of falls did not have a significantly increased risk of major bleeds and that these patients should receive OAC treatment (74). Yet another study concluded that a propensity to fall is not an important factor in the decision of OAC treatment, and that elderly AF patients must fall about 295 times every year for warfarin not to be the optimal treatment (75).

Current European guidelines recommend that an estimation of bleeding risk should be performed with the HAS-BLED score (59).

Recently, two additional risk score systems have been developed to predict bleeding risk in AF patients, the ORBIT bleeding score and the ABC-bleeding score.

The ORBIT score includes older age (≥75 years); reduced haemoglobin (<13 mg/dL in men and <12 mg/dL in women, haematocrit (<40% in men and <36% in women) or history of anaemia; bleeding history; insufficient kidney function (eGFR<60 mg/dL/1.73 m\textsuperscript{2}); and treatment with an antiplatelet agent (76). When compared in the ORBIT-AF cohort, C-statistics for the ORBIT score was 0.67 (95% CI 0.64-0.69), for the HAS-BLED score 0.64 (95% CI 0.62-0.67) and for the ATRIA score 0.66 (0.63-0.68).

In the ABC-bleeding score, age, history of bleeding and three biomarkers (haemoglobin, high-sensitivity troponin T and GDF-15 or cystatin C/CKD-EPI) are used for risk stratification (77). The ABC-bleeding score was found to outperform both the HAS-BLED score and the ORBIT risk score, with C-statistics of 0.68, 0.61 and 0.65, respectively, in the derivation cohort.
Rhythm control in atrial fibrillation

Two main treatment options are available for patients with AF, rate control where AF is accepted and the treatment aims to maintain a normal heart rate and rhythm control where the treatment aims to restore and retain normal sinus rhythm. In both treatment strategies oral anticoagulation is recommended if there are risk factors for stroke. When rhythm control strategy is preferred, cardioversion (electrical or pharmacological) and treatment with antiarrhythmic drugs as well as pulmonary vein isolation are established treatment options.

Pharmacological cardioversion

When pharmacological cardioversion is preferred and there is no or minimal structural heart disease, current ESC guidelines recommend intravenous flecainide, propafenone, ibutilide or vernakalant (59). Compared with electrical cardioversion, cardioversion with pharmacological agents has a lower success rate. In the multinational RHYTHM-AF study, sinus rhythm was restored in 89.7% of the patients undergoing electrical cardioversion, compared with 69.1% of the patients undergoing pharmacological cardioversion (78).

Electrical cardioversion

Historical background

In 1962 Bernard Lown et al. presented a new method for terminating cardiac arrhythmias; electrical cardioversion, although the method had been described earlier for treatment of both ventricular and atrial arrhythmias (10). Electrical cardioversion was considered to be the ideal form of antiarrhythmic therapy, if it could be performed safely. By depolarization of all cardiac cells simultaneously, the origin of the arrhythmia could be terminated and the sinus node recapture the function as the pacemaker of the heart. Alternating current countershock was the first electrical method to be tested. Unfortunately, the method was not as safe as desired. In animals with sinus rhythm, atrial and ventricular arrhythmias, myocardial infarctions and a high mortality rate were seen as complications to alternating current countershock (10). The findings led to the development of another method, direct current countershock, which showed promising results. However, still almost 2% of the animals with normal sinus rhythm
suffered ventricular fibrillation after treatment (10). A vulnerable period in the cardiac cycle had already been identified, occurring in late systole, just preceding the apex of the T-wave on the surface electrocardiogram. This knowledge led to the development of an electric synchronizer, which allowed a time-delay before delivery of a direct current countershock, thereby avoiding the vulnerable period of the cardiac cycle. The synchronizer was successful and eliminated all cases of ventricular fibrillation.

In 1963 Lown et al. presented their results regarding 65 cardioversions performed in 50 patients with AF, of whom 47 had severe mitral valve disease (11). Mean duration of AF was 26 months. In total 58 out of 65 episodes of AF were successfully terminated (89%). Patients not undergoing surgical procedures (40 patients) were treated with anticoagulation for three to four weeks before the procedure, and pre-treatment with quinidine and pentobarbital was used one or two hours before cardioversion. Some arrhythmias were seen after cardioversion, like atrial and ventricular extrasystoles and atrioventricular dissociation. No patient suffered ventricular tachycardia or ventricular fibrillation. One patient who had not been treated with anticoagulation suffered a splenic embolism two days after cardioversion.

Already in 1975 a number of conditions lowering the success rate of electrical cardioversion had been identified (13). These included the duration of AF, where duration of more than a year gave a poor success rate and was not recommended. Other conditions leading to poor prognosis were:

- Elderly patients with slow ventricular rate or the sick sinus syndrome.

- Patients with enlarged left atrium and pronounced mitral valve disease.

- Patients with a slow ventricular rate in combination with a small heart.

- Patients who had developed AF after recurrent atrial tachyarrhythmias.

- Patients with a rapid relapse into AF despite adequate treatment with antiarrhythmic drugs.

- Patients who did not tolerate antiarrhythmic drugs.

It was also known that higher energies were needed for cardioversion of outpatients, patients with alcohol abuse, patients with Wolff-Parkinson-
White’s syndrome and patients with other concurrent illnesses such as cardiomyopathy, severe coronary heart disease or acute myocardial infarction, uncontrolled congestive heart failure or AF with rapid ventricular rate (13). Horn et al. also concluded that an antiarrhythmic drug like quinidine often was needed to maintain sinus rhythm after cardioversion.

Antithrombotic treatment

An electrical cardioversion confers a risk of thromboembolic events (79-81). Observational studies suggest that the risk of thromboembolic events is highest within 72 hours after cardioversion, and that most thromboembolic events occur within 10 days (82, 83). Echocardiographic studies have shown that it may take several weeks to normalize atrial mechanical activity after cardioversion to sinus rhythm (84), and that impaired atrial mechanical activity is related to the duration of AF (85). It is still unclear what duration of AF it takes for the development of a thrombus, several echocardiographic studies have investigated this issue and left atrial thrombi have been found in up to 14% of patients with short duration of AF (86, 87). Still this question is difficult to examine. The duration of AF is often assumed to be since start of symptoms, but asymptomatic AF is very common, and symptoms indicating AF does not necessarily mean that AF is present (88). Therefore, the results are often difficult to interpret. In clinical praxis, however, cardioversion of AF of duration <48 hours has been considered safe and is performed without prolonged pre-cardioversion OAC treatment (18, 89). According to current European guidelines, cardioversion of AF of less than 48 hours duration should be preceded by intravenous unfractioned heparin (UFH), followed by heparin infusion or subcutaneous low molecular weight heparin (LMWH). In patients with risk factors for stroke, OAC is recommended after cardioversion and should be continued lifelong (18). In patients with lone AF, no OAC is recommended.

In patients with AF duration of ≥48 hours or unknown duration, therapeutic OAC treatment is recommended for at least three weeks before and four weeks following cardioversion (18). This recommendation is largely based on observational data (90, 91). It has also been shown that an INR value of 1.5-2.4 at the time of cardioversion conferred more thromboembolic events than an INR value of ≥2.5 (92), which highlights the importance of therapeutic OAC in conjunction with cardioversion. Analysis of data from a randomized controlled trial showed a thromboembolic event rate of 0.9% in patients undergoing cardioversion according to current anticoagulation guidelines (93).

An alternative to three weeks with therapeutic OAC treatment is to exclude the presence of left atrial thrombi via transoesophageal echocardiography (TEE) before cardioversion (18). Thrombus in the left
atrium or in the left atrial appendage (LAA) is currently the only echocardiographic finding that contraindicates cardioversion, though, it has been shown that also LAA sludge, defined as “a dynamic, viscid, layered echodensity without a discrete mass, visualized throughout the cardiac cycle” was associated with both thromboembolic events and all-cause mortality in AF patients (94). OAC during and after cardioversion is still recommended in the TEE approach. One randomized controlled trial (RCT) has suggested that LMWH has similar efficacy as unfractionated heparin before a TEE guided cardioversion (95). The assessment of cardioversion using Transesophageal echocardiography (ACUTE) RCT compared conventional OAC three weeks prior to cardioversion with a TEE guided approach and found no differences in thromboembolic events between the groups (96). Importantly, the use of OAC in AF patients decreases, but does not eliminate, the risk of thromboembolic events (61), and the prevalence of left atrial thrombi has been shown to be 7.7% in patients with persistent AF and effective anticoagulation (97).

Antiarrhythmic drugs

After an electrical or pharmacological cardioversion, antiarrhythmic drugs are often needed to retain sinus rhythm. Antiarrhythmic drugs used in rhythm control in AF patients mainly acts by reducing the excitability and the conduction velocity by blocking sodium channels (class I antiarrhythmic drugs, eg. flecainide) or by prolongation of refractoriness by potassium channel blockade (class III antiarrhythmic drugs, eg. amiodarone) (98).

Pulmonary vein isolation

Historical background

Since the discovery of the main foci of electrical impulses in AF at the entrance of the pulmonary veins by Haissaguerre et al. in the late 1990’s (7), the method pulmonary vein isolation (PVI) has developed and become accepted as a treatment option for patients with AF, paroxysmal AF in particular (59). A PVI aims to isolate the substrate of the arrhythmia at the entrance of the pulmonary veins in the left atrium and thereby prevent the rest of the atrium from the electrical impulses, and is most often performed with radiofrequency. There are different techniques for achieving isolation of the electrical impulses in AF, like circumferential radiofrequency lesions around the pulmonary vein ostia (99), linear ablation of the left atrial roof in combination with PVI (100), box isolation (which aims to isolate the pulmonary veins as well as the posterior left atrium) (101), ablation of areas
with complex fractionated atrial electrograms (areas with complex electrical activity, for example slow conduction, allowing AF wavelets to re-enter and thereby maintaining AF) (102) and ablation of left atrial ganglionated plexi (the autonomic nervous system has been suggested to play an important role in the initiation and maintenance of AF) (103). As recommended in the latest ESC guidelines, catheter ablation of AF should target isolation of the pulmonary veins (59).

Complications to pulmonary vein isolation

A PVI is an invasive procedure associated with risk of complications. A worldwide study based on questionnaires answered by centers performing catheter ablation for AF included 16 309 patients between 2003-2006 (104). The overall complication rate was 4.5%, including cardiac tamponade (1.31%), pneumothorax (0.09%), hemothorax (0.02%), infections (sepsis, abscess or endocarditis, 0.01%), permanent diaphragmatic paralysis (0.17%), total femoral pseudoaneurysm (0.93%), total arterio-venous fistulae (0.54%), valve damage (requiring surgery, 0.07%), atria-oesophageal fistulae (0.04%), stroke (0.23%), TIA (0.71%), pulmonary vein stenosis (0.29%) and death (0.15%). A smaller study including 100 patients undergoing PVI reported complications in form of cardiac tamponade (3%), pericardial effusion managed conservatively (3%), pulmonary vein stenosis (1%), arteriovenous fistulae (1%), anaphylactic shock due to propofol administration (1%) and ventricular fibrillation secondary to cardioversion (1%) (105).

Pulmonary vein isolation vs. antiarrhythmic drugs

Several studies have compared the results after PVI with antiarrhythmic drug therapy. The APAF (Ablation for Paroxysmal Atrial Fibrillation) study with 198 patients randomized to either radiofrequency catheter ablation or antiarrhythmic drug therapy showed a higher freedom of recurrent AF four years after randomization in those assigned to catheter ablation compared with antiarrhythmic drug therapy (72.7% vs. 56.5%, p=0.017) (106). Randomization to the catheter ablation group also significantly improved quality of life. Importantly, the crossover frequency from antiarrhythmic drug therapy to catheter ablation was 87.9%.

