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REAL-LIFE CHALLENGES OF STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION

– The FibStroke Study

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To my family

ABSTRACT

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REAL-LIFE CHALLENGES OF STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION - THE FIBSTROKE STUDY

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Background: Oral anticoagulation (OAC) significantly reduces the risk of stroke and mortality in patients with atrial fibrillation (AF). The purpose of this dissertation was to analyze stroke patients with previously diagnosed AF and to identify the circumstances predisposing these patients to cerebral thromboembolism.

Methods: The FibStroke registry includes 4311 patients with previously diagnosed AF, who suffered 3252 ischemic strokes, 956 transient ischemic attacks and 794 intracranial bleeds during 2003-2012. The data were retrospectively collected from four hospitals in Finland.

Results: 1) Almost half (49.1%) of the ischemic strokes and transient ischemic attacks occurred in patients who were not using OAC. 2) In patients with paroxysmal AF, 6.4% of the strokes occurred after cardioversion of AF. Of these strokes, 78.2% occurred after cardioversion of acute AF, while 65.4% occurred to patients who were not using OAC. 3) Postoperative ischemic strokes accounted for 6.0% of all strokes in patients with AF. Previously used OAC was interrupted for 81.2% of the operations preceding ischemic stroke. Of the postoperative intracranial bleeds, LMWH bridging was used in 54.5% of the operations. 4) Mortality during the 30 days following a stroke was significantly lower in patients with paroxysmal AF compared to patients with chronic AF (10.2% vs 20.3%).

Conclusions: A significant proportion of the strokes in patients with AF occurred in patients who had not been using OAC or who had undergone cardioversion or operation during the previous 30 days. The type of AF (paroxysmal/chronic) may be a more important prognostic marker than previously thought.

Keywords: Atrial fibrillation, stroke, anticoagulation

TIIVISTELMÄ

LL Antti Palomäki

TOSIELÄMÄN HAASTEET ETEISVÄRINÄPOTILAIDEN AIVOVERENKIERTOHÄIRIÖIDEN EHKÄISYSSÄ – FIBSTROKE-TUTKIMUS

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Tausta: Antikoagulaatihoito vähentää huomattavasti eteisvärinäpotilaiden aivoverenkiertohäiriöitä ja kuolleisuutta. Tämän väitöskirjan tavoitteena oli tutkia aivoverenkiertohäiriöön sairastuneita eteisvärinäpotilaita, ja erityisesti niitä seikkoja, jotka altistivat nämä potilaat aivoverenkiertohäiriölle.

Menetelmät: FibStroke aineisto sisältää tiedot 4311 eteisvärinää sairastavasta potilaasta, joilla todettiin yhteensä 3252 aivoinfarktia, 956 ohimenevää aivoverenkiertohäiriötä (TIA-kohtausta) ja 794 kallonsisäistä verenvuotoa vuosina 2003–2012. Aineisto kerättiin takautuvasti neljän suomalaisen sairaalan potilastietojärjestelmistä.

Tulokset: 1) Aivoinfarkteista ja TIA-kohtauksista 49,1 % ilmaantui potilaille, joilla ei ollut antikoagulaatiohoitoa käytössä. 2) Kohtauksellista eteisvärinää sairastavien potilaiden aivoinfarkteista 6,4 % ilmaantui 30 päivän kuluessa rytminsiirrosta. Näistä aivoinfarkteista 78,2 % ilmaantui akuutin eteisvärinän rytminsiirron jälkeen ja 65,4 %:lla potilaista ei ollut antikoagulaatiohoitoa ennen rytminsiirtoa. 3) Aivoinfarkteista 6,0 % ilmaantui potilaille, joille oli tehty toimenpide edeltävän 30 vuorokauden aikana. Aikaisemmin käytössä ollut antikoagulaatiohoito oli tauotettu 81,2 %:ssa aivoinfarktia edeltäneistä operaatioista. Potilailla, jotka saivat kallonsisäisen vuodon leikkauksen jälkeen, 54,5 %:lla oli käytetty varfariinihoidon tauotuksen aikana siltahoitona pienimolekylaarista hepariinia. 4) Kuolleisuus 30 päivän sisällä aivoinfarktin jälkeen oli huomattavasti matalampi kohtauksellista eteisvärinää kuin kroonista eteisvärinää sairastavilla potilailla (10,2 % vs. 20,3 %).

Päätelmät: Merkittävä osa eteisvärinää sairastavien potilaiden aivoverenkiertohäiriöistä ilmaantuu potilaille, joilla ei ole käytössä antikoagulaatiohoitoa, tai joilla on tehty viimeisen 30 vuorokauden aikana rytminsiirto tai toimenpide. Kohtauksellisen eteisvärinän ennustemerkitys saattaa olla suurempi kuin aikaisemmin on ajateltu.

Avainsanat: Eteisvärinä, aivoverenkiertohäiriö, antikoagulaatiohoito

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ABBREVIATIONS

AF	Atrial fibrillation
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, prior Stroke, transient ischemic attack or thrombo-embolism (doubled)
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category female
CI	Confidence interval
ECG	Electrocardiography
ESC	European Society of Cardiology
IQR	Inter-quartile range
LMWH	Low-molecular weight heparin
OAC	Oral anticoagulation
OR	Odds ratio
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
NOAC	Non-vitamin K antagonist oral anticoagulant
RR	Risk ratio

LIST OF ORIGINAL PUBLICATIONS

I. Palomäki A, Mustonen P, Hartikainen JE, Nuotio I, Kiviniemi T, Ylitalo A, Hartikainen P, Airaksinen KE. Underuse of anticoagulation in stroke patients with atrial fibrillation — the FibStroke Study. Eur J Neurol. 2016 Jan; 23(1): 133-9.

II. Palomäki A, Mustonen P, Hartikainen JE, Nuotio I, Kiviniemi T, Ylitalo A, Hartikainen P, Lehtola H, Luite R, Airaksinen KE. Strokes after cardioversion of atrial fibrillation—The FibStroke study. Int J Cardiol. 2016 Jan 15; 203: 269-73.

III. Palomäki A, Kiviniemi T, Hartikainen JE, Mustonen P, Ylitalo A, Nuotio I, Hartikainen P, Jaakkola J, Luite R, Airaksinen KE. Postoperative strokes and intracranial bleeds in patients with atrial fibrillation: The FibStroke Study. Clin Cardiol. 2016 Aug; 39(8): 471-6.

IV. Palomäki A, Kiviniemi T, Mustonen P, Odei C, Hartikainen JE, Nuotio I, Ylitalo A, Hartikainen P, Biancari F, Airaksinen KE. Mortality after stroke in patients with paroxysmal and chronic atrial fibrillation—The FibStroke study. Int J Cardiol. 2017 Jan 15; 227: 869-74

1 INTRODUCTION

Patients with atrial fibrillation (AF) have a significantly increased risk of ischemic stroke compared to the general population. In numerous studies, treatment with oral anticoagulation (OAC) has been shown to dramatically decrease this risk and thus improve the prognosis of these patients. Prevention of stroke has been widely accepted as one of the key goals in the treatment of patients with AF.

The modern approach to stroke prevention is based on the systematic evaluation of stroke risk. Current guidelines recommend OAC for all patients who do not have a truly low risk of stroke according to risk stratification. For decades, the cornerstone of OAC treatment has been warfarin. While warfarin is efficacious in stroke prevention, it has certain well-known problems limiting its use, including the need for blood test monitoring, narrow therapeutic range, slow onset and offset of action, numerous food and drug interactions and increased risk of bleeding. While the approach to anticoagulation is very straightforward in the clinical guidelines, the real-life scenarios are often far more complicated. Numerous patient characteristics, co-morbidities and even personal preferences affect the clinicians' and patients' inclination to start and maintain anticoagulation treatment.

Most often, AF begins with short paroxysms, which over time become longer and more resilient, until eventually the ability to maintain sinus rhythm is lost and the patient develops chronic AF. It has long been debated whether the risk of stroke is similar in patients with paroxysmal and chronic AF. Data are limited regarding the differences and prognosis of ischemic strokes in these patients.

Restoring sinus rhythm with cardioversion is an effective treatment in patients who have not yet developed chronic AF but have symptomatic persistent AF paroxysms. While this treatment is efficacious, it is known to temporarily increase the risk of thromboembolism. Recent studies have increased our knowledge about estimating this risk, but surprisingly little is known about the characteristics and quantity of cardioversion-related strokes in these patients.

Invasive procedures in patients using OAC carry an inherent dilemma: Continuing OAC increases the risk of perioperative bleeding, while discontinuing OAC exposes the patient to thromboembolism. Replacing warfarin temporarily with short acting low-molecular weight heparins (LMWH) has not solved this problem despite the theoretical benefits.

In the FibStroke study, we identified all ischemic strokes, transient ischemic attacks and intracranial bleeds that occurred in patients with AF during 2003-2012. The data were collected from four major hospitals in Finland. With thorough col-

lection of data on the patient characteristics, preceding circumstances, co-morbidities, antithrombotic medications, cardioversions and invasive procedures, we aimed to identify the high-risk situations preceding the cerebral events in these patients.

By knowing the most important reasons leading to stroke in these patients, we can focus our clinical efforts in the right direction and ultimately improve patient care and outcomes.

2 REVIEW OF LITERATURE

2.1 Epidemiology and impact of atrial fibrillation

Atrial fibrillation is a common cardiac arrhythmia affecting a large proportion of the population. It has been estimated that the prevalence of AF is approximately 3% in adult populations (Bjorck et al., 2013; Haim et al., 2015). The prevalence increases sharply with increasing age. In an Italian population, the prevalence rates were 4.2% in the age group of 65-74 years, 9.4% in the age group of 75-84 years and 17% in the age group of 85 years or older (Bilato et al., 2009). The lifetime risk for development of AF is approximately 25% in men and women of 40 years of age and older (Lloyd-Jones et al., 2004).

