Atrial fibrillation is the most common cause of cardioembolic stroke. The aim of this thesis was to explore anticoagulated patients with atrial fibrillation who suffer either ischaemic stroke or intracranial haemorrhage. The impact of concomitant carotid artery disease on stroke recurrence was studied. In addition, patients who suffer ischaemic stroke or intracerebral haemorrhage as well as patients with traumatic and spontaneous haemorrhage were compared.
Ischaemic stroke and intracranial haemorrhage in anticoagulated patients with atrial fibrillation
HEIDI LEHTOLA

Ischaemic stroke and intracranial haemorrhage in anticoagulated patients with atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common aetiology of cardioembolic stroke; oral anticoagulation (OAC) prevents approx. 60% of strokes caused by AF. The aim of this thesis was to obtain information about stroke patients with AF during OAC. Strokes were classified in two: ischaemic stroke including patients with infarcts and transient ischaemic attacks (TIAs), and haemorrhagic strokes, including intracranial haemorrhage. We analyzed the effect on stroke recurrence in AF patients with concomitant carotid artery stenosis (CAS) after an ischaemic stroke. We analyzed differences in the characteristics of patients receiving OAC treatment in first ever ischaemic strokes compared to haemorrhagic strokes, especially in patients with therapeutic INR values. Furthermore, we compared the traumatic and spontaneous haemorrhages during OAC.

FibStroke is a multicenter study investigating AF patients with a cerebral event (either ischaemic or haemorrhagic) during 2003-2012. Data was collected case by case from electronic patient records in four hospitals in Finland. Altogether 5629 patients were included with detailed data on comorbidities, thromboembolic and bleeding risk scores, medication, laboratory tests and type of AF.

1) Ischaemic stroke patients with AF and CAS (n=165) were older and had more comorbidities than patients without CAS (n=734). Patients with CAS had 4-fold higher 30-day mortality than patients without CAS (7.9% vs. 1.9%). CAS was an independent predictor for stroke recurrence (HR 2.02), even though all patients received similar antithrombotic treatment. 2) There were 1290 patients with ischaemic and 167 patients with haemorrhagic stroke. Patients with ischaemic events, 553 (42.9%) occurred with an INR within the therapeutic range, and 96 (57.5%) in patients with intracerebral haemorrhage (ICH). Congestive heart failure (OR 2.3) and hypercholesterolemia (OR 2.5) were associated more with an ischaemic event than haemorrhagic, whereas a bleeding history (OR 0.30) was less common. 3) During the study period, 592 intracranial haemorrhages occurred in AF patients receiving treatment with vitamin K antagonist (VKA). Out of the haemorrhagic strokes, 234 (40%) were traumatic and 358 (60%) spontaneous. Most (64%) of the traumatic haemorrhages were subdural (SDH), and most (67%) of the spontaneous haemorrhages were ICHs. The 30-day mortality was lower in
patients with traumatic haemorrhages than in those with spontaneous haemorrhages (25% vs. 36%).

CAS was an independent risk factor for 30-day mortality and stroke recurrence in patients with AF in ischaemic stroke. In AF patients with a therapeutic INR, congestive heart failure and hypercholesterolemia were over-represented in ischaemic strokes compared to patients with ICH, whereas a history of bleeding was less common. Traumatic haemorrhages constitute a significant proportion of all intracranial haemorrhages in AF patients during OAC (40%), although traumatic haemorrhages have a lower 30-day mortality than their spontaneous counterparts.

Medical Subject Headings: Ischemic Attack, Transient; Intracranial Hemorrhages; Cerebral Hemorrhage; Atrial Fibrillation; Anticoagulants/administration and dosage; Carotid Stenosis; International Normalized Ratio; Risk Factors; Comorbidity; Heart Failure; Stroke; Hemorrhage; Hypercholesterolemia; Recurrence; Mortality; Warfarin/administration and dosage; Multicenter Studies as Topic; Finland
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TIIVISTELMÄ


1) Iskeemisen AVH:n aivotapahtumat ja TIA:n sairastaneet eteisvärinäpotilaat, joilla oli merkittävää kaulavaltimoahtauta (n=165), olivat vanhempia ja sairaampia kuin potilaat, joilla ei todettu kaulavaltimoahtauta (n=734). Kaulavaltimoahtautapotilailla havaittiin nelinkertainen 30 vuorokauden kuolleisuus kuin potilailla ilman ahtautua (7.9% vs. 1.9%) ja kaulavaltimoahtauta oli myös itsenäinen riskitekijä uusinta-AVH:lle (HR 2.02), riippumatta samankaltaisesta verenohennuslääkityksestä. 2) Tutkimuksessa oli 1290 aivotapahtumaa (TIA potilasta ja 167 aivotapahtuma (ICH) potilasta. Iskeemisistä tapahtumista, 553 (42.9%) ja ICH:sta 96 (57.5%) tapahtui INR:n ollessa hoitoalueella. Sydämen vajaatoimintaa (OR 2.3) ja hyperkolesterolemiaa (OR 2.5) esiintyi useammin iskeemisen aivotapahtuman kuin ICH:n sairastaneilla, mutta aiempaa vuotohistoriaa (OR 0.30) oli harvemmin. 3) Eteisvärinäpotilailla todettiin 592 varfariinihoidon aikana ilmaantunutta kallonsisäistä aivotapahtumaa. 234 (40%) niistä oli traumaattisia ja 358 (60%) spontaneja.
Suurin osa traumaattisista vuodoista oli subduraalisia (SDH), 64%, kun suurin osa spontaaneista vuodoista oli ICH:ta, 67%. 30 vuorokauden kuolleisuus oli matalampi traumaattisisssa vuodoissa kuin spontaaneissa (25% vs. 36%).


Luokitus: QV 193, WG 330.5.A5, WL 355, WL 356, WL 357

Yleinen Suomalainen asiasanas to: aivoinfarkti; aivoverenvuoto; aivoverenkiertohäiriöt; ohimenevä aivoverenkiertohäiriö; iskemia; eteisvärinä; verenohennus; kaulavaltimot; ahtaumat; riskitekijät; komorbiditeetti; sydämen vajaatoiminta; verenkuoro; hyperkolesterolemia; kuolleisuus; Suomi
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List of the original publications

This dissertation is based on the following original publications:


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Abbreviations

AF  Atrial fibrillation
AHRE Atrial high rate episodes
CHADS2 Congestive heart failure, Hypertension, Age ≥75, Diabetes, Prior stroke, Transient ischaemic attack or thromboembolism (doubled)
CHA2DS2-VASc Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Prior Stroke, Transient ischaemic attack or thromboembolism (doubled), Vascular disease, Age 65-74, Sex category female
CI  Confidence interval
CrCl Creatinine clearance
CT  Computed tomography
CTA Computed tomography angiography
CV  Cardioversion
DOAC Direct oral anticoagulation
DSA Digital subtraction angiography
ECG Electrocardiography
ESC European Society of Cardiology
ESUS Embolic stroke of undetermined source
HAS-BLED Hypertension, Antiplatelet/Alcohol, Sex, Bleeding, Labile INR, Elderly, Diabetes
HEMORR2HAGES Hepatic or renal disease, ethanol abuse, malignancy, older (>75), reduced platelets, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, stroke history
ICH Intracerebral haemorrhage
INR International normalized ratio
IQR Interquartile range
LAA Left atrial appendage
LMWH Low-molecular weight heparin
MRI Magnetic resonance imaging
OAC Oral anticoagulation
OBRI Outpatient bleeding risk index
OR Odds ratio
SAH Subarachnoidal haemorrhage
SDH Subdural haemorrhage
TEE Transesophageal echocardiography
TIA Transient ischaemic attack
TOAST Trial Org 10172 in Acute Stroke Treatment
TTR Time in therapeutic range
VKA Vitamin-K antagonist
1 Introduction

Ischaemic cerebral events cause significant mortality and morbidity and therefore they impose a huge burden on the healthcare system. Atrial fibrillation (AF) is commonly thought to be responsible for approximately 26% of ischaemic strokes, and it is the most common cause of cardioembolic strokes (Grau et al., 2001). Approximately 60% of ischaemic strokes caused by AF can be prevented with proper oral anticoagulation (OAC) therapy, whereas aspirin results in only a 22% stroke reduction when compared to placebo (Hart et al., 2007). On the other hand, OAC increases the risk of bleeding events (Björck et al., 2016, Ruff et al., 2014). The patient is often exposed to a high risk of both thromboembolic and bleeding events and the clinician faces the challenge of balancing between the thromboembolic and bleeding risks (Friberg et al., 2012b, Gallego et al., 2012).

Two or more possible aetiologies of stroke can exist simultaneously in a patient with AF and therefore, optimization of treatment may be challenging. Previous studies have shown that a significant number, 8-24%, of AF patients have concomitant carotid artery stenosis (CAS) (Becattini et al., 2018, Chang et al., 2002, Kanter et al., 1994). OAC treatment is not superior in the secondary prevention of non-cardioembolic stroke when compared to antiplatelet therapy (ESPRIT Study Group et al., 2007, Chimowitz et al., 2005, Hart et al., 2000, Mohr et al., 2001). Carotid endarterectomy (CEA) is recommended in certain CAS patients (Barnett et al., 1998). There is limited data available about AF patients with concomitant carotid artery stenosis who suffer ischaemic stroke and their prognosis (Chang et al., 2002, Kanter et al., 1994, Kochar et al., 2018).

Intracranial haemorrhage is the most devastating bleeding complication encountered in AF patients on OAC. Risk scores, such as CHA2DS2-VASc and HAS-BLED, have been most commonly used to evaluate an AF patient’s risk for thromboembolic events and major bleedings (Lip et al., 2010, Pisters et al., 2010). These scores, however, share several risk factors, such as hypertension, age and stroke history. Thus, patients at a high risk of stroke are also at a high risk of bleeding. Even though earlier studies have found multiple risk factors for stroke and intracranial bleeding, there is still a need to identify the more specific risk factors especially associated with the increased risk of intracranial haemorrhage instead of ischaemic stroke in order to optimize the antithrombotic treatment (Friberg et al., 2012b, Gallego et al., 2012, McGrath et al., 2012).

Most (68-73%) of the intracranial haemorrhages occurring during OAC have been reported to be spontaneous (Hart et al., 2012, Lopes et al., 2017). Both spontaneous and traumatic intracranial haemorrhages are associated with high mortality (41-43% vs. 21%) (Hart et al., 2012, Lopes et al., 2017). Approximately every second intracranial
haemorrhage encountered during treatment with a vitamin-K antagonist (VKA) occur when the patient has therapeutic INR value (Hylek et al., 2003). More precise data is needed about the clinical characteristics of patients suffering ischaemic or haemorrhagic strokes during OAC.

The aim of the present doctoral thesis was to explore AF patients’ cerebral events such as ischaemic strokes and various types of haemorrhagic strokes in order to optimize the OAC future therapy in these patients. We evaluated the effect of concomitant carotid artery stenosis (CAS) on the prognosis of patients with AF suffering ischaemic stroke/transient ischaemic attack (TIA). We assessed the differences in anticoagulated AF patients with their first ever stroke, either ischaemic or haemorrhagic. Furthermore, we compared the types of haemorrhages and clinical characteristics in patients with traumatic and spontaneous haemorrhages on VKA therapy.
2 Review of the Literature

2.1 Atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia, i.e. in this condition, the ventricles contract irregularly and usually rapidly. Ion channel function and structural alterations of atria, such as fibrosis, hypertrophic changes in atrial myocytes and the presence of inflammation predispose to AF (Frustaci et al., 1997). Single or multiple ectopic wavelets in pulmonic veins often trigger AF (Haissaguerre et al., 1998).

The prevalence of AF increases with age; in the general population it is estimated to be in a range of 3.2-4.1%. In the Western population, the prevalence of AF has been shown to increase steeply in women aged >60 and in men >50 years (Magnussen et al., 2017). AF is rare in patients <50 years of age, whereas in octogenarians, the prevalence is higher, 17-23% (Björck et al., 2013, Williams et al., 2017). Other risk factors for AF are hypertension, heart failure, valvular heart diseases, diabetes, obesity and alcohol consumption (Psaty et al., 1997, Larsson et al., 2014, Schnabel et al., 2015). The prevalence of AF is strongly influenced by the screening method used (see chapter 2.4.1.).

AF is classified into first diagnosed, paroxysmal, persistent, long-standing persistent and permanent (Kirchhoff et al., 2017, Table1). At first, AF paroxysms are short and occur rarely but eventually after left atrium remodelling, paroxysms will become longer and occur more frequently. Finally, AF turns into a permanent condition.