The MANTRA-PAF trial (Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) compared PVI to antiarrhythmic drug therapy as first-line rhythm control treatment. 294 patients were enrolled in the trial, where the main results included better quality of life and lower symptom burden in both groups compared with baseline, with a more pronounced improvement in the PVI group (107).
Recurrence rate after PVI

Recurrence rate after AF ablation varies across different ablation techniques and across different AF classification groups. In a study including only patients with paroxysmal AF and normal left ventricular function undergoing circumferential PVI, recurrence rates of atrial tachyarrhythmias after first ablation were 22% within the first month, 47% within one year and 53% within 4.8 years (108). Another study included patients with paroxysmal, persistent and long-standing persistent AF where 20% of the patients had a CHADS2 score of ≥2 (105). Arrhythmia-free survival rates after a first ablation procedure (including PVI, ablation of the cavitricuspid isthmus and in patients with persistent AF also linear ablation) were 40%, 37% and 29% after 1, 2 and 5 years of follow up, respectively. Recurrence rate was higher in patients with long-standing persistent AF compared with paroxysmal or persistent AF. Overall success rate, defined as freedom from documented AF after a minimum follow up of four months, has been shown to be in total 80% (including all centers, patients with and without antiarrhythmic drugs and different techniques of AF ablation), decreasing to 62% when only centers including patients with long-lasting AF were taken into account (104). A study including only patients with persistent AF showed arrhythmia-free survival rates after a first time ablation (PVI, electrogram-based ablation and linear ablation) of 35%, 28% and 17% after 1, 2 and 5 years of follow up, respectively (109). Arrhythmia-free survival rate was improved after repeated procedures. In a study including patients from several European countries, one-year success rate (defined as survival free from ECG recorded atrial arrhythmia after a three-month blanking period) was 73.7% (110).

Antithrombotic treatment and stroke risk in conjunction with PVI

A PVI confers an increased risk of stroke (104, 111, 112). Several studies using magnetic resonance imaging of the brain have shown asymptomatic cerebral lesions after PVI (113-116), suggesting a clinical stroke to be the tip of an iceberg in the risk of embolization in conjunction with PVI. On the other hand, bleeding complications also occur in conjunction with PVI (eg. cardiac tamponade and hemothorax) (104, 105, 111). Today PVI is performed during therapeutic OAC treatment (warfarin treatment with INR 2-3) (59). Several studies have shown a low stroke risk after PVI (117, 118), suggesting a PVI could decrease the risk of stroke. In a Swedish register based study, the risk of stroke was decreased in AF patients undergoing PVI compared with a propensity score matched group of AF patients not undergoing PVI (119). In a study by Kornej et al., thromboembolic events after PVI were rare, and all three tested risk scores (CHADS2, CHA2DS2-VASc...
VASc and R2CHADS2 were associated with risk of thromboembolism (120). In this study, however, anticoagulation status was not taken into account, and some patients with risk factors for stroke according to CHADS2 or CHA2DS2-VASc replaced OAC treatment with aspirin (due to patient preferences, lack of symptoms and ECG recordings of sinus rhythm). A Danish register-based study could not find any significant differences in thromboembolic risk in patients continuing or discontinuing OAC treatment after PVI (121). Instead, risk of serious bleeding complications seemed to outweigh the benefit of OAC treatment. Another study showed that it is safe to discontinue OAC treatment after PVI if there is no evidence of AF recurrence on meticulous follow up (122). On the other hand, a study by Noseworthy et al. found an increased risk of thromboembolic events in all patients during three months following PVI, and in high-risk patients in the long term, suggesting patients with risk factors for stroke to be maintained on OAC after ablation (123). Most of these studies have, however, obtained OAC status from prescription data, making data on OAC treatment uncertain.

**Antithrombotic treatment in atrial fibrillation**

Since the Framingham study showed an increased risk of stroke in patients with AF, several studies have compared different regimes of anti-thrombotic therapy for the prevention of thromboembolic events. Also, several meta-analyses based on these studies have been published, concluding that oral anticoagulation (OAC) and antiplatelet agents all prevent stroke in patients with AF, however OAC substantially more efficacious than antiplatelet agents (61, 124, 125).

**Acetylsalicylic acid**

**Historical background**

The Greek physician Galen was the first to record the antipyretic and anti-inflammatory effects of the salicylate-containing willow bark, while both Galen and Hippocrates described the analgesic effects (126). The first modern scientific description of the medical effects of willow bark originates from 1763, when Edward Stone described treatment of malarial fever in 50 patients. In 1826, Henri Leroux isolated “salicin” from willow bark, Latin for “willow”. Salicylic acid was generated from salicin in 1838, and in 1853 acetylsalicylic acid was created for the first time, though, it was not used or
marketed at that time. It was not until 1897, when Felix Hoffman, a chemist working for the pharmaceutical company Bayer, recreated acetylsalicylic acid, which was named aspirin. As shown in figure 5, in acetylsalicylic acid, the hydroxyl group is acetylated, making the substance more tolerable to the gastric mucosa.

Figure 5: Chemical structure of salicylic acid and acetylsalicylic acid (aspirin).

Salicylic acid

Acetylsalicylic acid

The discovery that high doses of aspirin caused prolongation of the prothrombin time was established in 1950 (126), but even low doses appeared to prevent coronary and cerebral thrombosis. In the late 1960’s, Armand Quick found that low doses of aspirin prolonged the bleeding time.
without affecting the prothrombin time. Harvey J. Weiss theorized that the prolongation of bleeding time caused by aspirin might result from defective platelet aggregation, and he also found that salicylic acid did not have this effect on bleeding time, suggesting the acetylated hydroxyl group caused this effect. During the 20th century, hundreds of clinical trials have evaluated aspirin’s and other antiplatelet agent’s ability to prevent cardiovascular events, and it is today accepted that antiplatelet agents prevent stroke and myocardial infarction (127).

Aspirin treatment in atrial fibrillation

Seven randomised controlled trials have compared aspirin with placebo or control for stroke prevention in AF (128-134). Six of these studies failed to show any benefit from treatment with aspirin compared with placebo or control for the prevention of thromboembolic events (128, 130-134). The SPAF-I trial was the only trial to show a reduced risk of thromboembolic events in patients treated with aspirin compared with placebo (129), with a relative risk reduction (RRR) of 44% regarding ischemic strokes, TIA's and systemic emboli. When considering disabling ischemic stroke or vascular death, there was no significant difference between aspirin or placebo therapy (RRR 22%, p=0.33) In this trial, patients above the age of 75 years were not offered oral anticoagulation treatment in the start of the trial (this exclusion criteria was rescinded in November 1988 (135)), and no benefit was shown for aspirin compared with placebo in this age group (136). The last performed trial, JAST, showed a non-significant increase in ischemic stroke in Japanese patients treated with aspirin compared with no treatment (133). The trial was terminated early since it was unlikely that aspirin would reach superiority compared with no treatment. In the trials comparing aspirin with placebo or control, the aspirin dose varied greatly (50-1200 mg daily) as did the study design.

In 2007, Hart et al. performed a meta-analysis including all seven trials comparing aspirin alone with placebo or no treatment. In total 3990 patients had been randomised to either aspirin or control. The results showed no significant reduction in stroke rate between the groups, neither was there any significant difference when only ischemic strokes, disabling or non-disabling strokes were considered (61).

Other antiplatelet agents in atrial fibrillation

Two additional randomised trials have compared dipyridamole, dipyridamole and aspirin in combination, or aspirin combined with low-dose warfarin with control in AF patients (131, 137). When adding these trials to the aspirin trials in the meta-analysis, the number of patients increased to
Considering all 8 trials, antiplatelet therapy significantly reduced stroke rate by 22% (CI 6%-35%) (61).

In 2009, van Walraven et al. investigated the effect of age on stroke prevention therapy in AF, and found that the benefit of antiplatelet agents decreases with increasing age, whereas it does not change for oral anticoagulation treatment (138). The significant effect of antiplatelet agents in stroke reduction can be seen in AF patients up to 75 years of age. Above 75 years, the effect is no longer significant and by the age of 80, it turns to a non-significant negative effect.

**Blood coagulation**

**Haemostasis**

Haemostasis is by definition the phenomenon in which liquid blood form solid blood clots, a process that is mandatory for humans to prevent blood loss from damaged blood vessels. At the same time, the blood flow should not be impaired more than necessary. Haemostasis is composed of three main stages, primary haemostasis, secondary haemostasis and fibrinolysis.

**Primary haemostasis**

Vasoconstriction, produced by smooth muscle cells in the vascular wall, is the blood vessels first response to injury. Thereafter, platelets bind to the von Willebrand factor in the subendothelium and to collagen (139, 140). The thrombocytes change shape, sending out pseudopodia to cover the damaged area. The thrombocytes aggregate when two activated thrombocytes bind to a fibrinogen molecule. Activated thrombocytes release several kind of granule, where dense granule activates other thrombocytes.

**Secondary haemostasis**

Secondary haemostasis implies plasma coagulation. The coagulation system is an enzyme system, structured as a cascade, where an enzyme activates the next pro-enzyme through proteolytic cleavage. In each step, more enzymes are activated. Normally, when a blood vessel is damaged, damaged endothelial cells and other subendothelial structures expose tissue factor, which bind to factor VIIa (140). The complex with tissue factor and factor VIIa activates factor X to Xa (139). On the surface of activated thrombocytes, factor Xa and factor Va activates prothrombin to thrombin. In this initiation phase of the coagulation cascade, small amounts of thrombin and fibrin are
formed (139). The initiation phase is followed by an amplification phase, in which factor IXa binds to the thrombocyte together with factor VIII and X. Factor X activates to Xa, which builds a complex with factor V, activating prothrombin to thrombin (140). The coagulation cascade ends in the cleavage of fibrinogen to active fibrin, which constitutes the armour in a blood clot. The amplification phase generates large amounts of thrombin and fibrin (139). Anticoagulation, the opposite to coagulation, limits the thrombus formation and balance plasma coagulation. Anticoagulation is achieved through several mechanisms. When thrombin reaches intact endothelium, it binds to a membrane protein together with the coagulation inhibitor protein C. The complex activates protein C, which, together with protein S, leads to inactivation of factor Va and VIIa. Tissue factor pathway inhibitor is also a part of the anticoagulation system, inactivating the complex with tissue factor, factor VIIa and Xa (140).

Prothrombin time

Prothrombin time is a measure of the time it takes for blood plasma to coagulate after addition of tissue factor (141). Today, prothrombin time is expressed in international normalized ratio (INR), which is a ratio between the patient’s prothrombin time and the prothrombin time of normal blood plasma, corrected for differences in test methods (141).

Fibrinolysis

As soon as fibrin has formed, fibrinolysis starts to reorganise and resorb the thrombus. When the clot is formed, plasminogen binds to fibrin and is activated by tissue plasminogen activator to active plasmin (142). Plasmin mediates degradation of fibrin to several different degradation products (142). One of the degradation products is D-dimer (142), and increased levels of D-dimer therefore indicate prior thrombus formation and/or ongoing fibrinolysis.

Anticoagulation

Historical background

The first substance with anticoagulant effect used was hirudo medicinalis, the use of these medicinal leeches dates back to ancient Egypt (143). Leeches can be seen in wall paintings from 1567-1308 BC., and in the first century AD., literature from several continents contained information about the usage of leeches suggesting that the knowledge was already wide spread. The
Romans named the substance “Hirudo”. Hirudin acts by binding to thrombin and thereby inhibit blood coagulation (144). The French surgeon Broussais (1772-1832) proposed that all diseases resulted from blood excess and treated the condition with leeches and starvation. In this time, the use of leeches was very popular (143).

Jay McLean, a medical student at Johns Hopkins Medical School, claimed to have discovered heparin, although this is contested (145). McLean extracted a substance from canine liver with anticoagulant properties in vitro, which showed to cause excessive bleeds in experimental animals. McLean was working under William Henry Howell, who named the anticoagulant substance heparin. In 1926, Howell presented a water-soluble heparin, and production of this substance began at a pharmaceutical company. Unfortunately, the substance caused concerning side effects. In 1937, Murray et al. showed that heparin prevented thrombus formation in dogs, and shortly thereafter the new, purified form of heparin was used in a human without toxic side effects. Today, low molecular weight heparins (LMWH) have largely replaced unfractionated heparin (UFH) due to easier administration and a more predictable effect.

The story of warfarin began in the 1920’s, when cattle in Canada and northern America began dying of internal bleedings (145). It showed that the farmers could not afford to buy fodder for their cattle because of The Great Depression, instead feeding them with moulded hay. The haemorrhagic disease became known as “sweet clover disease” and local veterinaries demonstrated a potential cure through blood transfusion or removal of the mouldy hay. In 1940, dicoumarol was finally isolated from the hay. Of 150 variations of the coumarine, warfarin appeared to be most active and was initially used as rat poison. The possibility to reverse the effect by vitamin K was shown in 1942. In 1955, President Dwight Eisenhower started treatment with warfarin following a myocardial infarction, with dosage control in terms of measuring the prothrombin time (PT). Though, the laboratory method for measuring the PT turned out to be a major problem since it varied greatly between laboratories and methods used. The difficulty in measuring PT led to overdosing and bleeding complications. Therefore, the World Health Organisation (WHO) adopted in 1982 usage of international normalised ratio (INR) to standardise treatment control worldwide.