It is worth noticing that a significant proportion of AF in the population is undiagnosed or subclinical. Paroxysmal AF can be difficult to diagnose using the standard 12-lead ECG-recordings if the paroxysms are rare or short-lasting. On the other hand, AF can be asymptomatic or "silent". The prevalence of subclinical or silent AF has varied in previous studies depending on the method of screening. In a Swedish study of 75-year old population, previously undiagnosed subclinical AF was found in 4.7% of the population with stepwise screening procedure using standard 12-lead ECG and handheld-ECG event recordings, bringing the total prevalence of AF to 14% (Engdahl et al., 2013). In patients over 65 years with a recently implanted pacemaker or defibrillator and with no previous history of AF, the prevalence of silent atrial tachyarrhythmias was 10.1% in 3 months (Healey et al., 2012b).

Although considered to be a relatively benign condition, AF is associated with serious complications and increased mortality. Increased risk of ischemic stroke is well-known and is discussed in more detail in the following chapters. In addition to the increased risk of thromboembolism, patients with AF have increased all-cause mortality, increased risk of heart failure and decreased quality of life, as well as an increased demand for health care services, including frequent hospitalizations (Kirchhof et al., 2016). In a meta-analysis of 104 studies involving 9,686,513 participants, the relative risk (95% confidence interval (CI)) for all-cause mortality was 1.46 (1.39-1.54); for cardiovascular mortality, 2.03 (1.79-2.30); for stroke, 2.42 (2.17-2.71); for sudden cardiac death, 1.88 (1.36-2.60); for heart failure, 4.99 (3.04-8.22); and for chronic kidney disease, 1.64 (1.41-1.91) (Odutayo et al., 2016). Additionally, AF has been associated with an increased risk for dementia (de Bruijn, Renée F A G et al., 2015).

2.2 Atrial fibrillation as a risk factor for stroke

The increased risk of stroke in patients with AF is well recognized. Many of the data confirming the independent role of atrial fibrillation as a risk factor for stroke have come from the Framingham study. In a much-cited study of 5209 men and women from Framingham who were followed up for 34 years, the risk of stroke was found to be 4.8 times higher in patients with AF (Wolf et al., 1991). The Renfrew/Paisley Study, with a cohort of 15,406 persons who were followed up for 20 years, demonstrated a 3.2-fold risk of stroke for women and 2.5-fold risk of stroke for men associated with the presence of AF (Stewart et al., 2002).

In placebo-controlled trials of stroke prevention in patients with AF, the yearly stroke rate in the patients assigned to a placebo was 13% in patients with a previous stroke or TIA and 4.1% in patients without previous ischemic event (Hart et al., 2007). The prevalence of atrial fibrillation is high among stroke patients but is also highly age-dependent. In a study from a Canadian stroke network with 10,528 patients, the prevalence of AF was 26% in all patients with stroke, but the prevalence rose from 1.9% in patients less than 40 years of age to 46% in patients over 90 years of age (McGrath et al., 2013). In a Swedish registry, AF was diagnosed in 38% of patients with ischemic stroke, with the prevalence rising from 0% in patients under 40 years of age to more than 50% in patients over 90 years of age (Bjorck et al., 2013). Strokes in patients with AF are also associated with higher mortality and disability than strokes in patients without AF (McGrath et al., 2013; Wolf et al., 1998).

2.2.1 Assessment of stroke risk, $CHADS_2$ and CHA_2DS_2-VASc score

The stroke risk among patients with AF is not uniform; rather, it is highly influenced by other risk factors. To guide clinicians in their treatment decisions, various methods for estimating the risk of stroke have been proposed (Fang et al., 2008). The $CHADS_2$-score was published in 2001(Gage et al., 2001) and was subsequently adopted in the clinical guidelines (Fuster et al., 2006; European Heart Rhythm Association et al., 2010). The score calculation is depicted in Table 1. The original study cohort consisted of 1733 patients with AF who suffered 94 ischemic strokes during a follow-up period of a minimum of 365 days. Using the $CHADS_2$ score, the annual risk of stroke could be stratified from 1.9% to 18.2% (Table 2).

While it was easy to detect high-risk patients using the $CHADS_2$ score, the score was not accurate enough in the low- and intermediate-risk patients to guide clini-

cal decision making. Even patients with 0 or 1 points could have a significant risk of stroke (Olesen et al., 2012). A more thorough scoring system, the CHA_2DS_2-VASc score, was published in 2010 (Lip et al., 2010b), with data derived from the Euro Heart Survey for AF. Score calculation is depicted in Table 1, and the stroke risk with the CHA_2DS_2-VASc score is depicted in Table 2. The new score was more clinically useful than the previous scores and quickly became the recommended approach to stroke risk estimation also in the clinical guidelines (Camm et al., 2012; January et al., 2014).

Measurement of biomarkers such as cardiac troponins and N-terminal fragment B-type natriuretic peptide (NT-proBNP) could help to increase the accuracy of stroke risk prediction in the future (Hijazi et al., 2016; Ruff et al., 2016).

Table 1 Calculation of $CHADS_2$ and CHA_2DS_2-VASc score

Risk factor	***$CHADS_2$ points***	***CHA_2DS_2-VASc points***
Congestive heart failure	1	1
Hypertension	1	1
Age 75 years or older	1	2
Diabetes	1	1
History of **S**troke or TIA	2	2
Vascular disease		1
Age 65-74 years		1
Sex **c**ategory, female		1
Maximum score	6	9

Modified from (Gage et al., 2001; Lip et al., 2010b).

Table 2 Adjusted stroke rate according to $CHADS_2$ and CHA_2DS_2-VASc score

$CHADS_2$	***Adjusted stroke rate (%/year)***
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

CHA_2DS_2-VASc	***Adjusted stroke rate (%/year)***
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Modified from (Gage et al., 2001; Lip et al., 2010a).

2.2.2 Assessment of bleeding risk

Prevention of thromboembolism with OAC is associated with an increased risk of bleeding. Intracranial bleeding is the most catastrophic form, associated with high mortality and disability (Fang et al., 2007). In the ATRIA cohort, the incidence of intracranial hemorrhage was 0.46/100 person years in patients using warfarin compared to 0.23/100 person years in patients without warfarin; still, however, all-cause mortality was 31% lower in patients using warfarin, owing to a 51% reduction in ischemic strokes (Go et al., 2003). In the large anticoagulation trials, the risk of intracranial bleeding in the warfarin arm has been 0.7-0.8 events/100 person years (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011). It has been estimated that, on average, warfarin increases the risk of intracranial hemorrhage by 0.2% per year (Schulman et al., 2008).

Scoring systems have been developed to estimate the risk of bleeding. The most widely clinically adopted of these is the HAS-BLED score published in 2010, with data based on the Euro Heart Survey of 3,978 patients, who suffered 53 major bleeds during the study (Pisters et al., 2010). Because of the practicality of the score, it was adopted in the 2010 ESC guideline, stating that three points or higher indicates "high risk" of bleeding (European Heart Rhythm Association et al., 2010). The HAS-BLED score is depicted in Table 3.

Table 3 The HAS-BLED score

Risk factor	***HAS-BLED Points***
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

Modified from (Pisters et al., 2010).

As seen from the scoring system, the risk factors for stroke and bleeding overlap (hypertension, previous stroke, age), and patients with a high HAS-BLED score usually have a high risk of thromboembolism as well. In previous studies, the risk of ischemic stroke has been significantly higher than the risk of intracranial bleeding in almost all patients with AF, including patients with a high HAS-BLED score (Friberg et al., 2012). Also, in a study comparing 391 patients with an intracranial bleed and 2806 patients with an ischemic stroke, there was no difference in the HAS-BLED scores (McGrath et al., 2012). These data imply that

the HAS-BLED score is not accurate enough to identify those patients with AF who would not benefit from OAC. Hence, the modern guidelines state that bleeding risk scores should not be used to withhold OAC from a patient but, rather, to identify potentially modifiable risk factors (Camm et al., 2012; Kirchhof et al., 2016).

2.3 Reducing the risk of stroke

2.3.1 Oral anticoagulation

Prevention of cardiogenic thromboembolism with OAC has been found in numerous studies to be the most effective intervention in reducing mortality and morbidity in patients with AF. For decades, the only viable option for long-term anticoagulation has been warfarin, which inhibits the action of vitamin K in the clotting factor synthesis in the liver. International normalized ratio (INR) is the laboratory test used to monitor the effect of warfarin on blood clotting. Since excessive anticoagulation leads to increased risk of bleeding, the optimal level of anticoagulation is essential for good outcomes. The optimal range for efficacy and safety seems to be an INR level between 2 and 3 in patients without mechanical valve or mitral stenosis (Hylek et al., 2003). This is also the target INR level recommended by clinical guidelines to patients with non-valvular AF (Culebras et al., 2014; European Heart Rhythm Association et al., 2010; Kirchhof et al., 2016).

The efficacy of warfarin in reducing ischemic strokes has been demonstrated in numerous clinical trials. A comprehensive meta-analysis published in 2007 included 29 clinical trials published so far comparing warfarin with placebo, warfarin with antiplatelet agents, and antiplatelet agents with placebo (Hart et al., 2007). The results were convincing: Compared to placebo, warfarin reduced ischemic stroke risk by 64% (95% CI 49%-74%) and all-cause mortality by 26% (95% CI 3%-43%). Strokes that occur during effective warfarin therapy are less often lethal and lead to less disability than strokes that occur in patients without OAC, or in whom the INR is at a subtherapeutic level (Hylek et al., 2003; O'Donnell et al., 2006).