Table 1. Classification of AF.

<table>
<thead>
<tr>
<th>AF pattern</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>First diagnosed AF</td>
<td>AF that has not been diagnosed before, irrespective of duration of the arrhythmia or the presence and severity of AF-related symptoms.</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. AF episodes that are cardioverted within 7 days should be considered as paroxysmal.</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as ‘long-standing persistent AF’.</td>
</tr>
</tbody>
</table>

Treatment of AF is stratified into rhythm control and rate control. In the rhythm control strategy, the ultimate goal is to restore and maintain a sinus rhythm whereas in the rate control strategy, AF is accepted as the permanent rhythm. In addition to rhythm or rate control, AF treatment focuses on the prevention of stroke and tachycardia-induced cardiomyopathy.

The EHRA score is used to assess the severity of symptoms caused by AF (Wynn et al., 2014, Table 2). The severity of symptoms, concomitant diseases and left atrial size are used to determine whether the treatment of AF is rate or rhythm control.

**Table 2. Modified EHRA classification.**

<table>
<thead>
<tr>
<th>Modified EHRA score</th>
<th>Symptoms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Normal daily activity not affected, symptoms not troublesome to patient</td>
</tr>
<tr>
<td>2a</td>
<td>Mild</td>
<td>Normal daily activity not affected but patient troubled by symptoms</td>
</tr>
<tr>
<td>2b</td>
<td>Moderate</td>
<td>Normal daily activity not affected but patient troubled by symptoms</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Normal daily activity affected</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Normal daily activity discontinued</td>
</tr>
</tbody>
</table>

Reference: (Wynn et al., 2014).

There is some evidence that the mortality of patients with permanent AF is higher than in those with paroxysmal AF (Palomäki et al., 2017, Steinberg et al., 2015, Takabayashi et al., 2015), but neither large randomized trials nor meta-analyses have been able to document differences in all-cause mortality of ischaemic stroke between rate and rhythm control (Al-Khatib et al., 2014, Caldeira et al., 2012). In acute AF (duration <48 hours), sinus rhythm can be restored either with pharmacologic (PCV) or electrical cardioversion (ECV) (Kirchhof et al., 2017). In permanent AF, the sinus rhythm is reinstated with ECV. If the duration of AF is > 48 hours or unknown, oral anticoagulation (OAC) should be used for at least three weeks before cardioversion (Kirchhof et al., 2017). Antiarrhythmic medication is often needed to maintain sinus rhythm and pulmonary vein isolation by ablation is a good option in certain patients. In permanent AF, it is important to maintain an adequate rate control in order to prevent the development of tachycardia-induced cardiomyopathy. To achieve this goal, lenient rate control (mean heart rate <110/minute) is warranted (Van Gelder et al., 2006).

### 2.2 Ischaemic stroke

According to the TOAST criteria (Adams et al., 1993), an ischaemic stroke can be divided into five categories based on its aetiologic entity: cardioembolic, large-artery
atherosclerosis, small vessel occlusion, stroke of other determined aetiology and stroke of unknown aetiology, such as embolic stroke of undetermined source (ESUS) and cryptogenic stroke. The prevalences of different stroke types are shown in Figure 1 (Grau et al., 2001). In younger patients (< 50 years), other aetiological factors are more frequent than large-artery atherosclerosis (Putaala et al., 2009).

![Figure 1. Aetiology of ischaemic stroke.](image)

### 2.2.1 AF related thromboembolic stroke

AF is a hypercoagulative state; in AF, atrial contraction is impaired resulting in a slowing of blood flow in the atria and left atrial appendage (LAA). Inflammation (vonWillebrandt factor, interleukin-6) causes activation of the coagulation cascade (D-dimer, prothrombin I and II, thrombin-antithrombin complex) and endothelial dysfunction and therefore it predisposes to thrombus formation (Choudhury et al., 2003, Okuyama et al., 2006). Approximately 90% of the thrombus caused by AF are found in the LAA (Blackshear et al., 1996). A thrombus may be detected by transesophageal echocardiography, computed tomography (CT) or magnetic resonance imaging (MRI). The thrombus can embolize from the LAA and enter the blood flow and this can cause thromboembolic complications such as stroke or transient ischaemic attack (TIA). Indeed, 26 % of ischaemic strokes have been reported to be cardioembolic (Grau et al., 2001). In severe enough strokes treated acutely with intravenous thrombolysis, up to 41% were cardioembolic (Mustanoja et al., 2011) this being in line with more recent studies where the prevalence of AF in ischaemic stroke patients has been reported to range from 26% up to 38% (Björck et al., 2013, McGrath et al., 2013). Other sources of cardioembolic stroke, e.g. myxomas and aortic plaque are less common. Cardioembolic strokes are usually multiple and therefore neurologic deficits are wide (McGrath et al. 2013).
Cardioembolic strokes result in higher mortality (1.1-5.3 –fold) and they are more disabling (1.8-3 –fold) than their non-cardioembolic counterparts (Pinto et al., 2006, Mustanoja et al., 2011). For example, Eriksson et al. (2001) reported that the 30-day mortality after cardioembolic stroke was 17% whereas it was zero after a stroke caused by a small vessel occlusion and 11% after stroke caused by large artery atherosclerosis. The incidences of fatal recurrent strokes were 30% (cardioembolic stroke) vs. 30% (small vessel occlusion) vs. 15% (large artery atherosclerosis). In the study of McGrath et al. (2013), AF related ischaemic strokes were associated with a more severe disability (OR 1.19) and higher mortality (OR 1.25) compared to strokes in patients without AF. In another study, the stroke subtype was a significant predictor of long-term survival; small vessel occlusion strokes were associated with better survival than cardioembolic strokes. On the other hand, there were no differences in the long-term stroke recurrence between the stroke subtypes (Kolominsky-Rabas et al., 2001).

2.2.2 Other forms of ischaemic stroke

The aetiology of stroke is classified as a large vessel atherosclerosis if a significant ipsilateral atherosclerotic disease is found, either in the carotid or intracranial artery (diameter of stenosis >50%), and other possible stroke aetiologies are excluded. Several studies have reported that patients with large-artery atherosclerotic strokes have the highest risk of stroke recurrence in comparison to the other ischaemic stroke subtypes (Lovett et al., 2004, Purroy et al., 2007). In a stroke caused by a small vessel occlusion, the neurological symptoms are usually minor without cortical deficits. Cardioembolic sources and ipsilateral large artery atherosclerotic disease should be excluded (Adams et al., 1993). Small vessel occlusion strokes usually enjoy the best prognosis (Eriksson et al., 2001).

Diagnostic criteria for ESUS are 1) stroke visualized by CT or MRI, not lacunar, 2) absence of intra- or extra-cranial atherosclerosis ≥50% stenosis or occlusion of the arteries supplying the area of ischaemia, 3) no major risk cardioembolic source of embolism (clinical history, electrocardiogram (ECG), echocardiography or cardiac rhythm monitoring) and 4) no other specific ischaemic stroke etiology defined (Hart et al., 2014). ESUSs are usually minor strokes and have a relatively low 30-day mortality, approx. 2%, compared to the 10% fatalities with cardioembolic strokes related to AF (Perera et al., 2016). The aetiology of ischaemic stroke is considered to be unknown, when there are two or more simultaneous possible aetiologies for a cerebral event, e.g. AF and >50 % carotid artery stenosis. If no possible aetiological factor for causing ischaemic stroke is found, it is classified as cryptogenic.
2.3 Evaluation of stroke risk in atrial fibrillation

Risk scores have been developed to estimate an anticoagulant naive AF patient’s annual risk of suffering an ischaemic stroke. The CHADS2 score was devised in 2001 and later the CHA2DS2-VASc score appeared in 2010 (Table 3). The CHA2DS2-VASc score was originally obtained from a relatively small AF cohort (n=1084), but subsequently it was validated in larger real life studies (Friberg et al., 2012b).

Table 3. CHADS2 and CHA2DS2-VASc scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHADS2</th>
<th>CHA2DS2-VASc score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

References: (Gage et al., 2001, Lip et al., 2010).

The risk of stroke varies between 0-15%/year depending on the patient’s risk profile in the AF cohort (Lip et al., 2010). In patients with CHA2DS2-VASc 1, the risk of stroke is 1.3%/year, in CHA2DS2-VASc 2 2.2%/year rising in CHA2DS2-VASc 9 up to 15.2%/year, respectively. The risk of stroke is significantly elevated in men with CHA2DS2-VASc >2 and in women with CHA2DS2-VASc >3. Correspondingly, the stroke risk is minimal in patients without any risk factors (CHA2DS2-VASc =0, 0%/year). However, there is some debate about the significance of a low CHA2DS2-VASc score (1 in men and 2 in women). In the study of Olesen et al. (2011), the annual stroke risk in AF patients with CHA2DS2-VASc 1 was 2.01% whereas in the study of Friberg et al. (2015), the annual stroke risk was clearly lower, i.e. 0.1-0.2% in women and 0.5-0.7% in men.

It should be taken into account that CHADS2 and CHA2DS2-VASc risk scores do not incorporate additional established risk factors, such as smoking habits and the presence of hypercholesterolemia. For some risk factors, e.g. female sex, there are conflicting results on its impact on the stroke risk. Some studies have not found female sex to be an independent risk factor for stroke, but most of the larger studies do state that women, especially older women (>75 year of old), have an elevated i.e. a 1.31-fold, risk for stroke as compared to men (Wagstaff et al., 2014). Randomized studies are still lacking would have evaluated the benefits of OAC treatment in AF patients with low CHA2DS2-VASc scores.
2.4 Stroke prevention in patients with atrial fibrillation

Stroke prevention in patients with AF is based on multiple different interventions such as AF detection, assessment of risk factors and risk-factor based oral anticoagulation. Particularly, the detection of silent AF may be challenging. The main goal is to find the AF patients who benefit from OAC, since 60% of ischaemic strokes caused by AF can be prevented by OAC (Hart et al., 2007). The treatment of other well-known risk factors for stroke, e.g. hypertension and hypercholesterolemia, is also important in prevention of strokes in AF patients.

2.4.1 Screening of atrial fibrillation

The diagnosis of AF is based on ECG documentation. AF patients with severe symptoms often seek medical advice, but detection of asymptomatic AF is challenging. Several studies have aimed to identify silent atrial fibrillation in asymptomatic patients, patients with palpitations or patients surviving from an ischaemic cerebral event using mobile applications, 24-48-hour ECG recording, continuous loop recorders or event recorders (Aronsson et al., 2015, Hobbs et al., 2005, Van Gelder et al., 2017).

There is an ongoing debate on how long an AF episode needs to last to increase the risk of an ischaemic stroke, as well as the time causality between AF diagnosis and stroke. In a meta-analysis consisting of 50 studies, an AF duration less than 30 seconds did not seem to be associated with the risk of stroke although it can be found in more than 50% of patients with ischaemic stroke/TIA (Sposato et al., 2015a, Sposato et al., 2012). Screening for silent AF in asymptomatic patients with a 12-lead ECG or hand-held ECG, has been postulated to be cost-effective in patients with CHA2DS2-VASc score >2 i.e. in patients at a high risk of stroke (Aronsson et al., 2015, Hobbs et al., 2005). Currently this is used in clinical studies rather than in everyday practice.

A 24-72-hour continuous ECG recording is recommended in acute stroke patients without any previously known AF (Grond et al., 2013, Powers et al., 2018). The incidence of new AF in patients with acute ischaemic stroke/TIA has been reported to range from 4.3 to 24% (Grond et al., 2013, Sposato et al., 2012, Sposato et al., 2015b). The variation depends on the screening method being used, i.e. from 7.7% to 16.9%, when using continuous loop recorders or serial ECGs (Sposato et al., 2015b). In the CRYSTAL AF study, AF detection in patients with cryptogenic stroke (defined as AF duration >30 seconds) was significantly higher when using implantable loop recorders than in the control group (Sanna et al., 2014). During a 6-month follow-up, a new AF was diagnosed in 8.9% patients in the loop recorder group and in 1.4% patients in the control group and after a 12-month follow-up, AF was diagnosed in 12.4% and 2.0% of patients, respectively. Asymptomatic atrial high rate episodes (AHREs), defined as heart rate >180/minute, are commonly seen in pacemaker...
patients. In the recent ESC Guidelines, an AHRE with a duration >6-8 minutes was considered to be significant (Kirchhof et al., 2017). However, it is worthwhile noticing that all AHREs are not AFs, but can be caused by frequent ectopic beats or noise. In addition, AHREs detected by pacemakers or loop recorders carry a lower stroke risk than clinical AF (Hindricks et al., 2010). It has also been difficult to prove the time causality between AHREs and stroke. In the study of Van Gelder et al. (2017), only AHREs with a duration >24 h were related to increased stroke/systemic embolism risk when compared to pacemaker patients without AHREs (HR 3.2).