**Warfarin treatment in atrial fibrillation**

Six randomised controlled trials have compared the efficacy of vitamin K antagonists (usually warfarin) with either control or placebo for stroke
prevention in patients with AF (128-130, 146-148). One of these trials was a secondary prevention study (130), all of the others considered primary prevention. These studies differed considerably in study design and in intended anticoagulation target interval (INR target range between 1.4-4.5) (46). All six studies showed advantage of vitamin K antagonists compared with placebo or control, although not all of them with significant results. The CAFA study was terminated early (149) since results from two other similar randomized trials showed benefit for anticoagulation treatment.

A meta-analysis has been performed comparing oral anticoagulation with adjusted dose vitamin K antagonists to control (61), including 2900 participants from all six randomised controlled trials. The results showed a significant reduction in the relative risk of ischemic stroke compared with control. Average stroke rate in the control groups was 4.5% per year for primary prevention and 12% per year for secondary prevention, adjusted dose vitamin K antagonists decreased the relative risk of stroke with 64% (95% CI 49-74%). The stroke reduction was similar considering both disabling and non-disabling strokes. When only ischemic strokes were considered, OAC treatment was associated with a 67% relative risk reduction. Intracranial haemorrhages were included with ischemic strokes and are therefore included in the primary analysis. Another meta-analysis showed similar results regarding prevention of stroke, and could also show a significant relative reduction in all-cause mortality (31%, 95%CI 11-47%) (125). Given the different target INR intervals, the benefit of OAC with vitamin K antagonists with a target INR range of 2-3 could be even higher than reported.

Warfarin treatment quality

Warfarin treatment quality can be measured in several different ways, either directly as number of complications (bleedings and thromboembolic events), or indirectly as time in therapeutic range (TTR), hit rate or mean error (hit rate defined as the number of INR values within the intended target range 2-3 and mean error defined as the distance to the target INR 2.5). Another way of measuring quality is proportion of patients with indication for treatment receiving treatment. Under-treatment is an important aspect, but since OAC is a very potent treatment with severe possible side effects, over-treatment must also be considered in terms of treatment quality.

Time in therapeutic range (TTR)

The level of anticoagulation effect in warfarin treatment is measured by international normalized ratio (INR). Time in therapeutic range (TTR)
reflects the proportion of time a patient spends in the intended INR interval (usually between 2-3) (150). In the method developed by Rosendaal et al, a linear increase or decrease between two INR values is assumed (Figure 6). Very high TTR levels above 70% have repeatedly been reported from Sweden (151-153), probably due to a well-established organisation with anticoagulation clinics with specialized nurses and warfarin dosing algorithms. In the clinical trials of the NOACs, TTR ranged between 55-68% (154-157).

**Figure 6: Time in therapeutic range according to Rosendaal et al. The proportion of time spent in intended INR interval (usually 2-3), with an assumed linear increase or decrease between two INR values.**

TTR can be measured in an individual patient (iTTR) or in a center (cTTR). cTTR is calculated as a mean of all individual TTR values within a center.

Repeated studies have shown decreasing number of complications (bleedings and thromboembolic events) with increasing TTR level (151, 158, 159). iTTR has been shown to better predict risk of complications than cTTR.
At cTTR levels above 70%, further improvement did not correlate to fewer complications in AF patients (161)

New oral anticoagulants (NOACs) in atrial fibrillation

In recent years, new oral anticoagulants (NOACs) have been introduced as alternatives to warfarin for prevention of stroke in patients with AF.

Ximelagatran, an oral direct thrombin inhibitor launched in 2004, was shown to be non-inferior to warfarin regarding stroke prevention in AF (162). Unfortunately it was withdrawn in 2006 due to hepatotoxic effects.

Dabigatran, an oral direct thrombin inhibitor, was the next to achieve indication for stroke prevention in AF. In the RE-LY trial, dabigatran 110 mg twice a day (bis in die, bid.), dabigatran 150 mg bid and adjusted dose warfarin were compared, with the primary outcomes stroke or systemic embolism (154). Mean CHADS\(_2\) score was 2.1. In the warfarin group, mean time in therapeutic range (TTR) was 64%. Results showed that both doses of dabigatran were non-inferior to warfarin regarding the primary outcomes stroke and systemic embolism (rate of stroke or systemic embolism with dabigatran 110 bid 1.5%/year, with dabigatran 150 bid 1.1%/year and with warfarin 1.7%/year (p<0.001 for non-inferiority for both dabigatran doses compared with warfarin). Dabigatran 150 mg was also superior to warfarin regarding prevention of stroke and systemic embolism.

The third NOAC to be launched was the direct factor Xa inhibitor rivaroxaban. In the ROCKET AF trial patients were randomised to receive rivaroxaban 20 mg daily (or 15 mg daily in patients with creatinine clearance 30-49 ml/min) or adjusted-dose warfarin with target INR 2-3 (155). Primary end point was stroke (both ischemic and haemorrhagic) and systemic embolism. Mean CHADS\(_2\) was 3.5 and mean TTR in the warfarin group was 55%. In the intention-to-treat analysis stroke or systemic embolism occurred in 2.1%/year in the rivaroxaban group and 2.4%/year in the warfarin group (p<0.001 for non-inferiority).

Thereafter another direct factor Xa inhibitor, apixaban achieved indication for stroke prevention in AF. In the ARISTOTLE trial patients were randomised to treatment with apixaban 5 mg bid (or 2.5 mg bid if at least two of the following criteria were fulfilled: age ≥80, body weight ≤60 kg or serum creatinine ≥133 µmol/l) or warfarin with target INR range 2-3 (156). Primary efficacy outcome was stroke (ischemic, haemorrhagic or of uncertain type) or systemic embolism. Mean CHADS\(_2\) score was 2.1 and
mean TTR for warfarin treated patients was 62%. Rate of stroke or systemic embolism was 1.3%/year in the apixaban group and 1.6%/year in the warfarin group (p<0.001 for non-inferiority, p=0.01 for superiority).

Data from the fifth NOAC, the direct oral factor Xa inhibitor edoxaban, was presented in 2013, but it has not been launched until recently. In the ENGAGE AF-TIMI 48 trial, 21,105 patients with AF and moderate to high stroke risk were randomised to either adjusted dose warfarin or one of two doses of edoxaban, 30 or 60 mg once daily (157). Primary efficacy end points were stroke (ischemic or haemorrhagic) or systemic embolism. Mean CHADS₂ score was 2.8 and mean TTR for warfarin treated patients 68.4%. Annualized rates of the primary efficacy outcome were 1.50% with warfarin, 1.18% with 60 mg edoxaban and 1.61% with low dose edoxaban and both doses were found to be non-inferior to warfarin for prevention of stroke and systemic embolism and reduced rates of bleeding events.

**Oral anticoagulation vs antiplatelet agents in atrial fibrillation**

Oral anticoagulation with warfarin and apixaban has also been compared with antiplatelet agents. In total 12 randomised trials (12 963 participants) have compared adjusted dose warfarin to antiplatelet therapy for stroke prevention in AF. In a meta-analysis of these 12 trials adjusted dose warfarin yielded a 37% (CI 23-48%) reduction in relative risk of stroke (61).

When only aspirin in various dosages was compared to adjusted-dose warfarin (9 trials, 3647 participants) relative risk of stroke was reduced by 38% (CI 18-52%). Compared with aspirin, warfarin gave a doubled risk of intracranial haemorrhage, but the increase in absolute risk was small, 0.2%/year.

In the AVERROES trial patients considered unsuitable for warfarin treatment were randomised to receive apixaban 5 mg bid (or 2.5 mg bid if at least two of the following criteria were fulfilled: age ≥80, body weight ≤60 kg or serum creatinine ≥133 μmol/l) or aspirin at a dose of 81-324 mg per day (163). Primary efficacy outcomes were stroke (ischemic or haemorrhagic) or systemic embolism. Results showed a primary outcome rate of 1.6% per year in the apixaban group compared with 3.7% per year in the aspirin group (HR 0.45, 95% CI 0.32-0.62). Apixaban did not confer an increased risk of major bleeding.
**Under- and over-treatment**

A report from 2013 showed that 42% of AF patients in Sweden were treated with warfarin (21). Data from Rikssstroke indicates that use of OAC in patients with AF is increasing (31), but there is still a substantial undertreatment. Since there are patients with contraindications, the national board of health and welfare has set the goal to reach 80% OAC treatment in AF patients with risk factors for stroke (164). In a study by Gorin et al. 53% of AF patients had OAC treatment in agreement with guidelines, whereas 31% and 16% were classified as under- and over-treated, respectively (over-treatment defined as OAC treatment in patients with CHADS2 score 0, dual antiplatelet therapy at CHADS2 ≤1 or OAC combined with an antiplatelet agent at CHADS2 ≥1 and no history of coronary heart disease or peripheral vascular disease, guidelines adherence defined as OAC treatment at CHADS2 ≥1 and antiplatelet therapy at CHADS2 ≤1) (165). Under-treatment was associated with increased risk of stroke or all-cause mortality compared with guideline adherence.

Over-treatment is less studied compared with under-treatment, but a register-based study by Friberg et al. found that 38% of men with CHA2DS2-VASc score 0 were on warfarin treatment, only 11% of those underwent cardioversion during the study period (166). Though, pulmonary vein isolation (PVI) is another possible indication for OAC treatment in this patient group not taken into account in this study. Two other studies have found 42% OAC use 12 months after PVI in patients with CHADS2 0 without known AF recurrence (167), and 13% OAC use in conjunction with cardioversion of AF with duration <48 hours in patients with CHA2DS2-VASc score ≤1 (168). CHA2DS2-VASc score 1 is, however, an indication for OAC treatment.
Aims of the thesis

The general aim of this thesis is to improve stroke prevention for patients with AF.

**Paper I:** To evaluate if warfarin dose suggestions from a computer aided dosing algorithm can perform as well as, or better than warfarin doses that have been changed manually, measured as hit rate and mean error, with decisions based on information about two or three previous INR values.

**Paper II:** To investigate the prevalence and the net clinical benefit of acetylsalicylic acid as monotherapy for stroke prevention in patients with atrial fibrillation.

**Paper III:** To evaluate if the risk of thromboembolic and haemorrhagic complications during a follow-up of 30 days differs between AF patients undergoing electrical cardioversion with or without OAC pre-treatment.

**Paper IV:** To investigate the proportion of patients discontinuing OAC after PVI, to identify factors predicting stroke after PVI and to assess the risk of ischemic stroke, intracranial haemorrhage and death after PVI in patients continuing and discontinuing oral anticoagulation in relation to current guidelines.
Materials and methods

All studies in this thesis are based on register data on patients with atrial fibrillation and/or warfarin treatment from several different Swedish quality registries.

Auricula

Auricula is a Swedish national quality register for atrial fibrillation and anticoagulation that combines a quality register for patients with atrial fibrillation, for patients with anticoagulation treatment irrespective of indication, and a web-based dosing system for anticoagulation treatment. The register was launched in 2006 and has continuously grown, both in participating centres and in registered patients. In 2015, 224 centres and 14 out of 20 county councils in Sweden were using any part of Auricula (169). About 150,000 patients are registered in Auricula, approximately 20,000 patients in the AF register and approximately 122,000 patients in the anticoagulation register. More than 1,200,000 warfarin dosings are performed annually.

The anticoagulation register contains information about demographic data, indications for anticoagulation treatment, information about every dosing period with start- and stop dates, time in therapeutic range (TTR, proportion of time spent in intended INR interval), warfarin dose ordination and resulting INR values, complications, bridging with low molecular weight heparin (LMWH) in conjunction with elective invasive procedures, time from start of anticoagulation treatment until performance of elective electrical cardioversion and monitoring of treatment with new oral anticoagulants (NOACs).