Novel agents for replacing warfarin have long been sought. Direct thrombin inhibitor ximelagatran seemed to have similar efficiency for stroke prevention than warfarin, but unfortunately was found to be hepatotoxic (Diener, 2006). Since then, four new oral agents have been approved for stroke prevention in patients with non-valvular AF: one direct thrombin inhibitor—dabigatran (Connolly et

al., 2009)—and three clotting factor Xa inhibitors—rivaroxaban (Patel et al., 2011), apixaban (Granger et al., 2011) and edoxaban (Giugliano et al., 2013). Collectively, these new agents have been called "novel oral anticoagulants", "direct oral anticoagulants", "target-specific oral anticoagulants" or "non-vitamin K antagonist oral anticoagulants (NOAC)". The acronym NOAC seems to be the term most widely adopted and used in the European guidelines (Camm et al., 2012; Kirchhof et al., 2016). In the meta-analysis of the clinical trials, NOAC therapy, compared to warfarin, reduced the risk of stroke or systemic embolism by 19% (risk ratio (RR) 0.81, 95% CI 0.73-.91) and all-cause mortality by 10% (RR 0.90, 95% CI 0.85-0.95) (Ruff et al., 2014). The most significant benefit compared to warfarin treatment seems to be the lower risk for intracranial bleeding (RR 0.48, 95% CI 0.39-0.59), while the risk for gastrointestinal bleeding is higher (RR 1.25, 95% CI 1.01-1.55) (Ruff et al., 2014). While no head-to-head prospective trials have been conducted, retrospective studies have analyzed the comparative properties of different NOACs (Larsen et al., 2016; Yao et al., 2016).

2.3.2 Antiplatelet agents

Inhibiting platelet aggregation is another approach to preventing thrombus formation. Acetyl-salicylic acid, more commonly known as aspirin, has been for decades the most important drug in preventing atherothrombotic events in patients with coronary heart disease, myocardial infarction or previous cerebrovascular event. In preventing cardiogenic thromboembolism in patients with AF, its effect has been modest compared to warfarin. In the meta-analysis, it reduced the risk of stroke by 22% (95% CI 6%-35%) compared to placebo (Hart et al., 2007). However, warfarin compared to aspirin was significantly more efficacious in stroke prevention, with a relative risk reduction of 39% (95% CI 22%-52%). There are also studies suggesting that, in patients with atrial fibrillation, aspirin has no protective effect against stroke (Sjalander et al., 2014). One argument supporting the use of aspirin in stroke prevention involves the assumed lower risk of bleeding compared to OAC. In a randomized controlled trial comparing the efficacy and safety of warfarin versus aspirin in patients over 75 years of age with AF, the risk of stroke was significantly higher in patients using aspirin (yearly risk with warfarin 1.8% vs 3.8% with aspirin, p=0.003), while there were no differences in the incidence of intracranial or extracranial bleeding (Mant et al., 2007). Another study compared apixaban and aspirin in patients who were considered unsuitable for warfarin. The yearly risk of stroke or systemic embolism was significantly lower with apixaban than aspirin (1.6 % vs 3.7%,

p<0.001), while there were no differences in the rate of bleeding events (Connolly et al., 2011).

Clopidogrel is another antiplatelet agent commonly used in the secondary prevention of atherothrombotic stroke or myocardial infarction, especially after percutaneous coronary intervention in combination with aspirin. Combination treatment with aspirin and clopidogrel compared to aspirin alone has also been studied in patients with AF. Combination was associated with a modestly decreased risk of vascular events (6.8% vs 7.6% per year, p=0.01) but with an increased risk of major bleeding (2.0% vs 1.3%, p<0.01) (ACTIVE Investigators et al., 2009).

2.3.3 Left atrial appendage occlusion

Since most of the cardiogenic thrombi are thought to originate from the left atrial appendage in patients with AF, it has been suggested that, by occluding this structure, thrombus formation can be prevented and the risk of thromboembolism could be reduced. The most studied means for doing so is the Watchman device, which can be implanted percutaneously under fluoroscopy. In clinical studies, its efficacy has been found to be comparable to that of warfarin therapy, although the procedure is associated with the risk of periprocedural complications, most commonly pericardial effusion, device embolization or procedure-related stroke (Holmes et al., 2014; Holmes et al., 2015). Avoiding anticoagulation treatment could benefit particularly patients with high bleeding risk conditions or previous bleedings. A clinical trial is underway randomizing AF patients with a prior intracerebral hemorrhage to left atrial appendage occlusion or medical therapy (SrokeClose trial, clinicaltrials.gov NCT02830152).

The left atrial appendage can also be occluded during cardiac surgery. There is no robust clinical data to prove the efficacy of this approach in stroke prevention (Kirchhof et al., 2016), although a randomized trial is underway (Whitlock et al., 2014). Another randomized trial is currently studying the efficacy and safety of prophylactic surgical closure of the left atrial appendage in patients without previously known AF undergoing aortic valve replacement surgery (LAACLOSURE trial, clinicaltrials.gov NCT02321137), based on the high incidence of postoperative AF and ischemic stroke in these patients.

2.3.4 Guideline approach to stroke prevention

Medical societies have been active in publishing clinical practice guidelines to recommend evidence-based treatment for patients with AF (Fuster et al., 2006; European Heart Rhythm Association et al., 2010; Camm et al., 2012). During the last decade, the recommendations have shifted to using the more thorough CHA_2DS_2-VASc score instead of the older $CHADS_2$-score. Since most patients with AF benefit from OAC treatment, the focus has shifted towards identifying the patients with a truly low risk of stroke, who do not benefit from OAC. Also, the role of aspirin has been significantly reduced in the new compared to the older guidelines. The approach to stroke prevention in the guidelines published (and potentially affecting clinical decision making) during our study period is presented in Table 4. Over the years, strong recommendations have been made for using OAC in patients with CHA_2DS_2-VASc or $CHADS_2$ scores of 2 points or higher, while the recommendation for patients with 0 or 1 point has changed somewhat in different guidelines and includes more shared decision making with the patient. After the data collection phase of our study, at least two significant clinical practice guidelines have been published, with minor updates in the stroke risk assessment and recommendations about choosing between warfarin and NOAC (January et al., 2014; Kirchhof et al., 2016).

Table 4 Approach to stroke prevention in guidelines published between 2006 and 2012

CHA_2DS_2-VASc	***ACC/AHA/ESC 2006 ($CHADS_2$-points)***	***ESC 2010***	***ESC 2012***
0	Aspirin	Aspirin or no antithrombotic therapy (prefer no antithrombotic therapy)	No antithrombotic therapy
1	Aspirin or OAC	OAC or aspirin (prefer OAC)	OAC should be considered
≥2	OAC	OAC	OAC

References: (Fuster et al., 2006; European Heart Rhythm Association et al., 2010; Camm et al., 2012).

2.4 Underuse of anticoagulation

Despite robust evidence of the benefit of OAC and strong recommendations by the clinical guidelines, underuse of anticoagulation has been common among patients with AF. In an analysis of previously published AF populations from 2000 to 2007, the proportion of patients receiving OAC ranged from 9% to 86%, with a median of 52% (Ogilvie et al., 2011). In European cardiology clinics, 49%-67% of patients with AF were prescribed warfarin in 2003-2004 (Nieuwlaat

et al., 2005) and 80% in 2012-2013 (Lip et al., 2014). Even after prescription, the discontinuation rates have been high. In the FRACTAL registry, 65% of patients were prescribed warfarin initially, while at 30 months only 44% were still taking it (Reynolds et al., 2006). In the ATRIA study, 26.3% of the patients discontinued warfarin within one year of prescription (Fang et al., 2010); in the more recent ORBIT-AF registry, 10.1% of the patients discontinued warfarin within one year (O'Brien et al., 2014a).

Underuse of anticoagulation has been exceptionally common in stroke patients with previously diagnosed AF. In previous studies, only 27%-32% of the AF patients had been using OAC prior to stroke (Gandolfo et al., 2008; Hylek et al., 2003). In another study in which patients with a contraindication to OAC were excluded, 39.9% of the patients were taking warfarin before hospitalization for stroke (Gladstone et al., 2009).

Some studies have examined the most common reasons for withholding warfarin. In a chart review of 364 atrial fibrillation patients, the most often documented reasons were gastrointestinal bleed (10.7%), secondary/transient AF (8.2%) and fall risk (6.3%) (Srivastava et al., 2008). In the ORBIT-AF outpatient registry of 10,130 patients, 13.1% had a documented contraindication for OAC (O'Brien et al., 2014b). The most commonly documented contraindications were prior bleed (27.7%), patient refusal (27.5%), high bleeding risk (18.0%), frequent falls/frailty (17.6%) and need for dual antiplatelet therapy (10.4%). Of the patients with a documented contraindication, 30% were taking OAC, compared to 83% of those without a documented contraindication.

2.5 Stroke risk after cardioversion of atrial fibrillation

2.5.1 Background

Many of the patients with AF are symptomatic, and their symptoms can be relieved by restoring and maintaining sinus rhythm, also called rhythm control. However, AF-related symptoms can also be treated by controlling the heart rate with medications without pursuing sinus rhythm; this is called rate control. Although rhythm control seems to be theoretically advantageous in patients with AF, this strategy has offered no clinical or mortality benefit in the clinical trials comparing rate and rhythm control (Van Gelder et al., 2002; Wyse et al., 2002), including in the case of patients with heart failure (Roy et al., 2008).

Direct current cardioversion was the first truly effective and safe method for restoring sinus rhythm in patients with AF, with the first patient series published in 1963 (LOWN et al., 1963). It was soon discovered that cardioversion was associated with an increased risk of cardiogenic thromboembolism. In the early experiments, cardioversion of long-lasting AF without anticoagulation led to stroke in 5% to 7% of patients (Arnold et al., 1992; Bjerkelund and Orning, 1969), while in the patients receiving anticoagulation the risk was significantly lower at 0.8% (Bjerkelund and Orning, 1969). The lower risk of thromboembolism with anticoagulation was also evident in a cohort of 16,274 patients from Denmark cardioverted between 2000 and 2008, with a thromboembolic incidence rate of 10.33 per 100 patient years during the 30 days after the cardioversion in patients without prior OAC, compared to 4.00 per 100 patient years in patients with prior OAC (Hansen et al., 2015).