2.4.2 Anticoagulation

OAC treatment has been shown to reduce the risk of stroke by approximately 60% in AF patients when compared to placebo (Hart et al., 2007). Recent ESC Guidelines recommend that OAC should be used in men with AF and a CHA2DS2-VASc score ≥2 and in women with CHA2DS2-VASc score ≥3 (Kirchhof et al., 2017). OAC is not indicated in AF patients with CHA2DS2-VASc score 0. In addition, OAC should be considered on an individual basis in men with CHA2DS2-VASc score ≥1 and in women with ≥2, unless there are contraindications for OAC or increased risk of bleeding. A meta-analysis of 10 studies (166 017 patient-years) reported that patients with CHA2DS2-VASc score ≥2 seemed to benefit from DOAC but in VKA treated patients, the bleeding risk exceeded the risk of thromboembolic events (Joundi et al., 2016). However, when comparing newly diagnosed AF patients with OAC to non-OAC AF patients who should be anticoagulated according to the current AHA AF Guidelines (from year 2014), but not according to previous guidelines (from year 2011, patients with CHA2DS2-VASc score ≥2 but CHADS2 <2), there was no difference in combined outcome of stroke, systemic embolism and death (Gray et al., 2018).

It has previously been demonstrated that antiplatelet therapy alone, i.e. aspirin or clopidogrel, is not sufficient enough to prevent ischaemic stroke in patients with AF (Hart et al., 2007). Aspirin has been shown to prevent approximately every fifth stroke (22%) whereas VKA prevents 64% of strokes when compared to placebo in primary prophylaxis of AF related stroke (Hart et al., 2007). The absolute stroke risk reduction rates were 2.7%/year for VKA but only 0.8%/year for aspirin. In secondary prevention, the reduction rates were 8.4%/year and 2.5%/year, respectively. In the meta-analysis conducted by Hart et al. (2007), VKA was associated with a 37% stroke reduction when compared to aspirin treatment. In another meta-analysis, VKA treatment decreased the stroke rate by 2.1 events/100 patient-years, when compared to aspirin treatment (van Walraven et al., 2002).

Concomitant use of antiplatelet drug and OAC has been reported to increase bleeding but not to decrease the risk of ischaemic stroke as compared to OAC alone (Björck et al., 2016, Hansen et al., 2010, Shireman et al., 2004).
Until recently, VKA has been the predominant form of OAC. VKA therapy decreases the activity of several vitamin K dependent clotting factors (II, VII, IX, X) by inhibiting vitamin K dependent epoxide reductase and inhibiting coagulative protein S and C (Ageno et al., 2012). VKA is monitored by the international normalized ratio (INR) laboratory test, which is obtained from the prothrombin time. The INR target level is usually 2.0-3.0, and higher for patients with mitral valve prosthesis (in whom the target is 2.5-3.5). In addition, the quality of VKA therapy can be assessed by calculating the proportion of time in which INR is within the therapeutic range (TTR). Usually a TTR higher than 70% is considered as adequate OAC control (Kirchhof et al., 2017, Morgan et al., 2009). Conflicting opinions also exist, as in the Nice Guideline the TTR recommendation is over 65% and higher in Finland over 80% (Lehto et al., 2017, Senoo et al., 2014).

A temporal decrease of TTR <70% is associated with an increased risk of cardiovascular events when compared to patients with consistent TTR ≥70% (HR 2.3) (Pastori et al., 2018). In a multicenter real life study, TTR <65% increased the risk of thromboembolic and bleeding events. In addition, there were no differences between the stroke rates when comparing OAC treatment to combination of clopidogrel and aspirin (Connolly et al. 2008). Labile INR and a high INR (especially ≥4.5) increase the risk for haemorrhages (Hylek et al., 2003, Pisters et al., 2010).

Lately, several direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban and edoxaban came into clinical use in Europe. The DOAC dose must individually be adjusted according to age, renal function (lower doses, if the estimated glomerular filtration rate (eGFR) is <50 ml/min/1.73m2) and weight.

All DOACs have been tested against VKA in randomized controlled trials. In all the trials, the primary outcome, including strokes and systemic embolism, was equal or lower in the DOAC groups when compared to the VKA groups (1.11%–1.76%/year vs. 1.60%–2.2%/year, respectively) (Granger et al., 2011, Giugliano et al., 2013, Patel et al., 2011, Connolly et al., 2009). In these trials, TTRs in VKA treated patients have been 55-65%. In reports based on real life data and good OAC control (TTR > 70%), the incidence of ischaemic stroke and stroke or systemic embolism in patients treated with DOACs and VKA has been similar (1.03% vs. 1.04% and 1.58% vs. 1.35%, respectively) (Sjögren et al., 2017). A large Danish nationwide cohort study also reported a similar incidence of ischaemic stroke AF patients on DOACs and VKA (Larsen et al., 2016). There are no randomized controlled head-to-head trials comparing the different DOACs. Haemorrhagic strokes will be discussed later (in chapter 2.6.).
2.4.3 Anticoagulation in patients with mechanical valve prosthesis

Currently VKA is the drug of choice in patients with mechanical valve prosthesis. A randomized study comparing dabigatran versus warfarin found higher stroke and major bleeding rates in patients on dagigatran, resulting in premature termination of the study (Eikelboom et al., 2013). The most common INR target is 2.5 in patients with mechanical aortic valve prosthesis and 3.0 in patients with mitral valve prosthesis. An even higher target INR level can be considered individually, if the patient has other thromboembolic risk factors. At odds with the ESC Valvular Heart Disease Guidelines, AHA Guidelines recommend concomitant aspirin in patients with mechanical valve prosthesis (Baumgartner et al., 2017, Nishimura et al., 2017).

2.4.4 Anticoagulation in patients with congestive heart failure

The risk of thromboembolic events is increased in heart failure due to several contributing factors: slowing down of blood flow in a large atria, a reduced left ventricle ejection fraction or myocardial infarction scar/ aneurysm and hypercoagulation due to abnormal hemostasis or endothelial dysfunction induced by heart failure (Choudhury et al., 2003). Consequently, congestive heart failure increases the risk of ischaemic stroke by 1.6-3.1 fold in patients with AF (Agarwal et al., 2014). This is especially true in those heart failure patients who have a reduced left ventricular ejection fraction (HFrEF, LVEF<40%), although contradictory results have also been reported (Banerjee et al., 2013, Ezekowitz et al., 1998, Gorin et al., 2010, Hart et al., 1999). The conflicting results are considered to be at least partly due to differences in the definition of HF. In cases of heart failure with preserved ejection fraction (HFpEF), the results are even more diverse. Two studies in HF patients with sinus rhythm reported that the risk of stroke was lower in VKA treated group as compared to the aspirin/clopidogrel treated group (Homma et al., 2012, Massie et al., 2009). Generally, in patients with heart failure and AF, the indications for OAC are similar as in other AF patients (Kirchhof et al., 2017, Lip et al., 2010).

2.5 Evaluation of bleeding risk in atrial fibrillation

Several risk scores have been developed to evaluate the risk of major bleeding in anticoagulated AF patients. The most commonly used score in current clinical practice is HAS-BLED (Pisters et al., 2010, Table4). HAS-BLED score ≥3 denotes a high bleeding risk. Particularly, in patients with HAS-BLED score higher than the CHA2DS2-VASc score, the risks and benefits related to OAC should be evaluated carefully, and all modifiable risk factors, such as hypertension, antiplatelet agents, NSAIDs should be stopped/avoided or withdrawn. The HAS-BLED score has been criticized because it shares partly the same risk factors as the CHA2DS2-VASc score and often patients with a high stroke risk also have a
high bleeding risk (Nielsen et al., 2015). Therefore other bleeding scores have been
developed, such as ABC, ATRIA, ORBIT and HEMORR2HAGES (Table 4). Conflicting data
exists surrounding the comparison of the different bleeding risk scores (Fang et al., 2011,
Friberg et al., 2012a, Olesen et al., 2011, Pisters et al., 2010, Roldan et al., 2013a). For
example, in the AMADEUS Trial, the risk scores had only modest abilities to predict major
bleeding in VKA treated AF patients, although HAS-BLED had better accuracy than ATRIA
and ORBIT risk scores (Senoo et al., 2016).

Table 4. ABC, ATRIA, ORBIT, HAS-BLED and HEMORR2HAGES bleeding risk scores.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>ABC</th>
<th>ATRIA</th>
<th>ORBIT</th>
<th>HAS-BLED</th>
<th>HEMORR2HAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic/renal disease(^a)</td>
<td>3</td>
<td>1</td>
<td>1 or 2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse(^b)</td>
<td></td>
<td></td>
<td></td>
<td>1 or 2</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Older(^c)</td>
<td>x</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Reduced platelets</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rebleeding risk(^d)</td>
<td>x</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Genetic factors</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Excessive fall risk</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>x</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Biomarkers(^e)</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Treatment with antiplatelet drug</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum score</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) ATRIA severe renal failure eGFR<30 ml/min/1.73 m\(^2\), \(^b\) HAS-BLED drugs or alcohol, \(^c\) HAS-BLED age ≥65 years, ATRIA and ORBIT ≥75 years, HEMORR2HAGES age >75 years, \(^d\) HAS-BLED
Bleeding either previous bleeding or bleeding tendency, ATRIA history of bleeding, ORBIT
history of bleeding or reduced haemoglobin/haematocrit/history of anemia, \(^e\) Biomarkers including
high-sensitive troponin (cTnT-hs), growth-differentiating factor-15 (GDF-15) or haemoglobin.
References: (Fang et al., 2011, Gage et al., 2006, Hijazi et al., 2016, O’Brien et al., 2015,
Pisters et al., 2010).

2.6 Intracranial bleedings during anticoagulation

2.6.1 Prevalence and prognosis

Intracranial haemorrhage is the most feared complication during OAC treatment due to its
high morbidity and mortality. The incidence of intracranial haemorrhage is relatively low
in the AF population.

The incidence of intracranial bleeding in AF patients in randomized controlled trials, with
TTR 55-65% has been 0.70%-0.85%/y in VKA and approx. 0.30%/y in DOAC treated patients
(Granger et al., 2011, Hylek et al., 2014, Lopes et al., 2017, Patel et al., 2011). However, some
of the studies have excluded dialysis patients and patients with mechanical valve
prosthesis, traumatic haemorrhage or a previous intracranial haemorrhage. In a real life
study, Larsen et al. (2016) reported a lower bleeding incidence in AF patients on apixaban or dabigatran when compared to patients on VKA (TTRs were not reported). Björck et al. (2016) reported a lower incidence of intracranial bleeding, 0.44%/y, in patients with well-controlled VKA treatment (median TTR 68%) compared to the DOAC RCT studies mentioned above. A similar incidence has been reported in other real life AF cohorts on OAC, 0.44-0.60%/100 patient-years (Larsen et al., 2016, Steinberg al., 2017b). In AF patients on VKA therapy, the risk of intracranial bleeding is remarkably higher with high INR (especially >4.0), labile INR and low TTR values (Björck et al., 2016, Fang et al., 2004, Hylek et al., 2003, McGrath et al., 2012, White et al., 2007). Approximately every second intracranial bleeding during VKA therapy occurs even though these patients have INR values within the therapeutic range (Hylek et al., 2003).

The 30-day mortality after intracranial haemorrhage in patients on OAC is high, 33-43% (Giugliano et al., 2013, Hankey et al., 2014, Hart et al., 2012, Lopes et al., 2017). In these randomized controlled DOAC trials, the mortality rates were similar between AF patients on VKA and those on DOACs (apixaban, dabigatran, edoxaban or rivaroxaban). Several factors i.e. Glasgow Coma Scale (GCS) points, a large volume of intracranial haematoma, age and high INR on admission were associated with increased mortality (Flaherty et al., 2008, Huhtakangas et al., 2011, Sjöblom et al., 2001, Zubkov et al., 2008, Wilson et al., 2017). To prevent the enlargement of haematoma in patients with VKA related major bleeding, it is recommended to administer vitamin K and prothrombin complex concentrate (PCC) with the goal of attaining an INR value <1.3 within 4 hours and to treat systolic blood pressure <160 mmHg (Kuramatsu et al., 2015). There are no randomized clinical trials which have investigated the use of PCC and the recommendation is based on small observational clinical studies (Parry-Jones et al., 2015). Despite the adequate anticoagulation reversal therapy, mortality in anticoagulated AF patients with intracranial haemorrhage has remained high (Dowlatshahi et al., 2012). In the multicenter analysis, both mortality and functional outcomes were similar between intracranial haemorrhage patients receiving either DOAC or VKA therapy (Wilson et al., 2017).