Auricula also contains a dosing algorithm, which suggests a weekly warfarin dose if certain criteria are met. The algorithm bases the dose suggestions on the results of previous weekly doses and INR values. To obtain a suggestion from the algorithm, at least two previous INR values must be present, not have a very wide distribution and target INR must be 2.5 (range 2-3). The algorithm suggestion can be that the warfarin dose should be unchanged, or that the weekly dose should be increased or decreased by 5, 10 or 15%. The algorithm in Auricula contains 720 rules, where 72 base the suggestion on two, and the remaining 648 rules on three previous INR values. In most of the cases, if the distribution between two
INR samples is more than 1.6, the algorithm will suggest that manual dosing should be performed, which is the case in 123 rules.

**Swedish National Patient Register (NPR)**

The Swedish National Patient Register (NPR) is a Swedish national quality register founded in 1964. In 1987, all Swedish counties had entered the NPR with all somatic and psychiatric inpatient care linked to personal identity numbers (64). Since 2001, the counties are also obliged to report hospital outpatient visits. Primary care is, however, still not included in the NPR. The coverage in the inpatient register, which is a part of the NPR, is almost 100% but coverage of the hospital outpatient care is lower, about 80%, due to missing data from private caregivers. Since the start of NPR, primary diagnosis is missing in 0.8% of hospital discharges from somatic care. Variables included in the NPR are personal identity number, age, gender, dates of admission and discharge, primary and additional diagnoses, external causes of injury or poisoning and diagnoses related to surgical procedures etc. Validation of the NPR has shown that the positive predictive values (PPVs) were 85-95% for a majority of evaluated diagnoses, but a lower sensitivity (64). PPV for AF was 97% (170). The NPR has been considered suitable for epidemiological research (64). Information from the NPR was included since use of ICD10 (International Classification of Disease, 10th edition) started in January 1st 1997

**Dispensed Drug Register**

The Dispensed Drug Register has been in operation in the present form since 1st of July 2005, where all prescriptions are linked to an individual’s personal identity number (171). It is mandatory for pharmacies in Sweden to report to the register, which therefore contains information about all purchases of prescribed medications from Swedish pharmacies. Number of prescribed purchases is today about 100 million every year. For every prescribed purchase there is information about date of purchase, type of medication, quantity and dosage. Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification.

**Cause of Death Register**

The Cause of Death Register comprises data from 1961 and contains information about all deceased persons who were inhabitants in Sweden at
time of death, even if death occurred abroad. Variables in the register includes personal identity number, date of death, age when death occurred, gender and main cause of death as well as contributing death causes and how the cause of death was confirmed (e.g. examination before death or autopsy). Cause of death is missing in 1.3% of all deaths (172).

**Swedish Catheter Ablation Register**

Catheter ablations for cardiac arrhythmias have been performed in Sweden since 1991. The number of procedures have continuously increased, PVI is presently performed in ten Swedish centres, which all report to the Swedish Catheter Ablation Register (173). Participation in the register is still optional. The coverage of the register was 2011-2013 94%. The Catheter Ablation Register was launched in 2004 and holds demographic data, information about diagnosis and procedure as well as radiation times. The register also contains information about complications, and complications occurring during the intervention will to a very high degree be registered. Information about late complications is uncertain since reporting of these complications requires an active search for events.

**Riksstroke**

Riksstroke is a Swedish national quality register for patients with stroke. Riksstroke has an active registration of patients with stroke and includes patients from all hospitals in Sweden admitting patients with stroke. Validation of data from the NPR has shown that some patients with a stroke diagnosis were discharged without a secure base for the diagnosis. The most common reason for this is that patients with previous stroke, transient ischemic attack (TIA), traumatic brain injuries or uncertain symptoms obtain a stroke diagnosis in the NPR. After correction for this overuse of stroke diagnoses, which is estimated to be 6% in the NPR, the coverage in Riksstroke is about 96% (31). The fact that Riksstroke applies active registration minimizes the risk for old events counting as new events.

**Statistical methods**

In paper I, we analysed the INR value resulting from every warfarin dose, evaluating algorithm suggestions and manually changed doses separately. All INR values were measured with one decimal and the highest INR value was 9. Two different outcome measures were used, mean error and hit rate, and
for both outcome measures results after algorithm and manual dosings were compared. The error was defined as the distance to target INR 2.5 and the tests conducted are of Mann-Whitney type. Hit rate was defined as number of INR values within the intended INR interval 2-3. In an ideal analysis, the risk associated to the INR value should be reflected by the outcome measure, but in this case the exact risk associated with an INR value is unknown. Therefore two different outcome measures were used, to in different ways show the performance of manual ordinations compared with algorithm dose suggestions. We also evaluated the TTR for each of the 125 centers in Auricula (cTTR), and compared cTTR with degree of acceptance of algorithm dose suggestions.

In papers II-IV data was analysed with SPSS Statistics, versions 21-23 (SPSS Inc., IBM Corporation, NY, USA) and in paper II R version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria) was also used for propensity score matching analyses. Information about the study populations at baseline was presented descriptively in numbers with percentages for dichotomous variables or in means with standard deviations (SDs) for continuous variables. In papers II-III differences between groups were tested with Chi-2-tests and T-tests.

Rates of complications are presented in study II and IV, and are calculated as events per 100 patient years at risk, with the result expressed as percent.

In paper III, patients were stratified according to CHA\textsubscript{2}DS\textsubscript{2}-VASc score, where patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc 0-1 were considered to have low, CHA\textsubscript{2}DS\textsubscript{2}-VASc 2-3 medium and CHA\textsubscript{2}DS\textsubscript{2}-VASc 4-9 high stroke risk.

In paper IV, predictors for ischemic stroke were calculated using logistic regression analyses, as were risk of complications in paper III.

Risk of complications in AF patients treated with aspirin compared with no antithrombotic treatment as well as in AF patients undergoing PVI with or without oral anticoagulation (OAC) per time unit was calculated using Cox regression analyses in papers II and IV. In paper IV, the result was also presented as a survival curve.

In clinical trials, the golden standard for evaluating treatment benefit without bias is the randomized controlled trial (RCT). Unfortunately, randomization is not always possible due to study design, in for example retrospective and observational studies. In 1983, Rosenbaum and Rubin introduced a new method for these studies, the calculation of a propensity score (174). Propensity score matching was used in paper II-III. This method aims to make different groups as similar as possible, to enable comparisons also between non-equivalent groups. At first, a logistic regression analysis is performed, in which pre-specified factors (in these studies risk factors such as age, gender and concurrent illnesses) are taken into account to calculate the propensity score, i.e. the probability of assignment to a treatment group. Thereafter, the propensity score is used to match patients in different groups
with as similar propensity score as possible. The goal with the propensity score is to balance the distribution of potential confounders. The dissemination limit is chosen by the researcher, a propensity score of 0 indicates a perfect match and a propensity score of 1 indicates totally divergent background information. In paper II a calliper of 0.2 was used, and in paper III a calliper of 0.1 was used.

P-values below 0.05 were considered as significant, all p-values are 2-sided. Confidence intervals (CIs) are 95%.

**Table 3: Statistical methods used in the indicated papers.**

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive statistics:</strong> Numbers, Percent, Means, Standard deviations</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>T-tests</strong></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Chi-square tests</strong></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complication rates</strong></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Linear regression</strong></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Logistic regression</strong></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Cox regression</strong></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Mann-Whitney</strong></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Propensity score matching</strong></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Paper I

From Auricula we collected data on all warfarin doses with resulting INR values in patients with target INR 2.5 from the start of the register in 2006 until March 1st 2011. Data from all centers using Auricula was included, consisting of 53 779 patients from 125 centers, with a mean TTR of 73%. There were in total 1 061 529 INR values, of which 228 868 were excluded due to missing values since it turned out that the algorithm initially did not cover all possible INR combinations. The algorithm is now corrected and includes the missing possibilities. In 123 rules, the algorithm suggestion is that dosing should be made manually, the 62 728 INR values resulting from these rules were therefore not included. In total 769 933 values were included in the analysis, 590 939 resulting from algorithm suggestions and 178 994 from manually changed doses.

Paper II

By means of the NPR we identified all patients with a diagnosis of AF between July 1st 2005 and January 1st 2009. Information about comorbidities was also collected from the NPR as well as information about events during the follow up period.

Information about exposure to antithrombotic treatment was collected from the Dispensed Drug register. Medication at baseline was defined as a drug collected at a pharmacy between 100 days before and two weeks after index date. The dose of antiplatelet agents was not taken into account in the analysis.

We defined index date as the first episode of AF in a patient after July 1st 2005. For complications during follow up, we used a blanking period of two weeks after AF diagnosis, since transfer between different hospital units, clinics and hospitals are common. A new diagnosis of for example stroke or intracranial haemorrhage within two weeks after index admission was considered to be related to the cause of first admission and not to a new event. Therefore, counting of time at risk starts two weeks after index date. Diagnoses obtained before index admission and during the blanking period were considered as comorbidities.

The risk of ischemic stroke and bleeding events were assessed using the risk score systems CHA₂DS₂-VASc and HAS-BLED. When calculating HAS-BLED, no score points were given for the use of NSAID or for labile INR values, since this information was missing.

Complications were ischemic stroke, thromboembolic events (ischemic stroke, unspecified stroke, TIA and systemic embolism), intracranial
haemorrhage and major bleeding (intracranial haemorrhage, gastrointestinal bleeding and anaemia secondary to bleeding).

**Paper III**

Patients undergoing electrical cardioversion between January 1st 2006 and December 1st 2010 were identified from the NPR. Information about concurrent illnesses and risk factors as well as complications during the follow up period were also collected from the NPR. Regarding concurrent illnesses all diagnoses were considered, both primary and additional, but regarding complications only primary diagnoses were considered. This approach was chosen to avoid for example an old stroke diagnosis to be counted as a complication. Information about exposure to oral anticoagulants was collected from the Dispensed Drug register. Treatment with oral anticoagulation was defined as a warfarin prescription dispensed at a pharmacy within 6 months prior to cardioversion, and treatment with an antiplatelet agent was defined as an antiplatelet drug (acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel or ticlodipine) collected within three months prior to cardioversion. Date of death was collected from the Cause of Death Register.

Date of cardioversion was defined as index date, only the first cardioversion in a patient was considered. Complications were defined as a diagnosis of ischemic stroke, systemic emboli, TIA or a bleeding event in the NPR, or date of death in the Cause of Death register, that occurred within 30 days after cardioversion. Risk of ischemic stroke and bleeding events was calculated for each patient using the risk score systems CHA₂DS₂-VASc and HAS-BLED. When calculating CHA₂DS₂-VASc score, women with no other risk factors for stroke were considered to have CHA₂DS₂-VASc score 0.

Regarding HAS-BLED, we had no information about labile INR values and the use of NSAID, thus these factors did not lead to a score point in HAS-BLED.

**Paper IV**

From the Swedish Catheter Ablation Register we collected information about all patients undergoing pulmonary vein isolation (PVI) between 1st of January 2006 and 31st of December 2012. The information was cross-matched with information about patients with oral anticoagulation (OAC) in Auricula, and only patients with information about OAC (start- and stop date for OAC) were included. By cross-matching with Riksstroke, the National Patient Register, the Cause of Death Register and the Dispensed Drug Register we collected information about concurrent illnesses and risk factors, complications, treatment with antiplatelet agents and in case of death, date
of death. For all patients we calculated CHA$_2$DS$_2$-VASc score and HAS-BLED score based on information from the NPR. Women with no other risk factors for stroke were considered as CHA$_2$DS$_2$-VASc score 0. No score points in HAS-BLED were given for NSAID use or labile INR values since these factors were unknown. Treatment with antiplatelet agents was defined as an antiplatelet drug dispensed at a pharmacy within three months before PVI. Date of PVI was defined as index date and complications were defined as a diagnosis of ischemic stroke or intracranial haemorrhage in Riksstroke, or date of death in the Cause of Death Register that occurred after PVI. Time at risk was defined as time from PVI until first complication of a kind, consequently time after an ischemic stroke was not considered as time at risk for a new ischemic stroke, but it was still considered as time at risk for intracranial haemorrhage and death. Only the first PVI in a patient was considered. Relapse into AF was defined as a diagnosis of electrical cardioversion in the NPR or a new PVI in the Catheter Ablation Register that occurred beyond 3 months after index PVI.