In modern practice, there are three approved approaches to conducting a safe cardioversion (European Heart Rhythm Association et al., 2010; Kirchhof et al., 2016). 1. AF has lasted less than 48 hours (cardioversion of acute AF); 2. A transesophageal echocardiography (TEE) is made and intracardiac thrombus, especially in the left atrium and left atrial appendage, is ruled out; 3. Patient has received therapeutic anticoagulation for at least 3 weeks (elective cardioversion).

2.5.2 Cardioversion of acute atrial fibrillation

In previous studies, the stroke risk in patients with cardioversion of acute AF (less than 48 hours) has been between 0% and 0.9% in patients without anticoagulation (Burton et al., 2004; Gallagher et al., 2002; Michael et al., 1999; Stiell et al., 2010; Weigner et al., 1997; Xavier Scheuermeyer et al., 2010), although the sample sizes have been quite small, between 104 and 414 cardioversions (considering studies including more than 50 cardioversions). The most comprehensive data on the thromboembolic risk after acute cardioversion was obtained from the FinCV study, which contained data on 7,660 cardioversions performed in 3,143 patients (Airaksinen et al., 2013a). In this study, the risk of thromboembolism was 0.7% in the whole population, but the risk was highly dependent on clinical risk factors for stroke. Depending on the clustering of risk factors, the thromboembolic risk varied between 0.2% and 9.8%. The most significant independent risk factor for thromboembolism was the presence of heart failure, with an odds ratio (OR) of 2.85 (95% CI 1.12-7.24) for thromboembolism in the multivariate analysis.

2.5.3 Cardioversion after transesophageal echocardiography

Intracardiac thrombi can be viewed with the use of echocardiography; to ensure adequate visibility of the atria and the left atrial appendage, a transesophageal approach must be used. In the clinical guidelines, it is suggested that if the AF has lasted for more than 48 hours, cardioversion can still be performed if intracardiac thrombus has been ruled out with the use of TEE and if effective anticoagulation is started before the procedure (European Heart Rhythm Association et al., 2010; Kirchhof et al., 2016). In the clinical studies, the stroke risk with the TEE-guided approach has been 0.8% (Klein et al., 2001; Seidl et al., 2002). It is worth noting that the pumping capacity of the left atrium is often not restored immediately after the cardioversion due to atrial stunning, which might result in a predisposition to thrombus formation after the cardioversion if adequate anticoagulation is not used (Grimm et al., 1993).

2.5.4 Elective cardioversion

In clinical trials, the 30-day stroke risk after elective cardioversion with adequate warfarin anticoagulation was 0.4%-0.5% (Apostolakis et al., 2013; Cappato et al., 2014; Klein et al., 2001). In a prospective trial comparing rivaroxaban and warfarin for elective cardioversion in 1504 patients, the risk of stroke was 0.2% in patients using rivaroxaban and 0.4% in patients using warfarin (Cappato et al., 2014). Retrospective analysis of the apixaban and dabigatran trials showed no differences in complication rates compared to warfarin (Flaker et al., 2014; Nagarakanti et al., 2011).

2.6 Perioperative anticoagulation in patients with atrial fibrillation

More than 10% of patients with AF undergo invasive procedure or operation each year (Garcia et al., 2014; Healey et al., 2012a; Sherwood et al., 2014; Steinberg et al., 2015a). Treatment with OAC increases the risk of bleeding perioperatively, while discontinuing OAC predisposes the patient to thromboembolism. Warfarin is especially problematic in temporary interruptions, because the slow onset of action predisposes the patient to a long interruption in therapeutic anticoagulation. Additionally, the re-initiation of warfarin has been associated with a transiently increased risk of thromboembolism (Granger et al., 2015).

Theoretically, the slow maneuverability of warfarin could be countered with the temporary use of another anticoagulant with a fast onset and offset of action.

Low-molecular weight heparins (LMWH) have these properties and have been used in temporary interruptions of warfarin therapy for invasive procedures, also called bridging therapy.

The decision of whether to discontinue warfarin for the procedure is dependent on the associated bleeding risk. Many procedures carry such a low risk for major bleeding that it is generally recommended to do the procedure without any interruption of OAC. Such procedures include most dental procedures (Bajkin et al., 2009), diagnostic endoscopy including mucosal biopsy (Acosta et al., 2016), most eye surgery (Bonhomme et al., 2013) and most cutaneous procedures. There is also an increasing body of evidence that the non-interrupted approach is equally safe or even superior compared to heparin bridging in many interventional cardiologic procedures, including pacemaker implantation (Airaksinen et al., 2013b; Birnie et al., 2013), coronary angiography and percutaneous coronary intervention (Annala et al., 2008; Jamula et al., 2010; Kiviniemi et al., 2015). In the randomized controlled trial of patients undergoing pacemaker implantation, the rate of device-pocket hematoma was 16.0% in patients with bridging therapy compared to 3.5% in patients with uninterrupted warfarin, with no difference in thromboembolic complications (Birnie et al., 2013).

If interruption of OAC is required for the procedure, a decision about LMWH-bridging must be made. In the clinical guidelines, bridging with LMWH is suggested for patients with a high thromboembolic risk, such as patients with AF and 5-6 $CHADS_2$ points, TIA or stroke within 3 months or rheumatic valvular heart disease (Douketis et al., 2012). Patients with mitral valve prosthesis, recent venous thromboembolism (within 3 months) and severe thrombophilia are also considered to be high-risk patients. The risk of thromboembolism is considered low, and no bridging is suggested in patients with AF and 0-2 $CHADS_2$ points. In patients with a moderate risk, the decision should be made individually.

The bridging guidelines rely mostly on expert consensus, since there are no evidence-based data on the benefits of bridging anticoagulation. In a meta-analysis, heparin bridging was associated with a significantly increased risk of bleeding, while there was no difference in the rate of thromboembolic complications (Siegal et al., 2012). Similarly, in the prospective ORBIT-AF registry, bridging was associated with a higher risk of bleeding without any benefit in reducing thromboembolic complications (Steinberg et al., 2015a). Only one relevant randomized controlled study exists comparing bridging with no bridging. In the BRIDGE trial, 1884 patients were randomized to receive either LMWH or placebo during interruption of warfarin for an elective invasive procedure or operation (Douketis et al., 2015). The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group ($p=0.01$ for non-

inferiority), while the incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (p=0.005 for superiority). Important exclusions were patients with a mechanical heart valve and patients who had experienced a TIA or stroke within the past 12 weeks. The $CHADS_2$ score was 3 or higher in 38.3% of the patients.

When all the evidence is combined, it seems that, in most situations with a low-bleeding-risk procedure, uninterrupted warfarin is the easiest and safest approach. In cases with a high-bleeding-risk procedure, bridging therapy seems to offer no benefit during the interruption of warfarin, although there are not much data concerning patients with the highest risk for thromboembolism.

In patients with NOACs, the approach to perioperative anticoagulation is more straightforward, since NOACs have a considerably faster offset and onset of action than warfarin. Therefore, LMWH bridging is not recommended during interruption of NOAC therapy for a procedure (Heidbuchel et al., 2015).

2.7 Stroke risk in paroxysmal and chronic atrial fibrillation

In most patients, AF starts with short, self-terminating episodes (paroxysmal AF). As time goes by, these episodes tend to become longer, requiring cardioversion to restore sinus rhythm. The ability to restore and maintain sinus rhythm is eventually lost in many of the patients, and AF becomes the prevalent rhythm (chronic or permanent AF) (Jahangir et al., 2007).

It has long been debated whether the risk of thromboembolism is different in patients with paroxysmal and chronic AF, and results from clinical studies have been somewhat conflicting (Al-Khatib et al., 2013; Disertori et al., 2013; Friberg et al., 2010; Hart et al., 2000; Hohnloser et al., 2007; Lip et al., 2008; Steinberg et al., 2015b; Takabayashi et al., 2015; Vanassche et al., 2015). The results of clinical studies have been summarized in Table 5. The post hoc-analyses of early trials and a large Swedish registry demonstrated a similar risk of thromboembolism in patients with chronic and paroxysmal AF, while the more recent trials and registries have shown a lower risk of thromboembolism in patients with paroxysmal AF. Probably the most clinically relevant data in the view of modern clinical practice have been obtained from the large randomized NOAC-trials, in which the risk of thromboembolism has been consistently lower in patients with paroxysmal AF (Al-Khatib et al., 2013; Steinberg et al., 2015b; Vanassche et al., 2015).

There are many factors that could potentially explain the varying results. Most of the data have been obtained from post-hoc analyses of clinical trials, which have not been designed specifically to compare outcomes according to the type of AF. Also, the definitions used for paroxysmal and intermittent AF have varied. For example, in the SPAF I and II trials, AF was considered intermittent if any sinus rhythm had been documented during the previous 12 months (Hart et al., 2000), while in most other studies the definition of paroxysmal AF was based on the definition used in the clinical guideline from year 2006 (AF episodes lasting less than 7 days) (Fuster et al., 2006). Furthermore, the use of OAC has varied between studies. For example, in the GISSI AF trial, 25% of patients with paroxysmal AF were using warfarin compared to 87% in patients with persistent AF (Disertori et al., 2013). Because of the increasing awareness of AF and AF-related complications, it is possible that, in the modern trials, patients have been recruited in the earlier phase of the disease process and could have a significantly lower burden of AF episodes compared to earlier trials.

In the previous clinical guidelines, it has been clearly recommended that patients with paroxysmal AF should receive OAC according to the same criteria as patients with chronic AF (European Heart Rhythm Association et al., 2010; January et al., 2014). In the most recent guideline, the question of how much atrial fibrillation constitutes a mandate for therapy has been declared to be one of the gaps in evidence, mostly stemming from the increasing use of portable ECG-recording devices, which are able to record even the shortest episodes of AF (Kirchhof et al., 2016).