2.6.2 Traumatic and spontaneous bleeding

Most of the intracranial haemorrhages during OAC are reported to be spontaneous (68-73%) and in some studies traumatic haemorrhages have been excluded (Björck et al., 2016, Fong et al., 2017, Giugliano et al., 2013, Hankey et al., 2014, Hart et al., 2012, Lopes et al., 2017, Nielsen et al., 2015, Sjögren et al., 2017). Head trauma naturally precedes traumatic intracranial haemorrhage. Hypertension, labile INRs and structural changes, e.g. AV-malformation, aneurysms and amyloidangiopathy, predispose to intracranial haemorrhages. One would assume that traumatic haemorrhages had occurred at lower INR levels than spontaneous haemorrhages. Age, heavy alcohol consumption and continuous falls are the
reasons when the physician should consider the termination of OAC treatment in an AF patient due to the fear of traumatic haemorrhage.

In the study of Lopes et al. (2017), 29% (n=47) of the intracranial haemorrhages were traumatic: 21% (n=10) in apixaban group and 79% (n=37) in VKA group. Correspondingly the proportion of traumatic haemorrhages was 30% in the study of Hart et al. (2012) and 7% in the study of Hankey et al. (2014). Most of the traumatic haemorrhages in AF patients with OAC treatment were subdural haemorrhages (62-67%) (Hart et al., 2012, Lopes et al., 2017). In contrast, OAC-related spontaneous intracranial haemorrhages have been mostly ICHs, 58%-79% (Hankey et al., 2014, Hart et al., 2012, Lopes et al., 2017). Mortality is reported to be higher after spontaneous haemorrhages than after traumatic haemorrhages, 41-52% vs. 21% (Hart et al., 2012). The types of intracranial haemorrhages and 30-day mortality during VKA treatment are summarized in Table 5.

Table 5. Earlier studies on traumatic and spontaneous haemorrhage in patients with atrial fibrillation on VKA therapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total n*</th>
<th>Spontaneous haemorrhage</th>
<th>Traumatic haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>ICH</td>
<td>SDH</td>
</tr>
<tr>
<td>Björck et al. (2016)</td>
<td>40449</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Giugliano et al. (2013)</td>
<td>21105</td>
<td>132**/0.85</td>
<td>0.42</td>
</tr>
<tr>
<td>Hankey et al. (2014)</td>
<td>14264</td>
<td>172*****</td>
<td>128(74)</td>
</tr>
<tr>
<td>Hart et al. (2012)</td>
<td>18113</td>
<td>66(73)</td>
<td>42(64)</td>
</tr>
<tr>
<td>Lopes et al. (2017)</td>
<td>18140</td>
<td>78(68)</td>
<td>63(80)</td>
</tr>
<tr>
<td>Nielsen et al. (2015)</td>
<td>58815</td>
<td>1639**</td>
<td>NA</td>
</tr>
<tr>
<td>Fong et al. (2017)</td>
<td>114</td>
<td>114</td>
<td>NA</td>
</tr>
<tr>
<td>Sjögren et al. (2017)</td>
<td>68</td>
<td>35(51)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values denote n(%) or n(%)/% per year. Total n* number of AF patients in the study cohort. ** any intracranial bleeding during VKA. *** total 30-day mortality. **** numbers include also intracranial haemorrhages during rivaroxaban treatment. ***** in addition of ICH, SDH and SAH, there was one extradural haemorrhage and in SDH and SAH number of traumatic haemorrhages were not reported. ICH, intracerebral haemorrhage; NA, not announced; SAH, subarachnoidal haemorrhage; SDH, subdural haemorrhage; VKA, vitamin K antagonist.
2.7 Optimization of stroke prevention in atrial fibrillation

2.7.1 Withholding anticoagulation

During the last 10 years, the risk scores have been utilized in clinical practice and the use of OAC therapy has increased in patients with AF (Huhtakangas et al., 2011, Lip et al., 2010, Steinberg et al., 2017a). Nonetheless, there is still an underuse of anticoagulation in AF patients (Hylek et al., 2003, Lip et al., 2014, Nieuwlaat et al., 2005, Palomäki et al., 2016).

The most common reasons for withholding OAC in spite of the fact that the patient has an increased thrombosis risk are alcohol abuse, dementia and a history of bleeding (Björck et al., 2015, Palomäki et al., 2016). In octogenerians (≥80 years), the reasons for not initiating OAC are old age, paroxysmal AF, bleeding history, chronic hepatic disease and difficulties in self-control (Hanon et al., 2017). It has been reported that chronic obstructive pulmonary disease, cancer and heart failure increase the risk of VKA discontinuation by 20% in AF patients, who suffered a stroke. In addition, the adherence to VKA was only 0.78 after one year and 0.47 after five years (Björck et al., 2015). In patients on VKA therapy, the patient’s poor adherence can be easily detected from a low INR value, but it is more difficult in patients prescribed DOACs.

2.7.2 Antithrombotic treatment in patients with carotid artery stenosis and AF

OAC is a well-established therapy in AF patients, but it has not been shown to be superior when compared to antiplatelet drugs in the secondary prevention of non-cardioembolic stroke (ESPRIT Study Group et al., 2007, Chimowitz et al., 2005, Hart et al., 2000, Mohr et al., 2001). In patients with non-cardioembolic stroke, aspirin-dipyridamol and clopidogrel are more effective in preventing recurrent stroke than aspirin alone (Diener et al., 1996, ESPRIT Study Group et al., 2006, Sacco et al., 2008). Additionally, the benefit of statins in secondary prevention with a target LDL level below 1.8 mmol/l is well documented (Amarenco et al., 2009b). In the SPARCL trial (Amarenco et al., 2009b), atorvastatin treatment decreased strokes, regardless of the stroke aetiology, compared to placebo. In that trial, patients with a combination of AF and coronary artery disease were excluded. Carotid artery endarterectomy (CEA) is recommended in stroke patients with carotid artery stenosis ≥70% in the ipsilateral side unless the operative risk is too high (Barnett et al., 1998, ECST Trialists, 1998, ECST Trialists, 1991). CEA displayed an absolute risk reduction of 17% for a recurrent ipsilateral stroke with 2 years of follow-up and 11% for a major or fatal ipsilateral stroke when compared to medical treatment, respectively (North American Symptomatic Carotid Endarterectomy Trial Collaborators et al., 1991). In patients with major comorbidities, carotid stenting should be considered instead of CEA. Carotid
intervention should be performed within two weeks from the index stroke because of the high risk of stroke recurrence.

There is only limited data on AF patients and concomitant carotid artery stenosis (CAS) suffering ischaemic stroke (Table 6). In the study of Chang et al. (2002), stroke patients with AF and CAS had a worse combined outcome than those without CAS (Chang et al., 2002). In another trial, asymptomatic CAS doubled the risk of ischaemic stroke in anticoagulated AF patients (Kanter et al., 1994).
**Table 6.** Studies of AF patients with concomitant CAS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Study design</th>
<th>CAS (&gt;50%) prevalence</th>
<th>VKA</th>
<th>Antiplatelet</th>
<th>INR/TTR</th>
<th>Main result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al 2002</td>
<td>103</td>
<td>Stroke patients with AF, retrospective cohort</td>
<td>25 (24.3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CAS is associated with cortical infarctions and worse clinical outcome</td>
</tr>
<tr>
<td>Kanter et al. 1994</td>
<td>676</td>
<td>Retrospective AF cohort</td>
<td>81 (12.0)</td>
<td>33 (41)</td>
<td>26 (32)</td>
<td>NA</td>
<td>CAS patients had more hypertension, diabetes and were more often smokers. CAS was associated with a 2-fold stroke risk elevation in patients with VKA/antiplatelet. In multivariate analysis CAS was not related to stroke risk.</td>
</tr>
<tr>
<td>Becattini et al. 2018</td>
<td>587</td>
<td>Prospective AF cohort</td>
<td>45 (8)</td>
<td>587 (100)</td>
<td>6 (14)</td>
<td>Mean TTR CAS 70 vs. non-CAS 69</td>
<td></td>
</tr>
<tr>
<td>Bekwelem et al. 2016</td>
<td>724</td>
<td>Prospective AF cohort</td>
<td>*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>cIMT and carotid plaque were predictors of stroke</td>
</tr>
<tr>
<td>Basili et al. 2017</td>
<td>2027</td>
<td>Retrospective AF cohort</td>
<td>336 (17)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CAS was predictor of ischaemic stroke/TIA</td>
</tr>
<tr>
<td>Paciaroni et al. 2010</td>
<td>148 vs. 219</td>
<td>Stroke patients with AF vs. controls without stroke, prospective case-control study</td>
<td>20 (21)</td>
<td>148 (100)</td>
<td>NA</td>
<td>Admission INR above 1.8</td>
<td></td>
</tr>
<tr>
<td>Benbir et al. 2007</td>
<td>103</td>
<td>Stroke patients with AF, prospective cohort</td>
<td>21 (19.8)</td>
<td>103 (100)</td>
<td>6 (5.8)</td>
<td>INR 2.0-3.0, 103 (100)</td>
<td></td>
</tr>
<tr>
<td>Kochar et al. 2018</td>
<td>14264</td>
<td>Prospective AF cohort</td>
<td>593 (4)</td>
<td>453** (76)</td>
<td>245 (41)</td>
<td>NA</td>
<td>CAS patients were older and had more comorbidities (such as MI). No differences in endpoints (CAS vs. non-CAS).</td>
</tr>
</tbody>
</table>
Values denote n(%). INR, international normalised ratio; CAS, carotid artery stenosis; cIMT, carotid intima-media thickness; non-CAS, carotid artery stenosis; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist. * Carotid intima media thickness or carotid artery plaque (cIMT) as continuous variable. NA denotes not announced.

**Prior VKA use; 239 (49) randomized to rivaroxaban.

References: (Basili et al., 2017, Becattini et al., 2018, Bekwelem et al., 2016, Benbir et al., 2007, Chang et al., 2002, Kanter et al., 1994, Kochar et al., 2018, Paciaroni et al., 2010)

2.7.3 Hypertension

Hypertension is a well-known risk factor for both ischaemic and haemorrhagic cerebral events (Lip et al., 2010, Pisters et al., 2010). A history of self-reported hypertension increases more the risk of haemorrhagic stroke than ischaemic stroke. However, when hypertension was defined as a combination of self-reported hypertension or blood pressure higher than 160/90, hypertension was associated with both ischaemic and haemorrhagic strokes (O’Donnell et al., 2016). In addition, it has been shown that lowering the blood pressure by >12 mmHg (baseline blood pressure 147/76 mmHg) reduced the risk of intracranial haemorrhage by 76 % in patients with a previous stroke or TIA (Chapman et al., 2004) and in the substudy of AF patients (approx. 50 % in OAC therapy), lowering the blood pressure by > 7 mmHg reduced the risk of stroke by 34 % (Arima et al., 2005).

2.7.4 Renal failure

Several studies have reported that renal failure increases the risk of ischaemic stroke in AF patients (Bonde et al., 2014). In patients undergoing renal transplantation, AF increases the risk of stroke/thromboembolism by 1.6-5.5 fold in all CHA2DS2-VASc subgroups with 2 years of follow-up (Bonde et al., 2014). Renal failure increases the risk of thromboembolic events, mostly due to endothelial dysfunction and increased coagulation (Capodanno et al., 2012). In addition to thromboembolic events, renal failure is associated with an increased risk of bleeding due to platelet dysfunction (Capodanno et al., 2012, Olesen et al., 2012). Renal failure is included in the HAS-BLED score (Pisters et al., 2010), but not in the CHA2DS2-VASc score.