**Ethical considerations**

Sweden is unique since all inhabitants have a personal identification number that does not change throughout life. The personal identification number is used in all contacts with Swedish agencies and with the health care system. Sweden also has well-developed quality registries, in which all persons are registered with their personal identification number. Through Swedish registries it is therefore possible to follow an individual’s contacts with the health care system through life. Though, access to Swedish quality registries is strictly controlled to ensure personal integrity. Researchers must apply for ethical approval from a local ethical committee, and thereafter another ethical approval is needed from the agency providing data. Because of the large amount of patients included in register-based studies, it is not possible to obtain informed consent from them all. All data is anonymized before researchers get access to the material. Ethical approval will only be obtained if the research performed is considered to be of benefit for future health care.

Paper I was considered to be a quality assurance study of the dosing algorithm in Auricula, considering only warfarin ordinations and INR values and not individual patients. Therefore, no application for ethical approval was made.

Paper II was approved by the ethical committee of Karolinska Institute (2008/433-32).
Paper III was approved by the ethical committee of Stockholm (2010/852-31/3).

Paper IV was approved by the ethical committee of Umeå (2013/131-31).
Results

Paper I

In total 769,933 INR values were included, 590,939 resulting from accepted algorithm suggestions and 178,994 from manually changed doses. Number of centers contributing with data was 125. As shown in table 4 and figure 7, mean INR value was closer to 2.5 after accepted algorithm suggestions compared with manually changed doses. Also mean error was smaller and hit rate was higher after algorithm based dosing compared to manually changed doses (table 4).

Table 4: Descriptive statistics of mean INR values and mean error, as well as hit rate resulting from all warfarin dosings, and separated into values originating from algorithm suggestions and manually changed doses. The error is defined as the distance to INR 2.5 and hit rate is defined as number of INR values in the intended INR interval 2-3.

<table>
<thead>
<tr>
<th>Dosing option</th>
<th>Number of INR values</th>
<th>Mean INR value</th>
<th>Mean error</th>
<th>Hit rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>769 933</td>
<td>2.51</td>
<td>0.45</td>
<td>0.71</td>
</tr>
<tr>
<td>Algorithm</td>
<td>590 939</td>
<td>2.53</td>
<td>0.44</td>
<td>0.72</td>
</tr>
<tr>
<td>Manually changed</td>
<td>178 994</td>
<td>2.43</td>
<td>0.48</td>
<td>0.67</td>
</tr>
</tbody>
</table>
In general, both algorithm suggestions and manually changed doses performed better when three instead of two previous INR values were present. As shown in figure 8, hit rate was higher in most cases after accepted algorithm suggestions compared with manually changed doses.
Regarding cTTR there was a trend towards more acceptance of algorithm suggestions in centers with higher cTTR in a linear regression (p=0.09) (figure 9).
Figure 9: cTTR for the 125 participating centers versus acceptance of algorithm suggestions with regression line ($p=0.09$).
Paper II

A diagnosis of AF was found in 182 678 individuals, of those about one third (33%) were on oral anticoagulation, about one third were treated with antiplatelet agents only (36%) and about one third (31%) were without antithrombotic treatment at baseline. In total 115 185 patients were included in the study, 58 671 with aspirin treatment and 56 514 without antithrombotic treatment at baseline. As shown in table 5, patients on aspirin treatment had a higher mean age and more concurrent illnesses at baseline compared with the group without antithrombotic treatment.

Table 5: Description of the study population at baseline.

<table>
<thead>
<tr>
<th></th>
<th>No treatment (n=56 514)</th>
<th>Aspirin (n=58 671)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age y, mean±SD</td>
<td>75,1±13,8</td>
<td>80,3±10,1</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>29 352 (51,9)</td>
<td>28 021 (47,8)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>18 536 (32,8)</td>
<td>21 184 (36,1)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>21 038 (37,2)</td>
<td>27 211 (46,4)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 019 (16,0)</td>
<td>11 217 (19,1)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Ischemic stroke, n (%)</td>
<td>4 937 (8,7)</td>
<td>7 206 (12,3)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>2 485 (4,4)</td>
<td>3 875 (6,6)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Peripheral systemic emboli, n (%)</td>
<td>785 (1,4)</td>
<td>713 (1,2)</td>
<td>0,01</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
<td>10 729 (19,0)</td>
<td>16 229 (27,7)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>CHA2DS2-VASc score, mean±SD</td>
<td>3,3±2,0</td>
<td>4,0±1,8</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>3 639 (6,4)</td>
<td>3 583 (6,1)</td>
<td>0,024</td>
</tr>
<tr>
<td>Liver disease, n (%)</td>
<td>1 038 (1,8)</td>
<td>599 (1,0)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Intracranial bleeding, n (%)</td>
<td>1 427 (2,5)</td>
<td>1 242 (2,1)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Gastric/duodenal bleeding, n (%)</td>
<td>2 944 (5,2)</td>
<td>2 286 (3,9)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Any severe bleeding, n (%)</td>
<td>7 251 (12,8)</td>
<td>6 673 (11,4)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Anaemia, n (%)</td>
<td>7 845 (13,9)</td>
<td>6 923 (11,8)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Platelet/coagulation defect, n (%)</td>
<td>1 200 (2,1)</td>
<td>534 (0,9)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Alcohol related hospital contact, n (%)</td>
<td>2 038 (3,6)</td>
<td>1 469 (2,5)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>HAS-BLED score, mean±SD</td>
<td>1,9±1,2</td>
<td>2,9±1,0</td>
<td>&lt;0,001</td>
</tr>
</tbody>
</table>
After stratification of patients according to CHA\textsubscript{2}DS\textsubscript{2}-VASc score, patients on aspirin did not have lower rates of thromboembolic events compared to patients without antithrombotic treatment. Instead there was a trend towards higher rates of ischemic stroke in most CHA\textsubscript{2}DS\textsubscript{2}-VASc strata (figure 10), without any significant differences regarding rates of intracranial bleeding (figure 11).

Figure 10: Annualized incidence of ischemic stroke related to CHA\textsubscript{2}DS\textsubscript{2}-VASc score. Red line represents aspirin treated patients, blue line represents patients without antithrombotic treatment. Dashed lines are 95% confidence intervals (CIs).
Figure 11: Annualized incidence of intracranial bleeding related to CHA\textsubscript{2}DS\textsubscript{2}-VASc score. Red line represents aspirin treated patients, blue line represents patients without antithrombotic treatment. Dashed lines are 95% confidence intervals (CIs).

After multivariable adjustment for factors included in, and score sum of CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED, a higher risk of thromboembolic events, death and a combined endpoint with ischemic stroke, intracranial haemorrhage and death were seen in aspirin treated patients (table 6). There was no obvious difference regarding haemorrhagic complications.
Table 6: Risk of thromboembolic complications, bleeding complications and death in patients on aspirin treatment compared to patients without antithrombotic treatment after multivariable adjustment for risk factors included in CHA$_2$DS$_2$-VASc and HAS-BLED, as well as for CHA$_2$DS$_2$-VASc and HAS-BLED score points.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Multivariable adjustment for</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHA$_2$DS$_2$-VASc</td>
<td>HAS-BLED</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By score sum</td>
<td>By cofactors</td>
<td>By score sum</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>1,5 (1,4-1,5)</td>
<td>1,4 (1,4-1,5)</td>
<td>1,2 (1,1-1,2)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1,4 (1,4-1,5)</td>
<td>1,4 (1,3-1,4)</td>
<td>1,1 (1,1-1,2)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1,0 (0,9-1,1)</td>
<td>1,0 (0,9-1,1)</td>
<td>0,8 (0,7-0,9)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>1,1 (1,1-1,2)</td>
<td>1,1 (1,0-1,1)</td>
<td>0,9 (0,8-0,9)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1,4 (1,3-1,4)</td>
<td>1,3 (1,3-1,3)</td>
<td>1,2 (1,1-1,2)</td>
</tr>
<tr>
<td>Combined endpoint</td>
<td>1,4 (1,3-1,4)</td>
<td>1,3 (1,3-1,3)</td>
<td>1,2 (1,1-1,2)</td>
</tr>
<tr>
<td>Death</td>
<td>1,4 (1,3-1,4)</td>
<td>1,3 (1,3-1,3)</td>
<td>1,2 (1,1-1,2)</td>
</tr>
</tbody>
</table>
After a propensity score matching in which 49,447 patients in each group were successfully matched, the rate of ischemic stroke was 7.4%/year (95% CI 7.1-7.6) in the aspirin treated group as compared with 6.6%/year (95% CI 6.4-6.9) in the group without antithrombotic treatment (p<0.001). The rate of intracranial haemorrhage was 1.0%/year (95% CI 0.9-1.1) both in patients on aspirin and without antithrombotic treatment, respectively (p=0.46). When using wider definitions of thromboembolic events (ischemic stroke, TIA and systemic embolism) and major haemorrhages (intracranial haemorrhage, gastrointestinal haemorrhage and anaemia secondary to major haemorrhage), the same pattern was seen with higher rate of thromboembolic events in patients on aspirin treatment without significant differences regarding major haemorrhages (data not shown).
In total 22,874 patients undergoing electrical cardioversion were included, 10,722 with and 12,152 without OAC pre-treatment. Patients without OAC treatment in conjunction with cardioversion were in general younger and had fewer risk factors for stroke compared with patients on OAC treatment (Table 7).

Table 7: Description of the study population at baseline. Values are n (%) unless otherwise specified

<table>
<thead>
<tr>
<th></th>
<th>Warfarin prior to cardioversion (n=10,722)</th>
<th>No warfarin prior to cardioversion (n=12,152)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age y, mean±SD</td>
<td>67.5±10.5</td>
<td>64.6±13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>7116 (66.4)</td>
<td>8180 (66.7)</td>
<td>0.57</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3004 (28.0)</td>
<td>2044 (16.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5798 (54.1)</td>
<td>5662 (46.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1605 (15.0)</td>
<td>1475 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic stroke,</td>
<td>523 (4.9)</td>
<td>643 (5.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>TIA</td>
<td>175 (1.6)</td>
<td>203 (1.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Peripheral systemic emboli</td>
<td>39 (0.4)</td>
<td>49 (0.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1633 (15.2)</td>
<td>2432 (20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA2DS2-VASc score, mean±SD</td>
<td>2.5±1.7</td>
<td>2.2±1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>531 (5.0)</td>
<td>640 (5.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Liver disease</td>
<td>65 (0.6)</td>
<td>126 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>100 (0.9)</td>
<td>103 (0.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Gastric/duodenal bleeding</td>
<td>42 (0.4)</td>
<td>64 (0.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Treatment with antiplatelet agents</td>
<td>1517 (14.1)</td>
<td>4520 (37.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anaemia</td>
<td>513 (4.8)</td>
<td>691 (5.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Platelet/coagulation defect</td>
<td>57 (0.5)</td>
<td>58 (0.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Alcohol related hospital contact</td>
<td>121 (1.1)</td>
<td>199 (1.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>HAS-BLED score, mean±SD</td>
<td>1.4±1.0</td>
<td>1.5±1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Without adjustment for differences at baseline, there was a higher incidence of thromboembolic events in patients without OAC pre-treatment compared to patients on OAC prior to cardioversion during the 30-day follow up period, 0.9 vs. 0.3% (p<0.001). Patients without OAC pre-treatment also had a higher incidence of death compared to patients on OAC treatment, 0.7 vs. 0.2% (p<0.001). There was no significant difference regarding haemorrhagic complications (0.1 vs 0.2%, p=0.87).

After stratification of patients into low (CHA$_2$DS$_2$-VASc score 0-1), medium (CHA$_2$DS$_2$-VASc score 2-3) and high (CHA$_2$DS$_2$-VASc score 4-9) risk of stroke, patients with medium or high risk of stroke had more thromboembolic complications if no OAC pre-treatment was used compared to OAC pre-treated patients (data not shown). In patients with low risk of stroke, no thromboembolic complication was seen within 30 days after cardioversion.

In a propensity score matching analysis with a calliper of 0.1, 9 500 patients in each treatment group were successfully matched. After propensity score matching, patients without OAC pre-treatment suffered more thromboembolic events compared to patients on OAC treatment (Figure 12). No differences regarding haemorrhagic complications were seen.

**Figure 12:** Thromboembolic complications, haemorrhagic complications and death within 30 days after cardioversion comparing patients with or without OAC pre-treatment after propensity score matching. P-value regarding differences in death and thromboembolic events <0.001, p-value regarding differences in major bleeding 1.00.
In a univariable logistic regression analysis performed on the propensity score matched population, the risk of thromboembolic complications and death was higher in patients without OAC pre-treatment. No difference regarding haemorrhagic complications was seen (table 8).