Table 5 Risk of thromboembolic complications in patients with paroxysmal and chronic atrial fibrillation according to previous studies

	Risk of thromboembolism				
Study	***Paroxysmal***	***Chronic***	***p***	***Endpoint***	***Setting***
Hart 2000 (SPAF I-III)	3.2 %	3.3 %	NA	Ischemic stroke	Trial
Hohnloser 2007 (ACTIVE W)	2.0 %	2.2 %	0.50	Stroke or SE	Trial
Friberg 2010 (Stockholm Cohort of Atrial Fibrillation)	2.6 %	2.9 %	0.45	Ischemic stroke	Cohort
Disertori 2013 (GISSI-AF)	0.78 %	1.3 %	0.42	Stroke or SE	Trial
Lip 2008 (SPORTIF III and V)	0.9 %	1.7 %	0.04	Stroke or SE	Trial
Al Khatib 2013 (ARISTOTLE)	1.0 %	1.5 %	0.003	Stroke or SE	Trial
Vanassche 2015 (ACTIVE-A and AVERROES)	2.1 %	4.2 %	<0.01	Stroke or SE	Trial
Steinberg 2015 (ROCKET-AF)	1.7 %	2.2 %	0.048	Stroke or SE	Trial
Takabayashi 2015 (Fushimi AF registry)	1.4 %	3.1 %	<0.01	Stroke or SE	Cohort

SE=Systemic embolism; NA=Not available. References: (Al-Khatib et al., 2013; Disertori et al., 2013; Friberg et al., 2010; Hart et al., 2000; Hohnloser et al., 2007; Lip et al., 2008; Steinberg et al., 2015b; Takabayashi et al., 2015; Vanassche et al., 2015).

3 AIMS OF THE STUDY

1. To identify the proportion of patients with previously diagnosed AF who were not using OAC prior to ischemic stroke or TIA, and to evaluate the most important reasons for not receiving anticoagulation (I).

2. To evaluate the relative proportion of post-cardioversion strokes in patients with AF, and to study the typical characteristics of cardioversions leading to stroke (II).

3. To study postoperative strokes in patients with AF, and especially the features of perioperative antithrombotic treatment in these patients (III).

4. To compare the characteristics and prognosis of strokes in patients with paroxysmal and chronic AF (IV).

4 MATERIALS AND METHODS

4.1 Study population

The data for the FibStroke study were collected from four major hospitals in Finland: Turku University Hospital, Kuopio University Hospital, Satakunta Central Hospital and Keski-Suomi Central Hospital.

The FibStroke registry included all patients who:

1) Suffered an ischemic stroke, TIA or intracranial bleeding during 2003-2012 (in Keski-Suomi Central Hospital 2006-2012) and

2) Had ever been diagnosed with AF or atrial flutter (before, at the same time as or after the ischemic stroke, TIA or intracranial bleeding).

The initial screening was conducted from the hospital discharge records. The diagnosis codes used for the database search were:

1) 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, identifying ischemic strokes, TIA-episodes and traumatic and non-traumatic intracranial bleedings; and

2) I48, identifying AF and atrial flutter.

After the initial screening, all patient files were individually reviewed, and the diagnosis of AF and the neurological event were confirmed case by case. Patient characteristics, risk factors for stroke and bleeding, medications, laboratory results, operations and invasive procedures, bleeding events and cardioversions during the 30 days preceding the stroke, TIA or intracranial bleeding were recorded. Additionally, 30-day mortality data were obtained. Data were collected in a structured electronic case report form in an online database.

The whole FibStroke registry contained data on 5767 patients who suffered a total of 1338 TIA episodes, 4547 ischemic strokes and 830 intracranial bleeds during the study period. All of the research in this thesis was focused on the patients who were diagnosed with AF before the onset of TIA, ischemic stroke or intracranial bleed. A total of 4311 patients suffered 3252 ischemic strokes, 956 TIA episodes and 794 intracranial bleeds after the diagnosis of AF. The study population and timing of diagnosis of AF are outlined in Figure 1.

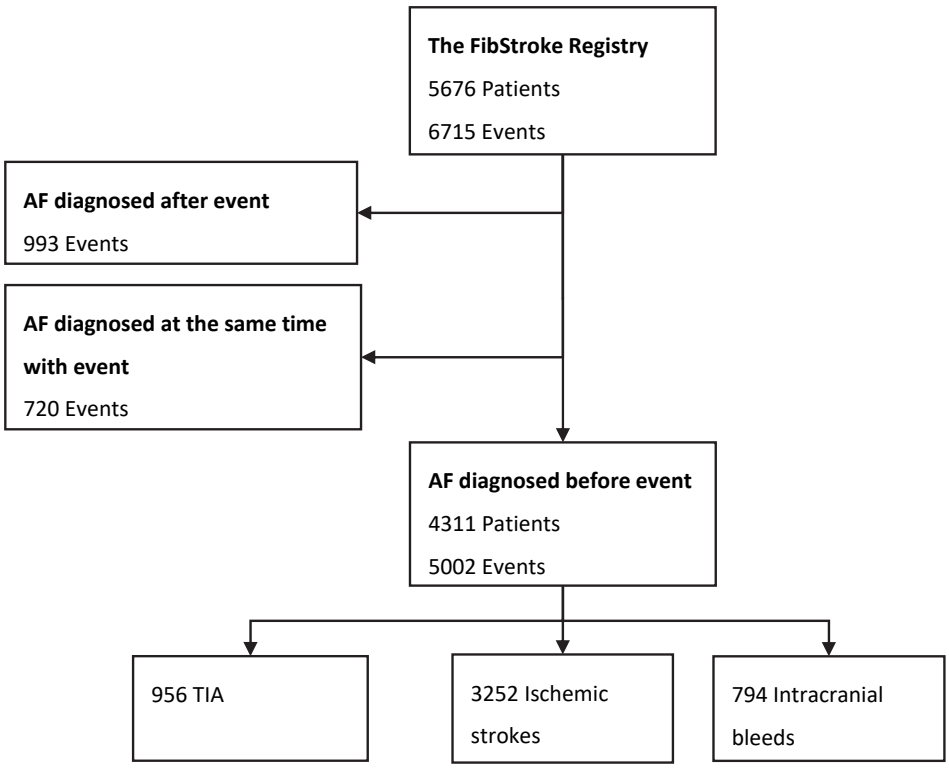

Figure 1 The FibStroke Study population

4.2 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. Informed consent was not required because of the registry nature of the study. The study conforms to the Declaration of Helsinki.

4.3 Definitions

The diagnosis of AF was confirmed by 12-lead electrocardiogram, according to the standard criteria. The diagnoses of stroke, TIA or intracranial bleed were confirmed from the patient records, as diagnosed by the treating neurologist. Only events considered definite by the treating physician were included in our study.

All patients were imaged by computed tomography or magnetic resonance imaging. Bridging therapy was defined as any dose of LMWH administered during the interruption of OAC. Low-bleeding risk procedures were identified according to previously published expert opinion review papers (Daniels, 2015; Spyropoulos and Douketis, 2012).

4.4 Statistical analysis

Continuous variables were reported as mean ± standard deviation if they were normally distributed and as median [inter-quartile range (IQR)] if they were skewed, unless stated otherwise. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between study subgroups were performed with Student's *t* test or the Mann-Whitney test as appropriate for continuous variables and the Chi-square test or Fisher's exact test as appropriate for categorical variables. All tests were two-sided, and statistical significance was set at 5%.

In Study I, clinically relevant variables with additional evaluation of the years of the event were used in univariate and multivariate logistic regression analysis with repeated measures option.

In Study IV, binary stepwise logistic regression analysis (backward Wald) was performed to identify independent predictors of mortality after TIA/stroke. Additionally, a propensity score-matching method was used to create two groups of patients with chronic and paroxysmal AF with similar baseline characteristics. The propensity score was estimated using a non-parsimonious logistic regression model with the treatment method as the dependent variable. Pairs of patients with chronic and paroxysmal AF having the same probability score (nearest neighbor method, caliper = 0.2 x standard deviation of the logit) have been matched. To evaluate the balance between the matched groups, univariate analyses were performed and the analysis of the standardized differences after matching was performed. A standardized difference less than 0.1 was considered as a negligible difference in the prevalence or mean of covariates between the study groups.

Statistical analysis was performed using IBM SPSS Statistics software version 22.0 and SAS version 9.3.

5 RESULTS

5.1 Underuse of anticoagulation in stroke patients with previously diagnosed atrial fibrillation (I)

In Study I, we analyzed patients who had been previously diagnosed with AF and who suffered an ischemic stroke or TIA during the study period. Of these patients, 50.9% were using OAC before the onset of the ischemic event. Of the high-risk patients who had $CHADS_2$ score ≥ 2, only 55.1% were using OAC before the diagnosis of stroke or TIA. Use of OAC was significantly lower in patients who had paroxysmal AF vs. chronic AF (40% vs. 65%), previous bleeding vs. no previous bleeding (26% vs. 58%), HAS-BLED ≥ 3 vs. HAS-BLED <3 (43% vs. 75%), sinus rhythm vs. AF at the time of event (38% vs. 61%) and alcohol abuse vs. no alcohol abuse (30% vs. 56%, $p<0.01$ for all comparisons).

In a subgroup of 987 patients, the most important reason for not receiving OAC was determined from the past and current medical records as reported by the treating physician. The most common reasons for withholding anticoagulation were infrequent paroxysms of AF (13.8%), previous bleeding episodes (13.4%), patient's decision to decline/discontinue treatment (9.3%) and alcohol abuse (5.2%). In 34.9% of cases, the reason was not documented in the patient charts.

There was a significant increase in the proportion of patients using OAC at the time of the ischemic event during the study period. The use of OAC increased from 49% in 2003 to 65% in 2012 in patients with $CHADS_2$ score ≥ 2 and from 46% to 63% in patients with CHA_2DS_2-VASc score ≥ 2.

5.2 Strokes after cardioversion of atrial fibrillation (II)

5.2.1 Proportion of post-cardioversion ischemic events

In total, there were 78 ischemic strokes and 22 TIA-episodes in 99 patients, which were preceded by a cardioversion within the preceding 30 days during the study period. Altogether, 2.4% of all ischemic events and 2.4% of ischemic strokes were preceded by a cardioversion. Cardioversions were only performed in patients with paroxysmal or persistent AF, and in these patients 6.1% of all ischemic events and 6.4% of ischemic strokes were preceded by a cardioversion.