Warfarin reduced all-cause mortality in renal failure patients with CHA2DS2-VASc score ≥2 (HR 0.85). In a Danish AF cohort, VKA therapy was associated with both a higher bleeding risk in all eGFR subgroups and a lower risk of thromboembolic events in eGFR subgroups >15 mL/min/1.73m² (Bonde et al., 2016). In a recent meta-analysis, VKA reduced the risk of ischaemic stroke/thromboembolism (HR 0.70, 95%-CI 0.54-0.89) and mortality (HR 0.65, 95%-CI 0.59-0.72) in AF patients with non-end stage chronic kidney disease, but had no effect on major bleedings (HR 1.15, 95%-CI 0.88-1.49) (Dahal et al., 2016). In end-state chronic kidney disease patients, VKA had no effect on ischaemic events (HR 1.12, 95%-CI 0.69-1.82) and mortality (HR 0.96, 95%-CI 0.81-1.13), but increased the risk of serious bleeding events (HR 1.30, 95%-CI 1.08-1.56) (Dahal et al., 2016).
Randomized DOAC studies have usually excluded patients with severe renal failure (eGFR either <25 ml/min or <30 ml/min) and patients requiring dialysis (Connolly et al., 2009, Giugliano et al., 2013, Granger et al., 2011, Patel et al., 2011). FDA has accepted that all DOACs can be administered at a reduced dose in patients with eGFR 15-50 ml/min (depending on DOAC), although there is no data from randomized clinical studies on patients with GFR 15-30 ml/min (Nishimura et al., 2018). In addition, FDA has approved edoxaban to be used in patients with end state renal disease and dialysis patients. In one observational study, treatment with dabigatran and rivaroxaban increased fatal bleedings and non-fatal bleedings in patients with severe renal failure or end-state renal disease (Chan et al., 2015). Large randomized studies are still needed to evaluate the benefits of DOAC treatment in patients with severe renal failure (<15 ml/min) because of the bi-directional risk of both thromboembolic and bleeding events in these patients.

2.7.5 Ageing

The prevalence of AF increases with age and 9% of patients >80 years present with AF (Go et al., 2001). Age ≥75 years is included in both CHA2DS2-VASc and HAS-BLED scores. VKA prevents stroke/systemic embolism more effectively than aspirin also in the elderly, whereas the incidence of haemorrhagic stroke was similar between VKA and aspirin treatment in the elderly (0.5% vs. 0.4%, in patients >75 years of old) (Mant et al., 2007, SPAF Investigators, 1994). Several studies have reported that age increases the risk of ICH in AF patients on VKA but also the risk of ischaemic stroke rate is high and thus, age per se should not be considered as a reason for OAC withdrawal (Fang et al., 2004, Mant et al., 2007, SPAF Investigators, 1994). In the RE-LY study (Eikelboom et al., 2011), the incidence of major bleeding in younger patients (<75 years) was lower with dabigatran 150 mg and 110 mg twice a day compared to VKA. In the elderly population (≥75 years), the risk of bleeding with low dose dabigatran and VKA was equal, whereas there was a trend toward a higher bleeding risk with high dose dabigatran as compared to VKA. In the ROCKET-AF, there was no difference between the rivaroxaban and VKA groups (Halperin et al., 2014). In the ARISTOTLE trial, patients receiving apixaban suffered less intracranial haemorrhages than patients being treated with VKA regardless of age (Halvorsen et al., 2014). In a subgroup of elderly (≥75 years) in the ENGAGE AF-TIMI 48 Trial there was no difference between the edoxaban and VKA groups with respect to ischaemic events although the risk of major bleeding was lower in the edoxaban treated patients (HR 0.83) (Kato et al., 2016). In clinical practice, estimation of the HAS-BLED score and an evaluation of bleeding risk are conducted similarly in the elderly and in younger patients irrespective of the OAC administered (DOAC or VKA).
2.7.6 Falls

In clinical practice, a patient’s tendency to fall is frequently used as reason to withdraw OAC because of the threat of traumatic bleedings, particularly intracranial bleedings, although this is not supported by scientific data (Donze et al., 2012, Gage et al., 2005, Man-Son-Hing et al., 2003). Cardiac diseases, such as hypotension, cardiac arrhythmias and heart failure, are associated with falls (Jansen et al., 2016). Gage et al. (2005) reported an increased risk of traumatic intracranial bleeding in AF patients who were prone to fall when compared to patients who were not expected to fall (HR 2.0 vs. HR 0.34). However, VKA protected AF patients with multiple risk factors from stroke (Gage et al., 2005). In randomized clinical DOAC trials self-reported history of falls were not related to the risk of intracranial bleeding (Giugliano et al., 2013, Hankey et al., 2014, Hart et al., 2012, Lopes et al., 2017). In my opinion, according to most of the studies, falls should not be the reason for OAC withdrawal.

2.7.7 Prevention of stroke after intracranial haemorrhage

Secondary prevention of stroke after OAC-related ICH is a specific challenge. There are no clear recommendations about the safety and optimal timing of the re-initiation of OAC after an OAC-related ICH and AF patients who have experienced a previous intracranial haemorrhage are usually excluded from pharmaceutical trials. AHA Guidelines recommend (IIb) at least 7-14 days’ discontinuation of OAC after an OAC-related intracranial haemorrhage and deferring antiplatelet or antiplatelet drugs after OAC-related ICH. Resuming OAC in AF patients with intracranial haemorrhage should be individually considered by evaluating the patient’s risk for ischaemic stroke and bleeding recurrence. The type of intracranial haemorrhage (traumatic or spontaneous, ICH or SDH), localization and aetiology of the ICH (lobar or deep), risk of falls, polypharmacy, untreated hypertension and whether the haemorrhage occurred with a therapeutic INR value, should be taken into account (Nielsen et al., 2015, Majeed et al., 2010). The ICH recurrence rate after OAC-related ICH has been reported to be high, 8.0 % per year, in OAC treated patients but equally high, 8.0 % per year, in patients without OAC (Nielsen et al., 2015). In addition, Nielsen et al. (2015) studied AF patients with a history of ICH and found that patients with OAC treatment had a lower rate of ischaemic stroke/systemic embolism and all-cause mortality than in patients treated with antiplatelet drug or patients without OAC (adjusted HR 0.55). Kuramatsu et al. (2015) reported fewer ischaemic events in patients on OAC in comparison to those without OAC (5.2% vs. 15.0%, respectively) and the risk of haemorrhagic complications did not differ between groups (OAC vs. no OAC, 8.1% vs. 6.6%, p=0.48). They concluded that the results favoured the resumption of VKA. Long-term all cause mortality was also lower in AF patients on OAC than in propensity-matched controls (HR 0.26).
Recently, left atrial appendage closure (LAAC) has become an alternative to prevent ischaemic stroke in AF patients who have previously suffered a major bleeding event and have absolute or relative contraindication for long-term OAC (IIbB) (Kirchhof et al., 2017). PROTECT-AF and PREVAIL trials reported a somewhat higher (statistically non-significant) risk of ischaemic strokes (HR 1.71) but a lower risk of haemorrhagic strokes (HR 0.20), all-cause death (HR 0.73) and fatal/disabling stroke (HR 0.45) in patients treated with LAAC (Reddy et al., 2017).
3 Aims of the study

In this study, we aimed to assess the clinical characteristics of anticoagulated patients with AF, who had suffered either an ischaemic or a haemorrhagic stroke. The specific aims were:

1. To study the impact of concomitant carotid artery disease on stroke recurrence and mortality in anticoagulated AF patients after ischaemic stroke.

2. To compare the clinical characteristics and risk profiles of anticoagulated AF patients who had suffered either an ischaemic or a haemorrhagic stroke.

3. To assess the distribution of different types of intracranial haemorrhage, and to compare clinical characteristics and mortality in warfarin treated patients with atrial fibrillation who had experienced either a traumatic or a spontaneous intracranial haemorrhage.
4 Materials and Methods

4.1 Study population

FibStroke study included all patients with a diagnosis of AF/atrial flutter and ischaemic stroke, TIA or an intracranial haemorrhage from two university hospitals (Turku University Hospital and Kuopio University Hospital) and two central hospitals (Satakunta Central Hospital and Keski-Suomi Central Hospital) during 2003-2012 (in one central hospital during 2006-2012). The FibStroke catchment area has 1.2 million inhabitants. The temporal relationship between stroke/TIA and AF/atrial flutter diagnosis was not restricted in the initial screening. A total of 5629 patients with 6715 cerebral events met the inclusion criteria. They had suffered from 4547 ischaemic strokes, 1338 TIAs and 830 intracranial haemorrhages.

For this thesis, sub-populations were selected with the following criteria:

I Patients i) with AF/atrial flutter diagnosed before or at the time of the cerebral event, ii) suffering an ischaemic stroke and iii) undergoing carotid artery ultrasound imaging during the index event hospitalization.

II Patients i) with AF/atrial flutter diagnosed before or at the time of the stroke, ii) suffering their first lifetime spontaneous intracerebral haemorrhage (ICH) or ischaemic stroke and iii) on OAC.

III Patients i) with AF/atrial flutter diagnosed before the index event, ii) suffering a traumatic or a spontaneous intracranial haemorrhage and iii) on OAC.

4.2 Data collection

The screening was performed from the electronic hospital discharge records using the following ICD-10 diagnosis codes:
1) I48; AF or atrial flutter, and

2) I60.0-I60.9, I61.0-I61.9, I62.0-I62.9, I63.0-I63.9, I64.0-I64.9, I65.0-I65.9, I66.0-I66.9, I69.0-
I69.9, G45.0-G45.9, G46.0-G46.9, S06.0-S06.9; ischaemic stroke, TIA and traumatic and spontaneous intracranial haemorrhage.

After the initial screening, each event was individually reviewed from the electronic discharge records and the diagnoses were confirmed case by case. Data were transferred into an online database via a structured electronic case report form. Clinical data, risk factors for ischaemic stroke and intracranial haemorrhage, medication (antiplatelet drugs, anticoagulation, selective serotonin reuptake inhibitors (SSRIs), non-steroidal anti-inflammatory drugs (NSAIDs), selected laboratory results (e.g. hemoglobin, creatinine, INR), operations/invasive procedures/bleeding events/cardioversions in the preceding 30 days before the index stroke, as well as the 30-day mortality and stroke recurrences were recorded. CHA2DS2-VASc and modified HAS-BLED scores were calculated.

4.3 Definitions

All patients underwent head CT or MRI. Stroke, TIA and intracranial haemorrhage diagnoses were collected from the electronic patient discharge records individually and the diagnoses were confirmed by the treating neurologist. Only definite strokes were included. Hypertension, hypercholesterolemia and diabetes were defined as treatment for that disease at the time of the cerebral event. Anemia was defined as hemoglobin <100 g/l. eGFR (ml/min/1.73 m²) was calculated by using the MDRD formula and renal failure was considered as eGFR<60 l/min./1.73 m². CHA2DS2-VASc and modified HAS-BLED without labile INR were calculated as previously described (Lip et al. 2010, Pisters et al. 2011). Carotid artery imaging was performed with selective carotid angiography or digital subtractive angiography (DSA) at the beginning of this study period, but during later years, these were gradually replaced by computed tomography angiography (CTA). Grading was performed by consulting radiologists in the participating hospitals using either North American Symptomatic Carotid Endarterectomy Trial (Barnett et al., 1998) or European Carotid Surgery Trialist criteria (ECST Trialists, 1998) and >50% stenosis was considered as significant.
4.4 Statistical analysis

Statistical analyses were performed using IBM SPSS Software program versions 23.0 and 24.0. The comparison between study groups in cases where there were continuous variables was performed using Student’s T-test and Mann-Whitney U-test, when appropriate. All continuous variables are reported as mean (±standard deviation, SD) if they were normally distributed and as median (interquartile range, IQR) if they were skewed. Categorical variables were analysed with χ² test and Fisher’s exact test, when needed. Categorical variables are reported as absolute numbers and percentages. Binary and multivariate analysis logistic regression analyses were used to obtain ORs (95 CI%). Cox regression analysis was used to evaluate stroke recurrence in substudy I. A p-value <0.05 was considered as statistically significant.

4.5 Ethical issues

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. This study conforms to the Declaration of Helsinki. Patient informed consent was not required because of its retrospective nature.
5 Results

5.1 Stroke recurrence in anticoagulated patients with atrial fibrillation and concomitant carotid artery stenosis (I)

In study I, there were 899 AF patients suffering an ischaemic stroke/TIA who underwent carotid artery ultrasound imaging during the index hospitalization. There were 165 patients with concomitant carotid artery stenosis (CAS) and 734 patients without CAS (non-CAS) (Figure 2). AF had been diagnosed either before or at the onset of the index stroke in all patients.

Figure 2. Study I flowchart. AF=atrial fibrillation, TIA=transient ischaemic attack, ICH=intracerebral haemorrhage, SAH=subarachnoidal haemorrhage.
Table 7. Baseline clinical characteristics in patients with and without carotid artery stenosis.