Table 8: Odds ratios for thromboembolic complications, major haemorrhage and death for patients not on OAC pre-treatment (n=9500), compared with patients with OAC pre-treatment (n=9500) in the propensity score matched AF population.

<table>
<thead>
<tr>
<th>Event</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic complication</td>
<td>2.51 (1.69-3.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major haemorrhage</td>
<td>1.00 (0.48-2.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Death</td>
<td>4.59 (2.67-7.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Paper IV

In total 1585 patients undergoing PVI, with information about start- and stop date for OAC treatment in Auricula, were included. Mean age in the study population was 59.0±9.4 years, mean CHA$_2$DS$_2$-VASc score was 1.5±1.4 and 73% were male (table 9). Mean follow up time was 2.6 years. Of 1585 AF patients undergoing PVI, 1581 (99.7%) had a diagnosis of AF in the NPR.

Table 9: Description of the study population at baseline. Values are n (%) unless otherwise specified.

<table>
<thead>
<tr>
<th></th>
<th>Entire study population (n=1585)</th>
<th>Patients with CHA$_2$DS$_2$-VASc &lt;2 (n=882)</th>
<th>Patients with CHA$_2$DS$_2$-VASc ≥2 (n=703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age y, mean±SD</td>
<td>59.0 ±9.4</td>
<td>55.0 ±9.4</td>
<td>64.1 ±6.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>1157 (73.0)</td>
<td>773 (87.6)</td>
<td>384 (54.6)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>168 (10.6)</td>
<td>34 (3.9)</td>
<td>134 (19.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>761 (48.0)</td>
<td>220 (24.9)</td>
<td>541 (77.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>106 (6.7)</td>
<td>9 (1.0)</td>
<td>97 (13.8)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>96 (6.1)</td>
<td>0 (0.0)</td>
<td>96 (13.7)</td>
</tr>
<tr>
<td>TIA</td>
<td>69 (4.4)</td>
<td>0 (0.0)</td>
<td>69 (9.8)</td>
</tr>
<tr>
<td>Peripheral systemic emboli</td>
<td>7 (0.4)</td>
<td>0 (0.0)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>133 (8.4)</td>
<td>11 (1.2)</td>
<td>122 (17.4)</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc score, mean±SD</td>
<td>1.5 ±1.4</td>
<td>0.4 ±0.5</td>
<td>2.8 ±1.0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>19 (1.2)</td>
<td>4 (0.5)</td>
<td>15 (2.1)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>5 (0.3)</td>
<td>1 (0.1)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>10 (0.6)</td>
<td>2 (0.2)</td>
<td>8 (1.1)</td>
</tr>
<tr>
<td>Gastric/duodenal bleeding</td>
<td>44 (2.8)</td>
<td>23 (2.6)</td>
<td>21 (3.0)</td>
</tr>
<tr>
<td>Treatment with antiplatelet agents</td>
<td>99 (6.2)</td>
<td>49 (5.6)</td>
<td>50 (7.1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>45 (2.8)</td>
<td>20 (2.3)</td>
<td>25 (3.6)</td>
</tr>
<tr>
<td>Platelet/coagulation defect</td>
<td>7 (0.4)</td>
<td>0 (0.0)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Alcohol related hospital contact</td>
<td>30 (1.9)</td>
<td>12 (1.4)</td>
<td>18 (2.6)</td>
</tr>
<tr>
<td>HAS-BLED score, mean±SD</td>
<td>1.3 ±1.0</td>
<td>0.8 ±0.7</td>
<td>1.9 ±0.9</td>
</tr>
</tbody>
</table>
Of all 1585 patients undergoing PVI, 390 (24.6%) were classified as having paroxysmal AF, 592 (37.4%) persistent AF, 104 (6.6%) permanent AF and for the remaining 499 patients (31.5%) no data on AF classification was available (table 10).

Table 10: Number of patients in different AF classification groups.

<table>
<thead>
<tr>
<th>Atrial fibrillation classification</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1585)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>390 (24.6)</td>
</tr>
<tr>
<td>Persistent (duration ≤7 days, cardioversion performed)</td>
<td>301 (19.0)</td>
</tr>
<tr>
<td>Persistent (duration &gt;7 days)</td>
<td>291 (18.4)</td>
</tr>
<tr>
<td>Permanent</td>
<td>104 (6.6)</td>
</tr>
<tr>
<td>Data not available</td>
<td>499 (31.5)</td>
</tr>
</tbody>
</table>

**OAC discontinuation**

In total 1175 patients had a follow up time of at least one year. Of these, 360 (30.6%) discontinued warfarin treatment within the first year after PVI (figure 13). In patients with CHA₂DS₂-VASc score 0, 42.4% discontinued warfarin within one year after PVI, the corresponding rates in patients with CHA₂DS₂-VASc score 1 was 34.9% and CHA₂DS₂-VASc score ≥2 20.1%.
**Figure 13**: Proportion of patients discontinuing OAC treatment within one year after PVI, separated into CHA$_2$DS$_2$-VASc score 0, 1 and ≥2. Only patients with at least one year of follow up were considered (n=1175).

**Complications during follow up**

In univariable logistic regression analyses considering all factors included in the CHA$_2$DS$_2$-VASc score as well as age as a continuous variable, previous ischemic stroke was the only significant predictor of ischemic stroke during follow up, OR 4.1 (95% CI 2.2-7.6, p<0.001).

After Cox regression analyses, patients with CHA$_2$DS$_2$-VASc score ≥2 and patients who had previously suffered from ischemic stroke had a higher risk of ischemic stroke during follow up if OAC treatment was discontinued, compared with patients on OAC treatment, HR 4.6 (95% CI 1.2-17.2, p=0.023) and HR 13.7, 95% CI 2.0-91.9 (p=0.007), respectively (figure 14).
Figure 14: Cox regression analysis showing time to ischemic stroke after PVI in patients with previous ischemic stroke (n=96), separated in time with and without warfarin treatment. HR 13.7, 95% CI 2.0-91.9 (p=0.007).

In patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of \geq 2, the rate of ischemic stroke was increased in patients discontinuing OAC treatment after PVI, compared with patients continuing OAC treatment, 1.60%/year vs 0.34%/year (p=0.046) (table 11). No differences were seen in rate of intracranial haemorrhage or death.
Table 11: Complication rates per year of follow up, given as number (%/year), in 1585 patients after PVI, subdivided into patients with and without OAC treatment and into patients with low or increased risk of stroke according to CHA\(_2\)DS\(_2\)-VASc.

<table>
<thead>
<tr>
<th></th>
<th>+ OAC</th>
<th></th>
<th>- OAC</th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ischemic Stroke</td>
<td>ICH</td>
<td>Death</td>
<td>Ischemic Stroke</td>
<td>ICH</td>
<td>Death</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc &lt; 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=882)</td>
<td>1 (0.08)</td>
<td>1 (0.08)</td>
<td>1 (0.08)</td>
<td>1 (0.12)</td>
<td>0 (0.00)</td>
<td>1 (0.12)</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc ≥ 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=703)</td>
<td>4 (0.34)</td>
<td>2 (0.17)</td>
<td>6 (0.50)</td>
<td>5 (1.60)</td>
<td>0 (0.00)</td>
<td>3 (0.94)</td>
</tr>
</tbody>
</table>

IS = Ischemic stroke
ICH = Intracranial haemorrhage

Recurrence of AF after PVI

After a three-month blanking period, 211 patients (13.3%) and 298 patients (18.2%) underwent an electrical cardioversion or a new PVI, respectively, during the first year after index PVI. During the whole follow up period of on average 2.6 years, 693 patients (43.7%) underwent electrical cardioversion and 580 patients (36.3%) underwent a new PVI. In total, at least 953 patients (60.1%) had an AF relapse during follow up (except for the three-month blanking period), leading to an electrical cardioversion and/or a re-ablation.
Discussion

The focus of this thesis is to improve stroke prevention in patients with AF. The results from the papers included in the thesis suggest several potential improvement areas. One way is to improve warfarin treatment quality using a dosing algorithm and thereby standardize the dosing. Another way is to avoid aspirin treatment as stroke prevention, in favour of effective stroke prevention with oral anticoagulation. A third way to improve stroke prevention is to offer effective stroke prevention to patients undergoing electrical cardioversion. Finally, since we today have no cure for AF, patients with risk factors for stroke should be maintained on oral anticoagulation despite a rhythm control strategy including pulmonary vein isolation.

Computer aided warfarin dosing

Adherence to a warfarin dosing algorithm has been shown to increase warfarin treatment quality, measured as TTR (175). Also older studies have shown that computerized dosing assistance improves TTR levels (176-179). Most of these studies also showed a shorter time to stable INR values. Increasing TTR levels have been shown to decrease the number of complications (151, 158, 159). Also INR stability has been shown to affect the risk of complications (180, 181), where a stable INR decreases the risk of complications, even though a stable INR above or below the intended target range leads to a low TTR.

One study found that computer-assisted warfarin dosing was cheaper and at least as clinically effective as manual dosing due to a reduction in the occurrence of venous thrombosis in the computer-assisted dosing group (182). Most of the studies showing increased TTR levels with a computerized dosing algorithm have shown an improvement from relatively low baseline TTR levels. A study by Dimberg et al. showed that introduction of the dosing algorithm in Auricula led to an improved or maintained high warfarin treatment quality measured as TTR, compared with manual dosing (183). These results are consistent to the results in paper I, which showed superiority of algorithm dosing regarding the outcomes hit rate and mean error compared with manually changed doses in most of the cases. The main difference between these studies is the control group, where paper I compare algorithm dosing with manually changed algorithm suggestions, while the study by Dimberg et al. compare algorithm dosing with ordinations made completely manual.
Doctors making warfarin ordinations tend to keep INR levels in the lower border of the intended INR interval (177), probably due to fear of harming the patient with serious haemorrhages. The same pattern was shown in paper I, where the normal distribution curve for the INR samples was displaced towards lower INR values after manually changed doses compared with doses made by the algorithm. Hence, algorithm dosing led to an average INR value closer to 2.5. Even though the doctor’s intentions are good, to avoid unnecessary haemorrhagic complications, it may result in harm for the patients in terms of subtherapeutic INR values and an increased risk of stroke in patients with AF. A warfarin dosing algorithm that aims to hit INR 2.5 will, however, not do the same mistake, at least not to the same extent. The dosing algorithm in Auricula is made to hit INR 2.5 but is consciously made to be cautious when there is a high variability between recent INR values. In the study by Dimberg et al., introduction of Auricula and the dosing algorithm led to shorter mean intervals between INR samples, which could be a contributing factor to the superiority of the algorithm compared with earlier manual dosing. There is, however, a discrepancy between doctors and nurses being too cautious when making the ordinations, leading to lower INR values and at the same time being courageous with longer time intervals between INR samples. One possible explanation could be if long time intervals are created to satisfy the patient (fewer appointments), but on the other hand leading to cautious ordinations and lower INR values. Empathy for the patient is a human characteristic, while the computerized algorithm only takes efficacy and safety of anticoagulation treatment in consideration. In contrast, an Italian randomized trial by Manotti et al. showed both shorter time to stable INR values, higher TTR (mainly due to a reduction of subtherapeutic INR values) and a reduction in the number of appointments per patient when warfarin dosing was made by an algorithm compared with manual dosing (177).

There is a risk that information (interacting medications, forgotten or doubled warfarin doses etc.) about a patient known by the person making the ordination but not by the algorithm, have led to a manually changed warfarin dose. Thus more advanced ordinations are made manually. If the toughest decisions are made manually, this could affect the results, leading to a better outcome for the algorithm suggested doses.