5.2.2 Characteristics of cardioversions leading to ischemic event

The characteristics of the cardioversions are depicted in. Of the 100 cardioversions leading to ischemic event, 77 were acute and 23 were elective, and 63 of the events occurred to patients who were not using OAC at the time of cardioversion. Ten patients were started on warfarin after cardioversion and before the onset of the ischemic event. LMWH was used during 5 cardioversions.

Table 6 Characteristics of 100 cardioversions leading to ischemic stroke or TIA

	Acute CV (n=77)	***Elective CV (n=23)***
Stroke	61 (79.2%)	17 (73.9%)
TIA	16 (20.8%)	6 (26.1%)
Method of CV		
Electrical	67 (88.3%)	23 (100%)
Pharmacological	9 (11.7%)	0
Successful CV	68 (88.3%)	21 (91.3%)
Spontaneous CV after unsuccessful CV	9/9	1/2
TEE-guided CV	3 (3.9%)	0
Warfarin prior to CV	14 (18.2%)	23 (100%)
INR at the time of CV, range	1.2-4.0	2.0-5.4
INR < 2	5/14 (35.7%)	0
Periprocedural LMWH	5 (6.8%)	0
Antiplatelet treatment (aspirin or clopidogrel)	45 (60.8%)	3 (15.0%)
Warfarin at the time of stroke or TIA	24 (31.2%)	22 (95.7%)
INR at the time of stroke or TIA, range	0.9-3.6	1.3-5.4
INR < 2	13/24 (54.2%)	5/22 (22.7%)
CHA_2DS_2-VASc, median [IQR]	3.0 [2.0-4.0]	3.0 [1.0-4.0]
0	8 (10.4%)	2 (8.7%)
1	7 (9.1%)	4 (17.4%)
≥ 2	62 (80.5%)	17 (73.9%)
Days from CV to stroke/TIA, median [IQR]	2 [1.0-3.0]	2 [2.0-5.0]
0-2 days	56 (72.7%)	12 (52.2%)
3-6 days	6 (7.8%)	8 (34.8%)
> 6 days	15 (19.5%)	3 (13.0%)

CV=Cardioversion; IQR=interquartile range

Of the 78 cardioversions leading to stroke, 61 (78.2%) were acute, 17 (21.8%) were elective, and 51 (65.4%) occurred in patients who were not using OAC. Before acute cardioversion, 10 patients (16.4%) were on warfarin, and four of these patients had subtherapeutic INR. Hence, only six (9.8%) of the 61 patients who developed a stroke after acute cardioversion had therapeutic anticoagulation at the time of cardioversion.

Most of the cardioversions leading to cerebral thromboembolism were successful in terms of restoring sinus rhythm. All nine patients who developed a stroke after unsuccessful cardioversion had cardioverted spontaneously to sinus rhythm before the onset of the stroke.

5.2.3 Risk factors for stroke

The CHA_2DS_2-VASc score was ≥ 2 in 79 (79%) of the patients who developed any ischemic event and in 65 out of 78 (83%) of the patients who developed a stroke after cardioversion. There were five patients without any risk factors for stroke as measured with the CHA_2DS_2-VASc score. All of these patients developed a stroke after cardioversion of acute AF, and none received anticoagulation before or after cardioversion.

5.2.4 Timing of cerebral thromboembolism after cardioversion

The delay from cardioversion to TIA or stroke is depicted in Figure 2. Most of the events occurred shortly after the cardioversion: 68% occurred during the first two days, 83% during the first 7 days and 93% during the first 14 days. The median delay from cardioversion to stroke or TIA was 2 days.

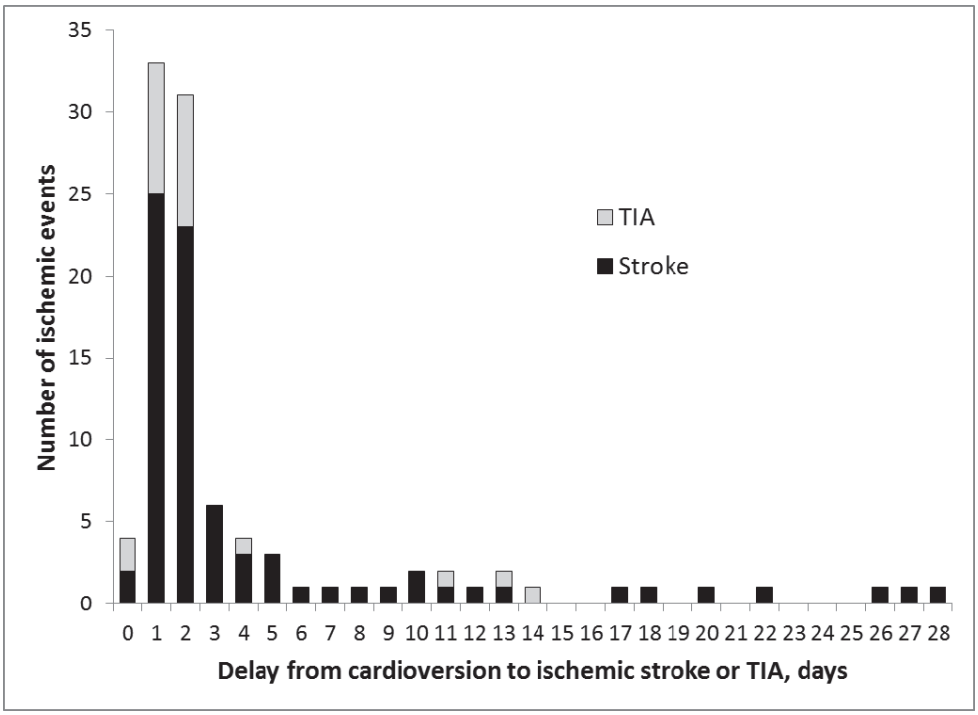

Figure 2 Timing of thromboembolic complications after cardioversion of AF. Modified from original publication II.

5.3 Postoperative strokes and intracranial bleeds in patients with atrial fibrillation (III)

5.3.1 Proportion and timing of postoperative ischemic strokes and intracranial bleeds

In total, 194 ischemic strokes developed within 30 days after an invasive procedure or operation, accounting for 6.0% of the 3252 ischemic strokes that occurred during the study period. The median time from the procedure to stroke was four days (IQR 1-12 days). The number of postoperative intracranial bleeds was 23, accounting for 2.9% of the 794 intracranial bleeds that occurred during the study period. The median delay from the procedure to intracranial bleed was 4 days (IQR 2-21 days).

5.3.2 Patient characteristics

Characteristics of the patients who suffered a postoperative ischemic stroke or intracranial bleed are depicted in Table 7. Most patients who suffered a postoperative ischemic or bleeding complication were high-risk patients characterized by CHA_2DS_2-VASc scores ≥ 2 in (94% and 96%, respectively), and their median ages were 78 and 76 years, respectively. The estimated bleeding risk (HAS-BLED score) was higher in patients with a postoperative intracranial bleed, and 69.6% of these patients had a HAS-BLED score ≥ 3. Also, diabetes, coronary artery disease and previous myocardial infarction were more common in patients with a postoperative intracranial bleed.

Table 7 Characteristics of patients with a postoperative stroke or intracranial bleed

	Ischemic stroke (n=191)	*Intracranial bleed (n=23)*	*p*
Female	108 (56.5%)	6 (26.1%)	0.006
Age, mean (SD)	78.0 (9.1)	75.9 (8.8)	0.29
CHA_2DS_2-VASc, median [IQR]	4.0 [3.0-5.0]	5.0 [3.0-6.0]	0.55
CHA_2DS_2-VASc ≥ 2	183 (94.3%)	22 (95.7%)	0.79
$CHADS_2$, median [IQR]	2.0 [1.0-3.0]	3.0 [1.0-4.0]	0.58
$CHADS_2 \geq 2$	139 (71.6%)	16 (69.6%)	0.83
HAS-BLED, median [IQR]	2.0 [2.0-3.0]	3.0 [2.0-4.0]	0.009
HAS-BLED ≥ 3	82 (42.9%)	16 (69.6%)	0.015
Diabetes	40 (20.9%)	9 (39.1%)	0.05
Coronary artery disease	72 (37.7%)	15 (65.2%)	0.011
Previous myocardial infarction	30 (15.7%)	10 (43.5%)	0.003
Previous stroke or TIA	47 (24.7%)	5 (21.7%)	0.75
History of heart failure	56 (29.3%)	7 (30.4%)	0.91
Mechanical heart valve	6 (3.1%)	1 (4.3%)	0.554

IQR=interquartile range; SD=standard deviation

5.3.3 Characteristics of the operations leading to postoperative ischemic stroke or intracranial bleeding

The operations and invasive procedures preceding ischemic strokes and intracranial bleeds are depicted in Table 8 and Table 9. A majority of the patients (69%) were on OAC before the procedure; it was interrupted for 69% of the procedures preceding intracranial bleed and 81% of the procedures preceding ischemic stroke. Of the patients with a postoperative intracranial bleed, 54.5% were using perioperative LMWH bridging, compared to 27.8% of patients with postoperative ischemic stroke (p=0.066). The use of antiplatelet agents, as well as the combination of anticoagulation (OAC or LMWH) with antiplatelet agents, was significantly more common in patients with a postoperative intracranial bleed than in patients with a postoperative ischemic stroke. The operations leading to postoperative intracranial bleed were more often urgent than the operations leading to ischemic stroke. Postoperative intracranial bleeds were also significantly more often fatal than postoperative ischemic strokes.

Of the procedures leading to ischemic stroke, 82 (42.3%) were classified as low-bleeding-risk procedures. Before these procedures, 59 (72.0%) of the patients were using OAC, which was interrupted in 50 (84.7%) patients. Many of the endoscopies were performed because of anemia or bleeding. If endoscopies were excluded, 61/168 (36.3%) of the operations were classified as low bleeding risk.