<table>
<thead>
<tr>
<th></th>
<th>CAS n=165</th>
<th>Non-CAS n=734</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y [IQR]</td>
<td>76.7 [9.6]</td>
<td>73.8 [11.6]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>99 (60.0)</td>
<td>326 (44.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Female</td>
<td>77 (46.7)</td>
<td>322 (43.9)</td>
<td>0.537</td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (77.0)</td>
<td>454 (61.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49 (29.7)</td>
<td>140 (19.0)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>104 (63.0)</td>
<td>322 (43.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>29 (17.6)</td>
<td>96 (13.1)</td>
<td>0.130</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>83 (50.6)</td>
<td>199 (27.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>29 (17.6)</td>
<td>42 (5.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>34 (20.8)</td>
<td>146 (19.9)</td>
<td>0.829</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>36 (21.8)</td>
<td>101 (13.7)</td>
<td>0.009*</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>94 (59.9)</td>
<td>475 (66.5)</td>
<td>0.072</td>
</tr>
<tr>
<td>≥30-&lt;60</td>
<td>62 (37.6)</td>
<td>228 (31.0)</td>
<td>0.101</td>
</tr>
<tr>
<td>&lt;30</td>
<td>2 (1.2)</td>
<td>4 (0.5)</td>
<td>0.303</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>19 (11.6)</td>
<td>54 (7.4)</td>
<td>0.073</td>
</tr>
<tr>
<td>Mechanical valve prosthesis</td>
<td>3 (1.8)</td>
<td>22 (3.0)</td>
<td>0.600</td>
</tr>
<tr>
<td>Biovalve prosthesis</td>
<td>6 (3.7)</td>
<td>10 (1.4)</td>
<td>0.094</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>≥2</td>
<td>155 (93.8)</td>
<td>614 (83.8)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (4.8)</td>
<td>81 (11.0)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (1.2)</td>
<td>40 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Type of index stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>110 (66.7)</td>
<td>476 (64.9)</td>
<td>0.658</td>
</tr>
<tr>
<td>TIA</td>
<td>55 (33.3)</td>
<td>258 (35.1)</td>
<td>0.695</td>
</tr>
<tr>
<td>AF type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>permanent</td>
<td>78 (52.7)</td>
<td>269 (40.1)</td>
<td>0.005*</td>
</tr>
<tr>
<td>AF rhythm on hospital admission</td>
<td>91 (56.5)</td>
<td>395 (56.7)</td>
<td>0.972</td>
</tr>
</tbody>
</table>

CAS= patients with carotid artery stenosis (>50%); Non-CAS= patients without carotid artery stenosis. TIA=transient ischaemic attack. IQR=interquartile range. The values denote n (%). *=p<0.05.
At the time of the index stroke, 55% of CAS patients and 44% of non-CAS patients were receiving some form of OAC (p=0.015). The OAC was VKA in 896 patients (only 3 patients were receiving dabigatran). The CAS patients were significantly older, were more likely to suffer from congestive heart failure, hypertension, diabetes and atherosclerotic diseases than patients with non-CAS (Table 7). The CHA2DS2-VASc score was also higher in the CAS patients (4 vs 3, p<0.001).

The long-term stroke recurrence (21.2% vs. 12.7%, p=0.005, Figure 3) was higher in CAS patients than in non-CAS patients despite similar antithrombotic treatment at the time of recurrence. Carotid endarterectomy was performed in 41 CAS patients (24.8%) after the index event. However, the incidence of stroke recurrence remained higher in the CAS patients than in the non-CAS patients whether the treatment was conservative or surgical (20.8% vs. 12.6%, p=0.015 and 25.6% vs. 12.6%, p=0.019, respectively).

Figure 3. Kaplan-Meier curve of stroke recurrence. CAS=AF patients with carotid artery stenosis. Non-CAS=AF patients without carotid artery stenosis. Reproduced from Study I (with permission of John Wiley & Sons).
CAS was an independent risk factor for ischaemic stroke recurrence (HR 2.02, 95%-CI 1.37-3.01, p=0.001) in multivariate analysis including age, hypertension, diabetes, hypercholesterolemia, coronary artery disease and congestive heart failure in the model.

The 30-day mortality after index stroke/TIA was also higher in the CAS group than in the non-CAS group (7.9% vs. 1.9%, p<0.001, Figure 4). This was true also in the subgroup of patients >75 years (10.1% vs. 3.7%, p=0.017, respectively).

![Figure 4](image)

*Figure 4.* 30-day mortality after index stroke/TIA in patients with and without carotid artery stenosis. Reproduced from Study I (with the permission of John Wiley & Sons).

### 5.2 Clinical characteristics and risk profiles in AF patients with ischaemic stroke or intracerebral haemorrhage on OAC (II)

Study II consisted of 1457 patients who while receiving some form of OAC, had suffered their first lifetime stroke or intracerebral haemorrhage (Figure 5). There were 1290 first ischaemic stroke/TIA patients and 167 ICH patients.
In the whole cohort, age and sex in patients with ischaemic stroke/TIA and ICH did not differ (Table 8). Patients suffering an ischaemic event presented more often with history of congestive heart failure, hypercholesterolemia, and mechanical valve prosthesis and had lower eGFR than patients with ICH. INR values were higher in ICH patients than in ischaemic stroke/TIA patients (2.7 vs. 2.0, p=0.001) and they had more often their INR value above the treatment target (>3.0) (32% vs. 9%, p=0.001, Figure 6). The CHA2DS2-VASc score was higher in patients who experienced an ischaemic event in comparison with the patients with ICH (4 vs. 3, p=0.001), but the HAS-BLED score did not differ between the groups (2 vs. 2, p=0.812). In the multivariate analysis, congestive heart failure (OR 2.30, 95%-CI 1.39-3.81), hypercholesterolemia (OR 1.94, 95%-CI 1.30-2.88), mechanical valve prosthesis (OR 4.41, 95%-CI 1.32-14.7) and low eGFR values (1.86, 95%-CI 1.23-2.80) were independently associated with an ischaemic event, whereas aspirin use (OR 0.52, 95%-CI 0.30-0.91) and high INR (OR 0.40, 95%-CI 0.33-0.48) were overrepresented in patients with ICH (Table 9).

When focusing only on the subgroup with therapeutic INR values on admission, congestive heart failure, hypercholesterolemia and low eGFR were more frequent in patients experiencing an ischaemic event than in patients with ICH. A bleeding history was more
common in the ICH patients than in patients suffering an ischaemic event (Table 8). The CHA²DS₂-VASc and HAS-BLED scores were similar (CHA²DS₂-VASc 4 vs. 4, p=0.146 and HAS-BLED 2 vs. 2, p=0.936). In the multivariate analysis, congestive heart failure (OR 2.33, 95%-CI 1.18-4.58) and hypercholesterolemia (OR 2.52, 95%-CI 1.51-4.19) were more associated with ischaemic events than with ICH, whereas a bleeding history (OR 0.30, 95%-CI 0.11-0.82) was associated with ICH (Table 9).

Figure 6. Admission INR in patients with ischaemic stroke/TIA and intracerebral haemorrhage. INR, international normalized ratio; TIA, transient ischaemic attack. Reproduced from Study II (with the permission of John Wiley & Sons).
Table 8. Baseline characteristics of the whole study cohort and in patients with therapeutic INR at the time of the event.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole study cohort (n=1457)</th>
<th>ICH (n=167)</th>
<th>P value</th>
<th>INR within therapeutic range (n=649)</th>
<th>ICH (n=96)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>78.4 [12.4]</td>
<td>78.0 [11.3]</td>
<td>0.339</td>
<td>77.6 [11.7]</td>
<td>78.1 [11.0]</td>
<td>0.888</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>314 (24.3)</td>
<td>42 (25.1)</td>
<td>0.815</td>
<td>144 (26.6)</td>
<td>25 (26.0)</td>
<td>0.914</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>857 (66.4)</td>
<td>109 (65.3)</td>
<td>0.775</td>
<td>355 (65.5)</td>
<td>64 (66.7)</td>
<td>0.824</td>
</tr>
<tr>
<td>Female sex</td>
<td>708 (54.8)</td>
<td>83 (49.7)</td>
<td>0.210</td>
<td>290 (53.5)</td>
<td>53 (55.2)</td>
<td>0.758</td>
</tr>
<tr>
<td>Treatment for</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>321 (24.9)</td>
<td>34 (20.4)</td>
<td>0.202</td>
<td>139 (25.6)</td>
<td>21 (21.9)</td>
<td>0.432</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>501 (39.0)</td>
<td>46 (27.5)</td>
<td>0.004</td>
<td>231 (42.7)</td>
<td>24 (25.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>188 (14.6)</td>
<td>20 (12.0)</td>
<td>0.369</td>
<td>74 (13.7)</td>
<td>10 (10.4)</td>
<td>0.387</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>468 (36.3)</td>
<td>57 (34.1)</td>
<td>0.582</td>
<td>191 (35.2)</td>
<td>32 (33.3)</td>
<td>0.718</td>
</tr>
<tr>
<td>Other vascular disease</td>
<td>111 (8.6)</td>
<td>8 (4.8)</td>
<td>0.094</td>
<td>51 (9.4)</td>
<td>4 (4.2)</td>
<td>0.092</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>350 (27.1)</td>
<td>25 (15.1)</td>
<td>0.001</td>
<td>138 (25.5)</td>
<td>11 (11.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>AF permanent</td>
<td>889 (74.4)</td>
<td>120 (79.5)</td>
<td>0.175</td>
<td>377 (75.0)</td>
<td>70 (79.5)</td>
<td>0.354</td>
</tr>
<tr>
<td>Bleeding history</td>
<td>43 (3.3)</td>
<td>11 (6.6)</td>
<td>0.036</td>
<td>12 (2.2)</td>
<td>7 (7.3)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mechanical valve prosthesis</td>
<td>67 (5.2)</td>
<td>3 (1.8)</td>
<td>0.053</td>
<td>24 (4.4)</td>
<td>1 (1.0)</td>
<td>0.154</td>
</tr>
<tr>
<td>Biovalve prosthesis</td>
<td>26 (2.1)</td>
<td>5 (3.0)</td>
<td>0.399</td>
<td>13 (2.5)</td>
<td>2 (2.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>CHA2DS2-VASc ≥ 2</td>
<td>1197 (92.7)</td>
<td>155 (92.8)</td>
<td>0.964</td>
<td>502 (92.6)</td>
<td>91 (94.8)</td>
<td>0.444</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>2 [1]</td>
<td>2 [1]</td>
<td>0.812</td>
<td>2 [1.0]</td>
<td>2 [1.0]</td>
<td>0.936</td>
</tr>
<tr>
<td>Modified HAS-BLED ≥ 3</td>
<td>221 (17.1)</td>
<td>34 (20.5)</td>
<td>0.283</td>
<td>82 (15.1)</td>
<td>18 (18.8)</td>
<td>0.368</td>
</tr>
<tr>
<td>Time from AF to CE (days)</td>
<td>1118 [1715]</td>
<td>1173 [1353]</td>
<td>0.580</td>
<td>1107 [1609]</td>
<td>1174</td>
<td>0.681</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>67 [29]</td>
<td>76 [35]</td>
<td>0.001</td>
<td>68 [28]</td>
<td>80 [37]</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR subgroups</td>
<td></td>
<td></td>
<td>0.014</td>
<td></td>
<td></td>
<td>0.066</td>
</tr>
<tr>
<td>&gt;60</td>
<td>783 (51.8)</td>
<td>121 (73.3)</td>
<td>350 (65.3)</td>
<td>73 (76.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-60</td>
<td>441 (34.8)</td>
<td>39 (23.6)</td>
<td>171 (31.9)</td>
<td>19 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>44 (3.5)</td>
<td>5 (3.0)</td>
<td>15 (2.8)</td>
<td>3 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>135 (19)</td>
<td>137 (16)</td>
<td>0.254</td>
<td>135 (18)</td>
<td>139 (16)</td>
<td>0.264</td>
</tr>
<tr>
<td>INR</td>
<td>2.0 [0.9]</td>
<td>2.7 [1.0]</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR 2.0-3.0*</td>
<td>553 (43.4)</td>
<td>96 (58.2)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR &lt; 2.0**</td>
<td>608 (47.8)</td>
<td>16 (9.7)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR &gt;3.0 ***</td>
<td>109 (8.6)</td>
<td>53 (32.1)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>1284 (99.5)</td>
<td>167 (100)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>6 (0.5)</td>
<td>0 (0)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>122 (9.5)</td>
<td>23 (13.8)</td>
<td>0.080</td>
<td>55 (10.1)</td>
<td>12 (12.5)</td>
<td>0.488</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>13 (1.0)</td>
<td>2 (1.2)</td>
<td>0.687</td>
<td>6 (1.1)</td>
<td>1 (1.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>26 (2.0)</td>
<td>0 (0)</td>
<td>0.064</td>
<td>13 (2.4)</td>
<td>0 (0)</td>
<td>0.234</td>
</tr>
<tr>
<td>SSRIs</td>
<td>37 (2.9)</td>
<td>7 (4.2)</td>
<td>0.569</td>
<td>15 (2.8)</td>
<td>4 (4.2)</td>
<td>0.700</td>
</tr>
</tbody>
</table>

The values denote mean ± SD, median [IQR] or n (%). AF, atrial fibrillation; CE, cerebral event; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischaemic attack; ICH, intracerebral haemorrhage.