The fact that paper I failed to show a significant improvement in cTTR level with increasing use of algorithm suggestions could be due to a high cTTR level already at baseline. A significant improvement is harder to achieve when the quality is high already at baseline.
Aspirin as stroke prevention in atrial fibrillation

The use of aspirin as stroke prevention in patients with AF has its background mainly in the SPAF trial, which showed a reduction in thromboembolic events in both patients treated with aspirin and OAC compared with placebo (129). Other trials have failed to show the same benefit of aspirin treatment. In paper II, we could not see any benefit of aspirin treatment in patients with AF. Instead, patients with AF and aspirin treatment tended to have a higher rate of thromboembolic events compared with AF patients without antithrombotic treatment. Even after adjustment for all available background information, we still could not see any benefit from aspirin treatment as stroke prevention. Patients with aspirin treatment could of course have another indication for treatment, for example vascular disease, and be considered having too high risk of bleeding for treatment with OAC. It is possible that aspirin treatment decreased the risk of other cardiovascular diseases in these patients, like myocardial infarction, which was not investigated in paper II. It is also possible that certain patient groups would benefit from aspirin also as stroke prevention in AF, for example young patients under the age of 75 with no further risk factors for stroke (e.g. CHA2DS2-VASc <2). Both the SPAF trial and a study by van Walraven et al. (138) have indicated that young AF patients might benefit from aspirin or other antiplatelet agents to prevent stroke. This question remains to be answered. A previous report has shown that the use of anticoagulation treatment in AF patients decreases with increasing age and CHA2DS2-VASc score (21), whereas the use of antiplatelet agents as stroke prevention in AF increases with increasing CHA2DS2-VASc score. In Sweden, mean age of the AF patient is 74 years (29). In paper II, mean age in the aspirin treated group was just above 80 years. Considering this, the main result in paper II, that patients with AF do not benefit from aspirin as stroke prevention, is not surprising. Not even the randomised controlled trials which form the basis for aspirin treatment in AF patients could in this patient group show any benefit of treatment, which therefore should be avoided. If the reason for aspirin treatment is another kind of cardiovascular or haematological disease, it could of course be indicated. Both positive and negative criticism has been published regarding paper II. In an editorial, Lau et al. agreed that aspirin confers little or no protection against ischemic stroke in AF patients, and that clinicians need to stop using aspirin as stroke prevention in AF patients (184). On the other hand, Paul Hjemdahl stated in an article on the web page of Stockholm County Council, that differences between groups are too large to enable comparisons, that indication for aspirin treatment treatment diverged in different patient groups and that confounding by indication makes it impossible to study treatment effect. In conclusion, we should rather rely on the randomized controlled trials performed (185).
I actually do not think that aspirin treatment in patients with AF leads to a higher risk of thromboembolic events, this result is probably due to baseline differences we have not been able to adjust for. Looking back, perhaps a lower accepted calliper between propensity scores in the matched groups could have led to even more equivalent groups, eliminating the higher rate of thromboembolic events that was seen in the group with aspirin treatment. Still, it is unlikely that a tighter matching would lead to a benefit from aspirin treatment. I am certain that our results, together with the results in the randomized controlled trials comparing aspirin treatment with placebo or no treatment give the answer that most patients with AF do not benefit from aspirin treatment for stroke prevention. Perhaps some patients under 75 years of age with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1 do, but in patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of \( \geq 2 \), aspirin probably causes more harm than good considering stroke prevention.

**Electrical cardioversion**

Paper III showed a higher risk of thromboembolic complications and death within the 30-day period after cardioversion if no OAC pre-treatment was used. There was no difference regarding haemorrhagic complications. The increase in thromboembolic risk was driven by an increased risk of thromboembolic complications in patients with increased risk of stroke (CHA\textsubscript{2}DS\textsubscript{2}-VASc score \( \geq 2 \)). In patients with low stroke risk (CHA\textsubscript{2}DS\textsubscript{2}-VASc score 0-1) there were no thromboembolic complications at all within the first month after cardioversion.

There are few and small trials regarding anticoagulation treatment in conjunction with electrical cardioversion of AF. Most recommendations are based on observational studies and data on pathophysiologic mechanisms. However, due to the results of observational studies showing a decreased rate of thromboembolic events with OAC treatment (90, 91) and an increased thromboembolic event rate in patients with subtherapeutic OAC treatment (92), a randomized controlled trial investigating this issue would not be feasible for ethical reasons.

Results from the Finnish CardioVersion (FinCV) Study suggest a low risk (\(<1\%) of thromboembolic events after acute cardioversion of AF with anamnestic short duration even without peri- or post-cardioversion anticoagulation treatment (83). Although, in certain patient groups the thromboembolic risk was substantially increased, up to 9.8\% in patients with diabetes mellitus and congestive heart failure.

In a register-based study by Hansen et al. the risk of thromboembolic events was significantly higher in patients without OAC treatment than in those with OAC treatment (186). The risk of thromboembolic events
increased with increasing number of risk factors for stroke also in this study. These results are supported in a study by Grönberg et al. who found CHA$_2$DS$_2$-VASc score to be a strong predictor of thromboembolic events after cardioversion of acute AF without OAC treatment (187). The preventive effect of OAC treatment in conjunction with cardioversion was significant in patients with a CHA$_2$DS$_2$-VASc score of ≥2.

Conversely, out of 1644 thromboembolic events occurring in patients with paroxysmal or persistent AF, 100 are preceded by a cardioversion, most of them in patients without or with subtherapeutic OAC treatment (188).

Results from paper III suggest that patients with CHA$_2$DS$_2$-VASc score ≥2 benefit from prolonged pre-cardioversion OAC treatment rather than undergoing acute cardioversion without anticoagulation treatment. The study included data from January 1st 2006 until December 1st 2010. We must keep in mind that paper III is a register-based study entailing limitations, and despite our efforts to adjust for baseline differences, there are probably factors not possible to adjust for that affects the results. Also, we have assumed that patients not on OAC prior to cardioversion have performed an acute cardioversion with less than 48 hours duration, which might not always be the case. The fact that AF often is asymptomatic makes the 48h rule difficult to apply, this holds for most studies regarding cardioversion of AF. The group without pre-cardioversion OAC probably includes also critically ill patients with haemodynamic instability, affecting the results. Though, haemodynamic unstable patients are probably found also in the OAC group. During the time period studied in paper III, it was not routine to use peri-cardioversion anticoagulation treatment with unfractionated heparin (UFH) or LMWH in Sweden as current guidelines recommend, a fact that could influence the results. Still, it is known that left atrial thrombi is common also in patients on therapeutic OAC (97), and since reversion to sinus rhythm confers a risk of thrombus dissemination, perhaps a rate control strategy would be preferable in patients at high risk of stroke. Though, due to severe symptoms, a rate control strategy is not always feasible. In these patients, a randomized controlled trial comparing acute cardioversion according to current guidelines with a prolonged pre-cardioversion OAC treatment could give an answer to the safest treatment strategy.

Paper III showed a higher risk of death in patients undergoing cardioversion without OAC pre-treatment. Since autopsies seldom are performed in Sweden today, causes of death in the Cause of Death Register are uncertain data. Causes of death were therefore not considered and can only be speculated on. Since the risk of death was higher in patients without OAC pre-treatment also after propensity score matching, large differences between the study groups at baseline are probably not the explanation to this difference. The increase in risk of death could be due to other concurrent
illnesses causing haemodynamic instability leading to cardioversion, like severe sepsis or acute myocardial infarction, which could be the underlying cause of death in some of these patients. This is, however, only a speculation.

**Pulmonary vein isolation**

Since PVI is not a curative treatment for AF, at least not in all patients, current ESC guidelines recommend continued OAC treatment after a PVI in the presence of stroke risk factors (59). In clinical praxis, however, patients may experience symptom relief after PVI and therefore choose not to continue OAC treatment (120).

Success rate after PVI can be defined in different ways. Relief of symptoms is a reasonable approach, since indication for PVI is symptomatic AF. If a re-ablation is performed, the PVI has definitely failed, defined by recurrence of symptomatic AF. If, however, AF recurs without symptoms, the procedure can be considered as successful (no longer indication for PVI) or failed (evidence of AF recurrence). Another point of view is the definition of AF recurrence. It could e.g. be defined as AF on surface ECG at readmission or as an AF episode on recurrent long term ECG recording. With an intense screening program more episodes of AF will probably be found. Since AF recurrence confers a risk of stroke, whether symptomatic or not, OAC should only be discontinued in patients without AF recurrences. The challenge is how to predict which patients will suffer from AF recurrence, symptomatic or not. Since recurrence of AF after PVI repeatedly has been shown to be common (104, 105, 108-110), all patients with risk factors for stroke should be on continued OAC treatment after PVI (59), a recommendation also supported by the results in paper IV.

The rate of AF recurrence after PVI in paper IV may be perceived high, but is compared to results from earlier studies not surprising. The success rate differs between different AF ablation techniques and between different AF classifications (104, 105, 108, 109). Since AF ablation techniques are constantly improving, success rate could possibly improve over time. Considering that only 24.6% of the patients in paper IV were classified as paroxysmal AF, a success rate of about 40% after 2.6 years can be considered to be as expected. An important limitation to this result is of course missing data of AF classification in almost one third of the patients. Interestingly, 6.6% of the patients undergoing PVI in paper IV were considered to have permanent AF, which is defined as abstained of failed cardioversion. According to the present ESC guidelines, these patients do not have indication for PVI (59).
**Study design**

Randomized controlled trials (RCTs) are the golden standard in research. RCTs evaluate the efficacy and safety of an intervention and provide results with high internal validity, which means the outcome of the trial can be attributed to the intervention, since confounding factors are eliminated in the randomization process. There is, however, not always possible to directly transfer the results from a RCT to the average patient in the clinical setting due to tough selection criteria in RCTs. In these cases, observational studies can complement RCTs with information of the effect of an intervention in a real-world setting. Well-designed and well-conducted observational studies have a high external validity, making the results generalizable for broader patient populations compared with RCTs. Consequently, all study designs have their strengths and weaknesses, complementing each other in decision making.

In Sweden and the other Nordic countries there are advantageous conditions for register-based research since health care is highly available to the whole population (the costs are largely covered by taxes) and due to the system with personal identification numbers (189). National health registers are developed through many years and are possible to link and cross-match through personal identification numbers. The ethical aspects on register-based research are heavily debated, today ethical committees represent the patients, protecting their personal integrity (190).

The quality of data in registers is dependent on how data is collected and reported. Several of the registers included in this thesis are shown to have a high validity. Though, this does not hold for all diagnoses and all registers. For example, a diagnosis of AF in the NPR has a validity of 97% (170). In paper IV, all patients had known AF, otherwise a PVI should not have been performed. In this study we could find a previous diagnosis of AF in the NPR in 1581 out of 1585 patients (99.7%), confirming previous results with a high validity of a diagnosis of AF in the NPR. Patients undergoing PVI are, however, a selected patient group with probably several visits to specialized heart care before decision about PVI. Therefore, the validity of an AF diagnosis could be lower in AF patients admitted to less specialized care. There are, however, other diagnoses with substantially lower positive predictive values, including e.g. congestive heart failure with positive predictive values between 82 and 88% (64). There are also previously non-validated diagnoses that can be assumed to have a very low validity, one such example is obesity. Not all AF patients have their body mass index measured at an acute admission and the diagnosis obesity is probably only given in extreme cases, leading to a presumably very low validity. We have chosen not to take diagnoses with a presumed very low validity into account in the papers included in the thesis. Missing or incorrect diagnoses are, however,
an important limitation to register based studies based on data from the NPR.

The largest challenge in retrospective, non-randomized research is how to control for confounding factors (factors influencing both the outcome and the investigated intervention). A number of methods aiming for adjusting for baseline differences exist, e.g. uni- and multivariable regressions and propensity score matching. These methods can, however, only control for known variables.

A p-value reflects the possibility to obtain a difference between two groups by chance, which means, a p-value of 0.05 gives a 5% possibility that the result does not reflect a real difference between groups. The most common level of significance is set to 0.05, meaning the risk of a false relationship between intervention and result is less than 5%. There is, however, a risk that the significance analysis gives a false positive answer, i.e. a p-value <0.05 although there is no difference between the groups. If only one analysis is made, the risk of a false positive result is 5%, but if multiple analyses are performed, the risk of a false positive result in any of the analyses is higher. This risk must be considered when multiple analyses are performed.

All the limitations with retrospective register-based studies must be weighed against the advantages of large number of patients available for analyses and the accurate reflection of clinical praxis as well as the lack of exclusion criteria often present in RCTs. In my opinion, future research should focus on register-based RCTs, reflecting real world patients with prospectively collected randomized data and few exclusion criteria.