Table 8 Characteristics of the operations preceding ischemic stroke or intracranial bleed

	Ischemic stroke (n=194)	***Intracranial bleed (n=23)***	***p***
Urgent/emergency procedure	74 (38.1%)	16 (69.6%)	0.004
OAC prior to procedure	133 (68.6%)	16 (69.6%)	0.92
Warfarin	130/133 (97.8%)	16 (100%)	
Dabigatran	3/133 (2.2%)	0	
OAC interrupted	108/133 (81.2%)	11/16 (68.8%)	0.24
LMWH bridging	30/108 (27.8%)	6/11 (54.5%)	0.066
Any periprocedural LMWH (regardless of previous anticoagulation)	64/194 (33.0%)	11/23 (47.8%)	0.157
Antiplatelet drug (aspirin or clopidogrel)	55 (28.4%)	12 (52.2%)	0.019
Antiplatelet with anticoagulation at the time of stroke or bleed	33 (17.1%)	10 (43.5%)	0.01
Death within 30 days after event	33 (17.0%)	9 (39.1%)	0.011

Table 9 Operations preceding ischemic stroke or intracranial bleed

	Ischemic stroke (n=194)	***Intracranial bleed (n=23)***
Endoscopy	26	3
Coronary angiography +/- PCI	23	5
Gastrointestinal surgery	22	
Orthopedic/trauma surgery	20	1
Vascular surgery	16	1
Plastic/general surgery	15	2
Peripheral angiography +/- PTA	14	5
Urologic surgery	12	2
Pacemaker implantation	11	3
CABG/heart valve surgery	9	
Ophthalmologic surgery	8	
Head and neck surgery	4	
Thoracocentesis	4	1
Gynecologic surgery	3	
Neurosurgery	3	
Dental procedure	2	
AF ablation	1	
Paracentesis	1	

CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention; PTA=percutaneous transluminal angioplasty

5.4 Mortality after stroke in patients with paroxysmal and chronic atrial fibrillation (IV)

5.4.1 Study population and type of atrial fibrillation

The FibStroke registry included 3677 patients who suffered a total of 3252 ischemic strokes and 956 TIA episodes after the diagnosis of AF. During the study period, 433 (11.8%) of the patients suffered more than one event. The first event for each patient was chosen for this analysis.

The type of AF was chronic in 1808 of the patients (49.2%), paroxysmal or persistent in 1448 (39.4%) and undefined in 349 (11.4 %) at the time of the first event. For the final analysis, we included 3256 patients with a defined type of AF, who suffered 707 TIA episodes and 2549 ischemic strokes.

5.4.2 Patient characteristics

The characteristics of patients with paroxysmal and chronic AF are depicted in Table 10. Patients with chronic AF had higher CHA_2DS_2-VASc and $CHADS_2$ scores; were older; and more often had diabetes, coronary artery disease and history of heart failure. The thromboembolic event was more often TIA in patients with paroxysmal AF. Importantly, 63% of the patients with paroxysmal AF were on sinus rhythm at the onset of event.

Patients with paroxysmal AF were using OAC significantly less often than patients with chronic AF (32% vs 64%), while antiplatelet agents were significantly more common in patients with paroxysmal AF (48% vs 29%).

5.4.3 Mortality

Patients with paroxysmal AF had significantly lower 30-day mortality after the ischemic event compared to patients with chronic AF. Mortality was lower after stroke (10.2% vs 20.3%, $p<0.01$), after TIA (0.3% vs 2.1%, $p=0.02$) and after all events combined (7.6% vs 16.9%, $p<0.01$). Higher CHA_2DS_2-VASc scores were associated with increased mortality. However, in all subgroups, patients with chronic AF had higher mortality (Figure 3). Patients who were in sinus rhythm had a significantly lower 30-day mortality after ischemic event than patients who

were in any other rhythm (5.2% vs 15.7, p<0.01). After stroke, the mortality was 10.2% vs 20.3% (p<0.01).

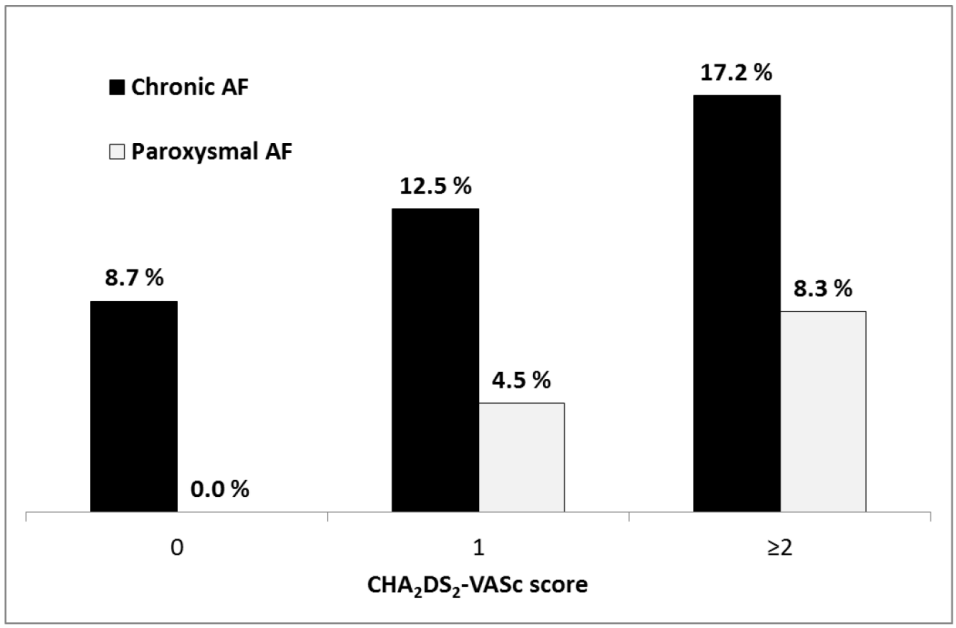

Figure 3 Mortality after stroke or TIA in patients with paroxysmal and chronic atrial fibrillation. Modified from the original publication IV.

In multivariate binary logistic regression, the independent predictors of mortality were increasing age (per year OR 1.06, 95% CI 1.04–1.07), the use of OAC (OR 0.7, 95% CI 0.6–0.9), chronic AF (OR 2.0, 95% CI 1.5–2.6), history of heart failure (OR 1.8, 95% CI 1.4–2.3), and estimated glomerular filtration rate of less than 30 ml/min/1.73 m2 (OR 2.1, 95% CI 1.3-3.3).

If only patients with paroxysmal AF were included, the independent predictors of 30-day mortality were increasing age (per year OR 1.08, 95% CI 1.05–1.1), previous stroke or TIA (OR 1.5, 95% CI 0.95–2.5), history of heart failure (OR 1.98, 95% CI 1.2–3.3), and any rhythm other than sinus rhythm at the onset of stroke (OR 1.9, 95% CI 1.2–2.9).

Table 10 Characteristics of all patients and propensity score matched pairs with paroxysmal and chronic atrial fibrillation

	All patients			*Propensity score matched pairs*			
	Paroxysmal AF (n=1448)	***Chronic AF (n=1808)***	***p***	***Paroxysmal AF (n=927)***	***Chronic AF (n=927)***	***p***	***Standardized difference***
Age, mean (SD)	75.3 (9.6)	79.6 (8.8)	<0.01	77.6 (9.1)	77.3 (9.9)	0.25	0.03
Female	834 (57.6)	994 (55.0)	0.13	513 (55.3)	504 (54.4)	0.67	0.02
Time from AF diagnosis (yrs), median [IQR]	1.5 [0.3–3.8]	3.6 [1.6–6.2]	<0.01	1.5 (3.5)	3.4 (3.5)	<0.01	0.45
Vascular disease	515 (35.6)	774 (42.8)	<0.01	354 (38.2)	359 (38.7)	0.811	0.10
Diabetes	276 (19.1)	441 (24.4)	<0.01	201 (21.7)	208 (22.4)	0.70	0.03
Previous myocardial infarction	228 (15.8)	274 (15.2)	0.64	142 (15.3)	154 (16.6)	0.45	0.08
Coronary artery disease	459 (31.7)	678 (37.5)	<0.01	311 (33.5)	320 (34.5)	0.66	0.03
Previous stroke or TIA	304 (21.0)	395 (21.9)	0.57	211 (22.8)	223 (24.1)	0.51	0.06
History of heart failure	183 (12.7)	540 (29.9)	<0.01	164 (17.7)	169 (18.2)	0.76	0.03
eGFR<30 ml/min/1.73 m^2	40 (2.8)	76 (4.3)	0.028	33 (3.6)	28 (3.0)	0.52	0.17
CHA_2DS_2-VASc, mean (SD)	3.7 (1.8)	4.3 (1.7)	<0.01	4.1 (1.7)	4.0 (1.8)	0.78	0.06
0	68 (4.7)	23 (1.3)		26 (2.8)	19 (2.0)	0.57	0.31
1	90 (6.2)	64 (3.5)		48 (5.2)	49 (5.3)		0.02
≥2	1290 (89.1)	1721 (95.2)		853 (92.0)	859 (92.7)		0.01
$CHADS_2$, mean (SD)	2.0 (1.3)	2.4 (1.3)	<0.01	2.2 (1.3)	2.2 (1.3)	0.39	<0.01
0	181 (12.5)	83 (4.6)		84 (9.1)	58 (6.3)	0.08	0.36
1	400 (27.6)	363 (20.1)		214 (23.1)	223 (24.1)		0.04
≥2	867 (59.9)	1362 (75.3)		629 (67.9)	646 (69.7)		0.03
HAS-BLED, mean (SD)	2.4 (1.1)	2.4 (1.0)	0.90	2.4 (1.0)	2.6 (1.1)	0.007	0.15
HAS-BLED ≥ 3	684 (47.2)	757 (41.9)	<0.01	431 (46.5)	464 (50.1)	0.13	0.07