* = 2.5-3.5, ** = < 2.5 *** = > 3.5 in patients with mechanical prosthetic valve.
Table 9. Multivariable analysis of the risk factors associated with ischaemic stroke/TIA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort (n=1457)</th>
<th>INR within therapeutic range (n=649)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%-CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.30 (1.39-3.81)</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment for hypercholesterolemia</td>
<td>1.94 (1.30-2.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR &lt;60 (ml/min./1.73m²)</td>
<td>1.86 (1.23-2.80)</td>
<td>0.003</td>
</tr>
<tr>
<td>INR</td>
<td>0.40 (0.33-0.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical valve prosthesis</td>
<td>4.41 (1.32-14.7)</td>
<td>0.016</td>
</tr>
<tr>
<td>Other vascular disease</td>
<td>1.60 (0.72-3.55)</td>
<td>0.248</td>
</tr>
<tr>
<td>Bleeding history</td>
<td>0.54 (0.25-1.17)</td>
<td>0.118</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>0.52 (0.30-0.91)</td>
<td>0.022</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7.02 (0.43-115.7)</td>
<td>0.998</td>
</tr>
</tbody>
</table>

TIA, transient ischaemic attack; ICH, intracerebral haemorrhage; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug.

5.3 Traumatic and spontaneous intracranial haemorrhage in patients with atrial fibrillation and warfarin therapy (III)

In study III, 592 AF patients suffering an intracranial haemorrhage during OAC were evaluated. AF diagnoses had been set before the index intracranial haemorrhage (Figure 7).
A total of 234 patients (40%) experienced a traumatic bleeding whereas in 358 (60%) of these bleedings, the cause was spontaneous. Approximately every second haemorrhage occurred when the subject’s INR value was within the therapeutic range in both study groups (traumatic 47% vs. spontaneous 50%, p=0.34, Table 10). The majority of the traumatic haemorrhages were SDHs (64%) and most of the spontaneous haemorrhages were ICHs (67%) (Figure 8). The CHA2DS2-VASc and HAS-BLED scores and INR values were similar between the groups (Table 10). Patients with traumatic haemorrhage were older, had more often congestive heart failure and anemia (Hb< 100 g/L) than patients with spontaneous haemorrhage. Patients with a spontaneous haemorrhage had a higher 30-day mortality than those with traumatic haemorrhage (36% vs. 25%, p<0.01, Figure 9). The difference remained in the multivariate logistic regression analysis, which included anemia and the CHA2DS2-VASc score as covariates (OR 1.84, 95%-CI 1.25-2.72, p=0.002).

Figure 8. Types of intracranial haemorrhage. SAH, subarachnoidal haemorrhage; ICH, intracerebral haemorrhage; SDH, subdural haemorrhage. Reproduced from Study III (with the permission of Wolters Kluwer).
Table 10. Demographic characteristics of patients with traumatic and spontaneous intracranial haemorrhage.

<table>
<thead>
<tr>
<th></th>
<th>Traumatic n=234</th>
<th>Spontaneous n=358</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-75 years, n (%)</td>
<td>98 (27)</td>
<td>98 (27)</td>
<td>0.10</td>
</tr>
<tr>
<td>&gt;75 years, n (%)</td>
<td>172 (74)</td>
<td>227 (63)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>96 (41)</td>
<td>1 (42)</td>
<td>0.78</td>
</tr>
<tr>
<td>Treatment for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>162 (69)</td>
<td>243 (68)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>54 (23)</td>
<td>82 (23)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>92 (40)</td>
<td>118 (33)</td>
<td>0.12</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
<td>95 (41)</td>
<td>148 (41)</td>
<td>0.86</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>41 (18)</td>
<td>59 (17)</td>
<td>0.74</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>83 (36)</td>
<td>131 (37)</td>
<td>0.79</td>
</tr>
<tr>
<td>Other vascular disease, n (%)</td>
<td>21 (9)</td>
<td>19 (5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous ischaemic CE, n (%)</td>
<td>58 (25)</td>
<td>97 (27)</td>
<td>0.55</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>70 (30)</td>
<td>58 (16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Permanent AF, n (%)</td>
<td>173 (74)</td>
<td>248 (69)</td>
<td>0.63</td>
</tr>
<tr>
<td>Bleeding history, n (%)</td>
<td>22 (9)</td>
<td>22 (6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Anemia (Hb&lt;100 g/L), n (%)</td>
<td>15 (7)</td>
<td>10 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>127 (20)</td>
<td>136 (18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alcohol abuse, n (%)</td>
<td>8 (4)</td>
<td>17 (5)</td>
<td>0.47</td>
</tr>
<tr>
<td>CHA2DS2-VASc score ≥2, n (%)</td>
<td>222 (95)</td>
<td>339 (95)</td>
<td>0.92</td>
</tr>
<tr>
<td>Modified HAS-BLED score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>score ≥3, n (%)</td>
<td>98 (42)</td>
<td>130 (36)</td>
<td>0.17</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60, n (%)</td>
<td>74 (32)</td>
<td>109 (30)</td>
<td>0.76</td>
</tr>
<tr>
<td>&lt;30, n (%)</td>
<td>19 (8)</td>
<td>17 (5)</td>
<td>0.09</td>
</tr>
<tr>
<td>INR on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.7 [1.3]</td>
<td>2.7 [1.1]</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>INR 2.0-3.0, n (%)</td>
<td>110 (47)</td>
<td>179 (50)</td>
<td>0.34</td>
</tr>
<tr>
<td>INR &lt;2.0, n (%)</td>
<td>38 (16)</td>
<td>57 (16)</td>
<td>0.37</td>
</tr>
<tr>
<td>INR &gt;3.0, n (%)</td>
<td>76 (33)</td>
<td>113 (32)</td>
<td>0.34</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>35 (15)</td>
<td>59 (17)</td>
<td>0.64</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>4 (2)</td>
<td>7 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>NSAID, n (%)</td>
<td>4 (2)</td>
<td>5 (1)</td>
<td>0.74</td>
</tr>
<tr>
<td>SSRI</td>
<td>13 (6)</td>
<td>18 (5)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

The values denote mean ± SD, median [IQR] or n (%). TIA, transient ischaemic attack; AF, atrial fibrillation; CE, cerebral event; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; INR, international normalized ratio; NSAID, non-steroidal anti-inflammatory agent; SSRI, selective serotonin reuptake inhibitor.
Figure 9. 30-day mortality in patients with either a traumatic or a spontaneous haemorrhage. Reproduced from Study III (with the permission of Wolters Kluwer).
6 Discussion

6.1 Stroke recurrence in anticoagulated patients with atrial fibrillation and concomitant carotid artery stenosis (I)

The main result in Study I was that AF patients with both a stroke and concomitant carotid artery stenosis had a doubled risk of stroke recurrence during long-term follow-up, and a 4-fold elevated risk of 30-day mortality, compared to patients without CAS, despite similar anticoagulation and INR values at the time of recurrence.

There are many reasons for the high stroke recurrence in patients with AF and CAS. For example, the CAS patients were older than their non-CAS counterparts, a finding which is in line with previous studies (Chang et al., 2002, Kanter et al., 1994, Kochar et al., 2018). It is recognized that the prevalence of CAS increases with age; CAS is found in 8% of asymptomatic patients over 60 years of age (Mineva et al., 2002) and in 12% of AF patients over 70 years of old (Kanter et al., 1994). However, in addition to age, CAS was also an independent predictor of stroke recurrence. In our study, CAS patients had more cardiovascular comorbidities such as hypertension, hypercholesterolemia, coronary artery disease, peripheral artery disease, diabetes, permanent AF, and therefore higher CHA2DS2-VASc scores. Similar findings were reported by Kochar et al. (2018), where their CAS patients also more often suffered from several comorbidities, such as lower eGFR, peripheral artery disease, prior stroke and myocardial infarction and higher CHADS2 than patients without CAS. CAS has been shown to be independently associated with tobacco use (RR 1.2), diabetes (RR 1.8) and hypertension (RR 2.4) in patients with AF (Kanter et al., 1994).

There are conflicting results about the role of CAS in stroke recurrence in patients with AF. In the study of Chang et al. (2002), AF patients with concomitant CAS had more often suffered a stroke compared to patients without CAS (48.0% vs. 23.1%). In contrast to our results, in the ROCKET-AF substudy after adjustment for baseline factors, CAS was not related to higher stroke/systemic thromboembolism or mortality in AF patients in those patients being treated with either VKA or rivaroxaban (Kochar et al., 2018). In our study, although CAS patients were older and had more comorbidities, CAS remained an independent risk factor for stroke recurrence after adjustment for the confounding risk factors known to be related to AF-related cardioembolism.

Our CAS patients had more often a history of hypercholesterolemia, peripheral and coronary artery disease than the non-CAS patients. This reflects the more severe atherosclerotic disease in CAS patients than in non-CAS patients, which may be one aetiological factor for stroke and
stroke recurrence in addition to AF. A greater atherosclerotic disease burden in CAS patients with stroke has also been described previously (Kochar et al., 2018). CAS and AF are two concomitant diseases, but they need different treatments, since stroke can be either due to thromboembolic or atherosclerotic origin in these patients.

OAC is a well-established treatment to prevent AF related ischaemic strokes (Hart et al., 2007). In strokes where the aetiological subtype is defined as unknown, e.g. where two possible aetiologies exist simultaneously, the optimal antithrombotic treatment is not so well documented. In our study, CAS patients had a 2-fold greater risk for stroke recurrence when compared to non-CAS patients despite similar OAC treatments and INR values at the onset of recurrent stroke. Several studies have shown that with respect to the secondary prevention of non-cardioembolic stroke, OAC is not superior to antiplatelet treatment (ESPRIT Study Group et al., 2007, Hart et al., 2000, Hart et al., 2018, Mohr et al., 2001). Previously, Kanter et al. (1994) followed a small population of 583 AF patients for 2.6 years, all of whom had undergone carotid ultrasonography and 12 % of these patients had concomitant CAS. CAS was associated with a higher occurrence of stroke (2-fold) despite OAC or antiplatelet treatment after age-adjustment (7 (10%) vs. 27 (5%), Kanter et al., 1994). When adjusted with all other known stroke risk factors (hypertension, age, diabetes and congestive heart failure) and antithrombotic treatment, CAS was no longer a predictor of stroke in AF patients who had not suffered a previous ischaemic stroke. The number of strokes was small (n=34) in this study and further conclusions cannot be drawn. Our study suggests that OAC treatment is not sufficiently effective to prevent ischaemic strokes in AF patients with CAS in contrast to the situation in patients with non-CAS.

In our study, carotid endarterectomy did not influence the stroke recurrence in CAS patients. On the other hand, carotid endarterectomy was performed only in 28% of CAS patients and our study did not have a randomized design. In the study of Kochar et al. (2018), they reported a similar rate of carotid endarterectomy/stenting (35%).

Our study and a few previous studies (Chang et al., 2002, Kanter et al., 1994) most commonly suggest that CAS is related to an increased risk of stroke recurrence and a higher mortality in AF patients despite the provision of antithrombotic treatment. Carotid artery stenosis should be investigated in AF patients with ischaemic stroke and in addition to the stroke risk factors, and the risk factors for atherosclerosis e.g. hypercholesterolemia and hypertension, should be treated. Larger studies will be needed examining this subgroup in order to obtain the optimal strategy for antithrombotic treatment.
6.2 Clinical characteristics and risk profiles in AF patients with ischaemic stroke or intracerebral haemorrhage on OAC (II)

Study II revealed that anticoagulated patients with their first lifetime ischaemic stroke/TIA and ICH did not differ with regards to age and hypertension. However, in the whole study population, congestive heart failure, hypercholesterolemia, renal failure and mechanical valve prosthesis were more associated with ischaemic stroke than with ICH, whereas concomitant aspirin use and higher INR were related to ICH. The admission INR levels were similar between the groups with approximately 50% of strokes occurring in those subjects with therapeutic INR values in both groups.