Gender differences in atrial fibrillation

There are several gender differences in AF. Firstly, men are more affected than women, with a prevalence of 3.3%, compared to 2.5% (21). Women, in contrast, show more symptoms of AF compared to men (191, 192), and female gender is also a risk factor for thromboembolic complications in AF patients (50). When it comes to treatment, several studies have shown that different treatment strategies often are chosen to men compared with women. For example, men are to a higher extent undergoing procedures like electrical cardioversion (191) and pulmonary vein isolation (121, 193), results that are confirmed by paper III and IV. There are several hypotheses to why gender differences arise, but the question is still unanswered. Women could be more cautious, choosing not to undergo invasive procedures. Women could be more sensitive to side effects caused by antiarrhythmic drugs. Or perhaps the physicians recommend different treatment strategies depending on what they think their patient would prefer or benefit from. Since men are
affected by AF at younger ages than women (29), age differences could perhaps explain at least part of the difference between men and women.

**Limitations**

As always in register-based research, the retrospective, non-randomised design is the main limitation. Studies without randomization can never completely balance differences between groups at baseline, regardless of adjustment methods. When calculating risk scores to determine OAC indication, we use diagnostic codes with sometimes low positive predictive values (64), leading to lower, or in some cases higher, score points than actually are present. Also, study II-IV together include data between 2005 until 2012, during these years both CHADS2 and CHA2DS2-VASc were used in clinical praxis. When the studies were conducted the CHA2DS2-VASc score was recommended, the reason why we have chosen to make risk stratification according to this risk score. It is possible that physicians have chosen to make the risk stratification according to the CHADS2 score, which classifies more patients into the low risk category compared with the CHA2DS2-VASc score. Therefore, the risk calculated at the time of the appointment may not be the same as the risk as we have calculated in the studies. Since CHADS2 consider more patients as low risk, this could have affected the low number of patients treated with OAC in study II, III and during follow up in study IV.

In paper I, the main limitation is the algorithms lack of knowledge about circumstances that could affect the suggested warfarin dose. When additional knowledge of the patient is present (like interacting medications, use of alcohol, forgotten or added warfarin doses), it will probably affect the dose suggestion. Since there is no way for the algorithm to take these factors into consideration the dose must be made manually. More knowledge about factors affecting the INR value is of benefit for a proper warfarin ordination. If additional knowledge leads to a manually changed warfarin dose and the toughest ordinations consistently are made manual, this will lower the outcome measures (hit rate and mean error) resulting from manual ordinations.

Limitations in paper II-IV include all the limitations that comes with register based research described earlier. Also, the groups compared in paper II-III, especially in paper II, are indeed very different at baseline making comparisons difficult. Despite all efforts to adjust for differences at baseline,
there are probably residual confounding, factors we were not able to adjust for, affecting the results. A possible way to sharpen the distinction between groups at baseline in paper II could be to use a lower calliper in the propensity score matching analysis. During data analysis, we used all possible relevant background information about the patients in the multivariable models. Further adjustment for baseline differences would probably not add that much extra information into the analyses. For an accurate answer to the question if AF patients benefit from treatment with aspirin, we need randomised controlled trials. Since several such trials already have been performed, another such trial would be hard to find financial support for. I believe the results in paper II confirms the results from previous RCTs, that patients with AF and risk factors for stroke do not benefit from treatment with aspirin.

In paper III, we assumed that cardioversions performed without OAC pre-treatment were performed acute, within 48 hours after onset of AF, except for those performed acute because of haemodynamic instability. This must, however, not be the case for all patients. Initially, we planned to compare patients with a diagnosis of acute cardioversion of AF (ICD10 code DF027) with elective cardioversions of AF (ICD10 code DF026). Since the vast majority of patients had received a diagnostic code for cardioversion without any further specification (DF010), the shortfall of patients would make the material too small to reach statistical power in the analyses. With a bigger material, perhaps this approach would have been more accurate to answer our research question. Although all patients in our study had received diagnostic codes for both AF and cardioversion, there is a possibility that some cardioversions were performed to treat other arrhythmias than AF. Treatment with OAC was defined as purchase of warfarin at a pharmacy within six months prior to the date of cardioversion. This approach was chosen since (1), the amount of warfarin needed to keep INR-levels in intended interval differs considerably between individuals, but the vast majority of patients would need a filled prescription at least twice a year, and (2), it would be unlikely with a termination of warfarin treatment shortly before a cardioversion. A purchase of warfarin at a pharmacy within six months before cardioversion must not, however, mean that warfarin treatment is actually ongoing. Information about OAC treatment from a more reliable source, e.g. Auricula, could have contributed with valuable information about exact start and stop date for OAC treatment making information about OAC treatment in relation to complication rate more accurate. Also here, a RCT, perhaps register based, could give more reliable results.
Also paper IV has the disadvantages of being a register based study. In this study, however, we had information from Auricula, making information about OAC treatment reliable. Adding information from Riksstroke, which applies active registration of stroke events, probably makes information about complications more accurate, given the low risk of an old event counting as a complication. This is a risk that is obvious in the NPR if an ICD code for ischemic stroke by mistake is given instead of the ICD code for “late effects of” ischemic stroke. AF classification has previously been shown to affect the outcome of a PVI, where paroxysmal AF leads to a better outcome compared with persistent AF (104, 105). Unfortunately, information about AF classification was missing in almost one third of the procedures in the Catheter ablation register. Out of 1086 patients with information about AF subtype, only 390 (35.9%) were classified as having a paroxysmal AF, suggesting that a poor outcome after PVI could be expected, which was also confirmed by the results.

Conclusions

In conclusion, there are several improvement areas regarding stroke prevention in patients with atrial fibrillation. If warfarin treatment is chosen to prevent stroke, a dosing algorithm can standardize and improve treatment quality compared with manually changed doses, possibly decreasing risk of complications. Aspirin should be avoided as stroke prophylaxis in AF patients, in favour of more effective stroke prevention in terms of oral anticoagulation. In patients with AF and risk factors for stroke undergoing electrical cardioversion, pre-treatment with oral anticoagulation could possibly decrease the risk of stroke following the procedure. Patients with AF and risk factors for stroke should continue oral anticoagulation despite a pulmonary vein isolation given the risk of AF recurrence and the residual stroke risk.

Future considerations

Today, a great proportion of patients with known AF and known risk factors for stroke do not receive an effective stroke prevention therapy with OAC. In paper II, we report that only about one third of all patients with AF are treated with OAC. With increasing knowledge and increasing awareness of risks associated with untreated AF, an increasing proportion of patients at risk are receiving effective treatment (31). Benefit of OAC in patients with AF must always be weighed against risk of serious haemorrhage, where intracranial haemorrhage is the most feared leading to a high mortality
In a study by Friberg et al. net clinical benefit of warfarin in AF patients was investigated, defined as number of avoided ischemic strokes minus number of excess intracranial haemorrhages in patients with OAC (intracranial bleeding obtained a weight of 1.5 because of generally more severe outcomes). The study concluded that patients with risk factors for stroke benefit more from treatment with OAC than it increases the risk of intracranial haemorrhage (195). The only exception was patients with very low stroke risk (CHA$_2$DS$_2$-VASc 0) and moderately increased bleeding risk. I therefore believe that the main challenge for the future is to offer all patients with AF and risk factors for stroke effective stroke prevention with OAC.

Another question is how we should define patients with low risk of stroke. According to guidelines, CHA$_2$DS$_2$-VASc is recommended, a risk score that classifies the least number of patients into the truly low risk category. This recommendation has been questioned recently, suggesting we treat too many patients at low risk of stroke with OAC, thereby increasing the risk of serious haemorrhages. Newer risk scores like ATRIA score and ABC score have in some studies showed better values of C statistic than the CHA$_2$DS$_2$-VASc score, which is interesting. There are, however, no data on how these risk scores perform in identifying truly low risk patients in whom we safely can abstain OAC treatment.

Since this work began in 2012 novel oral anticoagulants have been introduced and are used by a continuously increasing number of patients. The randomized controlled trials that form the basis for use in clinical practice all showed at least non-inferior results regarding stroke prevention in patients with AF (154-156). All of these studies had a lower TTR (55-68%) among warfarin treated patients compared to data from Auricula (76%) (153). A subgroup analysis from the RE-LY trial showed that cTTR levels did not affect the results in the trial (151), but the rate of stroke and systemic embolism in the highest cTTR-quartile were low in all treatment arms (1.23/100 person-years with Dabigatran 110 mg bid, 1.27/100 person-years with Dabigatran 150 bid and 1.34/100 person-years with adjusted dose warfarin and TTR above 72.6%). It is still unknown if patients in Sweden with the very high quality and well-established organization of warfarin treatment benefit more from warfarin treatment or NOAC. Ongoing studies will hopefully give real world data about efficacy and safety of NOACs compared with warfarin in Sweden and guide future choice of treatment.

Cost-effectiveness of OAC is another point of view. A cost-effectiveness analysis of NOACs compared with warfarin has shown that NOACs are cost-effective up to TTR 65%, but with higher levels of TTR, as in Sweden, warfarin is probably the preferred treatment (196).
There will also be patient groups continuing to benefit more from warfarin treatment than from NOAC. One of these groups is patients with severely impaired renal function, who were not included in the NOAC studies, another group is patients with valvular AF or mechanical heart valves.

To improve stroke prevention in patients with atrial fibrillation we must also find the patients with indication for OAC. Since studies have shown that silent AF (AF without symptoms) confers as high risk of stroke as symptomatic AF (37), screening to identify unknown AF is probably necessary to offer effective stroke prevention to as many AF patients as possible. Screening has been shown to discover AF in about 3% of the population aged 75-76 years (23), all of those with a CHA2DS2-VASc score of at least 2 (age ≥75) and therefore at increased risk of stroke and with indication for OAC. Since CHADS2 score and CHA2DS2-VASc score are both associated with the risk of new-onset AF (32), screening could possibly be of value in patients ≥75 years as well as patients in younger age groups with concurrent illnesses predisposing for AF.

Several studies have validated the existing risk scores and confirmed that the CHA2DS2-VASc score correctly identifies most patients with truly low stroke risk. Though, there are probably factors still not included in any risk score system that confer a risk of stroke in AF patients. Further research is needed to identify these factors that could indicate an increased stroke risk to further improve risk stratification. More effort should also be put on anamnesis and physical examination of patients with AF to discover for example untreated hypertension, diabetes mellitus, heart failure and vascular disease. Perhaps we should even perform screening for these conditions in AF patients.

New risk score systems are continuously being developed, hopefully giving us even better tools for predicting AF patients at risk of stroke. However, different studies have shown widely distributed C-statistic values, for example values between 0.56 and 0.82 for the CHADS2 score. Consequently they range from marginally better than chance to good. Perhaps these differences represent different populations with different genetic conditions. It might therefore be difficult to construct a risk score system with a perfect prediction for all AF patients. An option is to separate AF patients with truly low risk of stroke, and offer all other AF patients effective stroke prevention with OAC. OAC will markedly reduce the stroke risk. It will, however, not eliminate the stroke risk.
Left atrial appendage (LAA) closure is an upcoming method that is still not evaluated enough. Since thrombus formation most often occurs in the LAA, closure of this structure could prevent thrombi from forming. Theoretically it is an attractive method, especially for patients with AF and a high risk of bleeding events making long term OAC treatment hazardous. More evidence is needed before the method can be recommended, current guidelines state that it “may be considered” and that usefulness/efficacy is less well established by evidence/opinion (59).

A pulmonary vein isolation has been shown to improve quality of life in patients with AF (106), and could theoretically reduce the stroke risk if the patient is cured from AF. Today, however, AF often recurs after a PVI, in paper IV as often as in about 60% of the patients after a mean follow up of 2.6 years. A further development of this method, or a way of predicting patients at risk for AF recurrence could possibly give better tools to guide continuous OAC treatment.

For patients with CHA₂DS₂-VASc 1 point it is still unknown whether they benefit from OAC or not, and according to current guidelines the use of OAC is optional (59), even if it should be considered. Regarding this issue, different studies point in different directions. When comparing two register based studies with diverging results regarding OAC treatment in patients with CHA₂DS₂-VASc score 1 (62, 63), lower validity of for example a diagnosis of myocardial infarction in the Taiwanese National Health Insurance Research Database (NHIRD) could have led to lower CHA₂DS₂-VASc scores than are actually present, and thereby a higher stroke risk compared to the results in the study by Friberg et al.

A rather simple way to improve stroke prevention in patients with AF is careful information to the patients. Today, there are many patients who refuse to accept OAC, probably mostly because of inadequate knowledge and fear of bleedings. The truth is that most patients with AF and risk factors for stroke are at a higher risk of ischemic stroke due to AF than they are at risk of intracranial haemorrhage due to OAC treatment (195).

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