When the analysis was restricted to the subgroup of patients with therapeutic INR values, the ischaemic stroke/TIA patients more often were suffering from congestive heart failure and hypercholesterolemia than patients experiencing an ICH. The ICH patients had more often a previous bleeding history than ischaemic stroke/TIA patients. The CHA2DS2-VASc. and HAS-BLED risk scores were similar between groups with therapeutic INR values.

Congestive heart failure is a well-known risk factor for ischaemic stroke in patients with AF, with and without OAC (Lip et al., 2010). In patients with congestive heart failure, a low cardiac output and decelerated blood flow, endothelial dysfunction, and abnormalities in haemostasis contribute to a hypercoagulable state, which elevates the AF-related risk of thrombosis and ischaemic stroke (Jaffri, 1997). The over-representation of hypercholesterolemia in patients with ischaemic stroke suggests that the stroke aetiology is often more likely to have an atherosclerotic origin rather than a thrombotic source. A history of cardiovascular disease (myocardial infarction, coronary artery bypass grafting, percutaneous intervention or peripheral artery disease) increases the risk of ischaemic cerebral event rather than the risk of ICH in AF patients during OAC (McGrath et al., 2012). In contrast to our study, McGrath et al. (2012) did not report the rate of hypercholesterolemia and included also patients with a previous ischaemic stroke. In our study, other atherosclerotic diseases, such as coronary artery disease, were not associated with either stroke subtype.

We observed that a lower eGFR value was associated with ischaemic stroke/TIA rather than with ICH, but there was no difference in the multivariate analysis if only patients with therapeutic INR were included. Renal failure has been reported to increase the risk for both ischaemic stroke and major bleeding events, although it is included only in the HAS-BLED score but not in the CHA2DS2-VASc. score (Bonde et al., 2014, Lip et al., 2010, Pisters et al., 2010). Patients with end-state renal disease have often been excluded from RCTs. In the ROCKET-AF substudy, renal failure (CrCl <60 mL/min) was a strong predictor for systemic thromboembolism and stroke (Piccini et al., 2013). VKA was associated with a lower rate of thromboembolic events in patients with eGFR >15 mL/min/1.73 m² but on the other hand, with a
higher bleeding risk in all eGFR groups in comparison to patients not receiving VKA therapy (Bonde 2016). In a meta-analysis of AF patients with non-end state renal disease, VKA decreased the risk of thromboembolism/ischaemic stroke (HR 0.70) and mortality (HR 0.64) but increased the risk of major bleeding (HR 1.30) as compared to patients not being administered VKA therapy. In end-state renal disease, VKA therapy had no effect on the risk of stroke or mortality (Dahal et al., 2016).

A bleeding history has been reported to be a significant risk factor for ICH and other major bleeding in patients with AF during OAC (Gallego et al., 2012, Roldan et al., 2013b, Shireman et al., 2004). A high INR (>3.5) value increases the risk of ICH by 3- to 5-fold (Fang et al., 2004, Hylek et al., 2003). In our study, high INR levels on admission were more likely to be associated with ICH than with an ischaemic event, and if only patients with therapeutic INR values were analyzed, then a bleeding history was overrepresented in ICH group. It is known that concomitant use of aspirin and OAC increases the risk of a major bleeding by 1.5-1.8-fold and an ICH occurrence by 3-fold as compared to OAC alone (Hansen et al., 2010, Hart et al., 2012, Lopes et al., 2017, Shireman et al., 2004). The use of aspirin was relatively rare in our study, but in the multivariate analysis, aspirin use was more associated with ICH than with ischaemic events in the whole cohort, but not in patients with therapeutic INR levels.

In our study, the proportion of patients with the CHA2DS2-VASc score ≥2 as well as a HAS-BLED score ≥3 were not different between patients with ischaemic stroke or those with intracerebral haemorrhage. This is in line with the results of a large Danish cohort of AF patients (n=58 815), in which all patients were receiving VKA (Nielsen et al., 2015). In the study of Nielsen et al. (2015), the proportion of patients with CHA2DS2-VASc score ≥2 (68.7% vs. 74.5%) and HAS-BLED >3 (20.2 vs. 22.4%) did not differ between those patients experiencing an intracranial haemorrhage and those without a haemorrhage. The study of Nielsen et al. and our study underlines the problems of the current risk scores in differentiating the AF patients at risk of ischaemic stroke from those at risk of suffering an intracranial haemorrhage during OAC.

6.3 Traumatic and spontaneous intracranial haemorrhage in patients with atrial fibrillation and warfarin therapy (III)

In Study III, we showed that in VKA treated AF patients, 40% of the intracranial haemorrhages were traumatic with the remaining 60% being spontaneous. Approximately every other haemorrhage occurred in a patient with a therapeutic INR value in both study groups. The majority of traumatic haemorrhages were SDHs whereas spontaneous haemorrhages consisted mostly ICHs. Patients with traumatic haemorrhage were older and more often had anemia and congestive heart failure than patients with a spontaneous haemorrhage. The 30-day mortality
was lower in patients experiencing a traumatic haemorrhage than in those suffering a spontaneous haemorrhage.

Our findings, that a large proportion of VKA related haemorrhages were traumatic (40%), and two thirds of both traumatic and spontaneous haemorrhages occurred in patients with INR ≤3.0, are well in line with previous studies. The ARISTOTLE trial reported that 29% of intracranial haemorrhages were traumatic and 79% of all intracranial haemorrhages occurred in patients with INR ≤3.0 (Lopes et al., 2017). In the RE-LY and ROCK-ETF-AF trials, the proportion of traumatic haemorrhages was lower (11% and 7%), but they only included ICHs (Hankey et al., 2014, Hart et al., 2012). In RCT trials, the incidence of intracranial haemorrhages in patients with moderately controlled VKA (TTR 55-68%) was much higher than in patients on DOACs (0.70-0.85%/y vs. 0.30%/y) (Giugliano et al., 2013, Granger et al., 2011, Hart et al., 2012, Patel et al., 2011). In our study, most of the traumatic haemorrhages were subdural (64%) and most of the spontaneous haemorrhages were ICHs (67%), which corresponds with previous studies (Hankey et al. 2014, Hart et al., 2012, Lopes et al., 2017). A rather notable proportion of intracranial haemorrhages, both traumatic and spontaneous during VKA, occur within therapeutic INR. This reflects the fact that the current risk scores for a major bleeding event probably do not seem to recognize well some risk factors, which would help in the avoidance of intracranial haemorrhages in patients being treated with VKA, with our results pointing in a similar direction.

In our study, patients with traumatic haemorrhage were older and had more often anemia and congestive heart failure than patients experiencing a spontaneous haemorrhage. One explanation might be that older people have a higher risk for falls (Steffel et al., 2016). Balance problems, e.g. orthostatic hypotension, are related to age (Ricci et al., 2015). Heart failure has also been associated with a higher risk for falls and therefore this predisposes these patients to traumatic haemorrhages (Jansen et al., 2016). Conflicting results exist on falls and the risk for major bleeding in AF patients on OAC therapy. In most DOAC trials, falls have not been related to ICH (Giugliano et al., 2013, Hankey et al., 2014, Hart et al., 2012, Lopes et al., 2017). Only in the ENGAGE-AF TIMI 48 trial, was it noted that AF patients with an increased risk for falls had more major bleeding events (HR 1.30) and a higher risk for death (HR 1.67) during OAC (Steffel et al., 2016). Polypharmacy (HR 1.15) is reported to be a risk factor for severe bleeding in patients with VKA therapy, but the estimated high risk for falls was not associated with major bleeding events (Donze et al., 2016).

Elderly AF patients often have an increased risk for bleeding but at the same time an increased risk for thromboembolic events. Thus, age should not be the only reason for OAC withdrawal. Gage et al. (2012) evaluated AF patients who were anticipated to be likely to experience falls; they observed that the risk for thromboembolic event was elevated by 4.9 fold as compared to
risk for ICH. It is often challenging to find the correct balance between the risk of ischaemic stroke and bleeding events. Similarly, in our FibStroke study, both CHA2DS2-VASc and HAS-BLED scores were high in those patients suffering thromboembolic events as well as in patients with intracranial haemorrhage, but the median CHA2DS2-VASc score was higher than the median HAS-BLED score. This indicates that usually the risk for a thromboembolic event exceeds the risk for a major bleeding episode. Our study emphasizes that the HAS-BLED score is not capable of recognizing patients at risk of suffering an intracranial haemorrhage and it is not therefore recommended to use this score for deciding whether or not to withdraw OAC. It should be used to identify all modifiable bleeding risk factors to decrease the bleeding risk (untreated hypertension, concomitant use of other antithrombotic/NSAID/SSRI medication) (Kirchhof et al., 2017).

The 30-day mortality after intracranial haemorrhage during OAC has been reported to be high, 33-42% (Giugliano et al., 2013, Hart et al., 2012, Hankey et al., 2014, Lopes et al., 2017, Nielsen et al., 2015). In our study, mortality was of the same magnitude (32%). It is noteworthy that the mortality in our study was lower in patients with traumatic haemorrhage than in patients with spontaneous haemorrhage (25% vs. 36%). This is in line with the report of Hart et al. (2012) that mortality was 21% in patients experiencing a traumatic intracerebral haemorrhage vs. 41% in those patients who suffered a spontaneous intracerebral haemorrhage. The mortality associated with intracranial haemorrhage has remained high, whether or not the patient is receiving VKA or DOAC (Wilson et al., 2017).

Our study indicates that in half of the AF patients, intracranial haemorrhages during VKA occur in subjects with therapeutic INR values and although mortality in traumatic haemorrhages is lower than in their spontaneous counterparts, these conditions still constitute a significant source of mortality related to intracranial haemorrhages during VKA.

### 6.4 Limitations

One of the main limitations in our FibStroke study is its retrospective nature. Some relevant information, such as GCS and clinical outcome of stroke, could not be assessed reliably from patient records. Another significant limitation is that we only had data from AF patients who were hospitalized because of a cerebral event (ischaemic stroke, TIA or intracranial haemorrhage) and did not have access to the data from AF patients who did not suffer a cerebral event during the follow-up time.

Finally, we did not have reliable data on the INR values preceding the index stroke and we were only able to collect admission INR levels. We were unaware of the subjects’ serum cholesterol levels and thus the definition of hypercholesterolemia was based on a history of hypercholesterolemia (e.g. the patient had been prescribed cholesterol-lowering drugs). Thus,
we might have missed some patients with elevated cholesterol but not taking lipid-lowering agents.

Nevertheless, the participating hospitals treat all of the patients with stroke/TIA and intracranial haemorrhages in their catchment area indicating that there was excellent coverage of the clinical parameters. The data was collected from multiple sources (e.g. hospital database, individually from electronic patient records) and study personnel were given structured instructions about their interpretation.
7 Conclusions

(I) Carotid artery stenosis doubles the risk of stroke recurrence in anticoagulated patients with AF and also the 30-day mortality is higher in these patients than in their counterparts with AF alone. AF patients with concomitant carotid artery stenosis were older and suffered more comorbidities than AF patients without carotid artery stenosis.

(II) Congestive heart failure and hypercholesterolemia were overrepresented in adequately anticoagulated AF patients with ischaemic stroke/TIA, whereas the bleeding history was less common when compared to ICH patients. In the whole study population, congestive heart failure, hypercholesterolemia, renal failure and mechanical valve prosthesis were related more to an ischaemic event rather than to an ICH whereas a high INR value and aspirin therapy were more associated with an ICH rather than an ischaemic event.

(III) A large proportion of intracranial haemorrhages during VKA was traumatic (40%). Most of the traumatic haemorrhages were subdural (64%) whereas most of the spontaneous haemorrhages were ICHs (67%). In both groups, approximately 2/3 of intracranial haemorrhages in patients being treated with VKA occurred when they had therapeutic INR values. In warfarin treated AF patients, a traumatic intracranial haemorrhage was associated with a lower 30-day mortality in comparison with the mortality associated with a spontaneous intracranial haemorrhage.
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Atrial fibrillation is the most common cause of cardioembolic stroke. The aim of this thesis was to explore anticoagulated patients with atrial fibrillation who suffer either ischaemic stroke or intracranial haemorrhage. The impact of concomitant carotid artery disease on stroke recurrence was studied. In addition, patients who suffer ischaemic stroke or intracerebral haemorrhage as well as patients with traumatic and spontaneous haemorrhage were compared.