Table 10 continued

	All patients			*Propensity score matched pairs*			
	Paroxysmal AF (n=1448)	***Chronic AF (n=1808)***	***p***	***Paroxysmal AF (n=927)***	***Chronic AF (n=927)***	***p***	***Standardized difference***
Rhythm at the onset of stroke or TIA			<0.01			<0.01	
Sinus	836 (62.8)	0		504 (58.7)	0		1.42
AF	413 (31.0)	1585 (94.2)		298 (34.7)	815 (94.4)		0.84
Flutter	23 (1.7)	22 (1.3)		13 (1.5)	11 (1.3)		0.17
Paced	51 (3.8)	66 (3.9)		36 (4.2)	33 (3.8)		0.09
Other or unknown	9 (0.7)	10 (0.6)		7 (0.8)	4 (0.4)		0.58
OAC	465 (32.2)	1147 (63.6)	<0.01	420 (45.3)	409 (44.1)	0.61	0.03
INR < 2 if using warfarin	201 (43.9)	532 (47.0)	0.14	180 (43.4)	184 (45.3)	0.58	0.02
Antiplatelet drug (aspirin or clopidogrel)	691 (48.1)	512 (28.5)	<0.01	378 (40.8)	383 (41.3)	0.81	0.03
OAC + antiplatelet drug	73 (5.0)	114 (6.3)	0.12	65 (7.0)	54 (5.8)	0.30	0.19
Event						<0.01	-
TIA	371 (25.6)	336 (18.6)	<0.01	246 (26.5)	175 (18.9)		-
Ischemic stroke	1077 (74.4)	1472 (81.4)	<0.01	681 (73.5)	752 (81.1)		-
Death within 30 days	109 (7.6)	298 (16.9)	<0.01	80 (8.6)	137 (14.8)	<0.01	-
Death within 30 days after TIA	1/367 (0.3)	7/333 (2.1)	0.02	1/246 (0.4)	3/175 (1.7)	0.31	-
Death within 30 days after stroke	108/1058 (10.2)	291/1432 (20.3)	<0.01	79/681 (11.6)	134/752 (17.8)	<0.01	-
Cardioversion within 30 days	98 (6.8)	-	<0.01	59 (6.4)	-	<0.01	-

Values expressed as *number (percentage)* unless otherwise indicated. eGFR=estimated glomerular filtration rate; IQR=interquartile range; SD=standard deviation

5.4.4 Propensity score analysis

Because of the significant imbalance of risk factors between study groups, propensity score matching was used to provide comparable patient groups to analyze the independent role of AF type as a predictor of mortality.

Propensity score matching provided 927 pairs of patients with well-balanced patient characteristics and risk factors. The characteristics of the propensity-score-matched pairs are depicted in Table 10. Age, CHA_2DS_2-VASc and $CHADS_2$ scores and OAC were well balanced between the propensity matched groups, while minor differences remained in the presence of renal failure and HAS-BLED, as indicated by standardized difference > 0.1. Time from AF diagnosis was also significantly longer in patients with chronic AF.

In propensity-score-matched pairs, the 30-day mortality remained significantly higher in patients with chronic AF (14.8% vs. 8.6%, $p<0.01$). Mortality after stroke was 17.8% vs. 11.6% ($p<0.01$), while the mortality difference after TIA did not reach statistical significance (1.7% vs. 0.4%, $p=0.317$).

6 DISCUSSION

6.1 Underuse of anticoagulation in stroke patients with previously diagnosed atrial fibrillation (I)

In Study I, we demonstrated that, in patients with previously diagnosed AF, almost half of the ischemic strokes and TIA episodes occurred in patients who were not using OAC. The most frequently documented reasons for not using OAC were infrequent paroxysms of AF, previous bleeding episodes and the patients' own decision.

It is clinically tempting to conclude that if a patient with paroxysmal AF is in sinus rhythm, the risk of stroke is low and no OAC is needed. A significant problem with this reasoning, however, is that patients with symptomatic paroxysmal AF have also a significant proportion of asymptomatic recurrences of AF, and the asymptomatic paroxysms can even be more common than symptomatic ones (Israel et al., 2004; Page et al., 1994). This means that the symptomatic paroxysms leading to hospital visits are usually only the tip of the iceberg compared to the total frequency of the patient's AF paroxysms. Additionally, patients with paroxysmal AF frequently undergo cardioversions, which are known to significantly increase the thromboembolic risk temporarily. For these reasons, using the frequency of AF paroxysms as an indicator of thromboembolic risk is highly problematic.

During our study period, warfarin was by far the most commonly used OAC. The effectiveness of warfarin in stroke prevention in patients with AF has been proved in numerous studies. While the clinical benefit is significant in the vast majority of patients, warfarin is notorious among both patients and physicians for the associated increase in the risk of bleeding. The sensational media has focused on warfarin-associated bleeding deaths, particularly highlighting warfarin's history as a pesticide. While doctors always need to be careful when prescribing drugs with potential side effects, it is tempting to speculate that over-conservative prescribing habits in fear of bleeding complications have left many patients untreated, exposing them to a high risk of ischemic stroke. Obviously, the mental image of the infamous drug also significantly contributes to patients' reluctance to use it.

Bleeding episodes are highly problematic in patients using OAC, and the re-initiation of OAC might seem counter-intuitive in most cases. However, according to previous studies, long-term survival rates have been significantly better in patients who have resumed OAC after a gastrointestinal bleed (Staerk et al.,

2015) and even after intracerebral hemorrhage (Kuramatsu et al., 2015). Patients at high risk for thromboembolism and serious previous bleeding events often require multidisciplinary evaluation and shared decision making with the well-informed patient. Also, left atrial appendage occlusion is a potential option for selected patients with a contraindication to OAC (Reddy et al., 2013), although the safety and efficacy of this approach in this particular patient group is yet to be proven in a randomized clinical trial.

While many bleeding risk scores have been developed, none of them has been accurate enough to identify patients who do not benefit from OAC. The risk factors for thromboembolism and bleeding overlap significantly, which means that patients with high bleeding risk usually have a high risk for thromboembolism as well. In previous studies, even patients with high HAS-BLED scores have had significantly higher risk of ischemic stroke than intracranial bleeding, with the net clinical benefit clearly in favor of OAC in these patients (Friberg et al., 2012). The modern clinical guidelines suggest that bleeding risk scores should be used to identify potentially treatable risk factors for bleeding (e.g., hypertension, medications and excessive alcohol use) rather than using them as a reason to withhold OAC.

The proportion of patients using OAC increased significantly during the study period. The first national guideline on AF treatment in Finland was published in 2005 (Käypä Hoito). During the study period, three ESC guidelines were also published, in 2006, 2010 and 2012 (Fuster et al., 2006; European Heart Rhythm Association et al., 2010; Camm et al., 2012). It seems that these guidelines have increased awareness of stroke prevention in physicians treating patients with AF. Additionally, the pharmaceutical industry manufacturing NOACs has been active in promoting stroke prevention in patients with AF in recent years.

While warfarin is certainly efficient in stroke prevention, it has certain cumbersome features limiting its use in practice. Because of the narrow therapeutic range and multiple food and drug interactions, frequent blood test monitoring is required to ensure safe INR levels. For many patients, use of NOACs is more practical in everyday life and they seem to provide clinical benefit by decreasing hemorrhagic strokes and in some circumstances major bleeding (Ruff et al., 2014), which might further increase the use of OAC in AF patients in the future.

6.2 Strokes after cardioversion of atrial fibrillation (II)

In Study II, we demonstrated that more than 6% of the strokes in patients with paroxysmal AF were preceded by a cardioversion. Also, the majority of the

strokes (78%) occurred after cardioversion of acute AF, and 65% of the strokes occurred in patients who were not using OAC prior to cardioversion.

Surprisingly little data exist regarding the stroke risk after cardioversion of acute AF without anticoagulation, since most clinical trials have been conducted in patients undergoing elective or TEE-guided cardioversion (Apostolakis et al., 2013; Cappato et al., 2014; Klein et al., 2001; Seidl et al., 2002). The 48-hour time limit of cardioversion of acute AF has been based on expert opinion and small retrospective studies. The landmark FinCV trial was published in 2013 and demonstrated that while the risk of stroke was relatively low in the healthier population, the risk was more than 3% in patients with heart failure and nearly 10% in patients with heart failure and diabetes (Airaksinen et al., 2013a). Also, the 48-hour time limit was called into question, since the risk of stroke began to increase 12 hours after symptom onset (Nuotio et al., 2014). This finding is in line with previous findings, which have demonstrated a thrombus in the left atrial appendage in 4% of patients with AF lasting less than 48 hours (Kleemann et al., 2009). The additional problem with the 48-hour time limit is that it is calculated from the patient-reported onset of AF symptoms, and previous rhythm monitoring studies have demonstrated that a significant proportion of AF paroxysms are asymptomatic (Israel et al., 2004; Page et al., 1994).

Despite the lack of robust evidence, the ESC guideline from the year 2010 suggested heparin or LMWH in all patients undergoing cardioversion of acute AF, followed by long-term OAC in patients with risk factors for stroke (European Heart Rhythm Association et al., 2010). The American guideline from 2014 recommended heparin, LMWH or NOAC as soon as possible, either before or immediately after the cardioversion in patients with high risk of stroke, whereas in patients with low thromboembolic risk, no antithrombotic therapy could also be considered (January et al., 2014). According to the most recent ESC guideline from 2016, anticoagulation with heparin or NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter, and anticoagulation is recommended for 4 weeks after cardioversion even in patients without stroke risk factors (Kirchhof et al., 2016). While no randomized trial evidence exists regarding the benefit of anticoagulation in the setting of cardioversion of acute AF, observational data and clinical guidelines strongly support it.

While only a minority of the strokes occurred after elective cardioversion, it is good to acknowledge that even elective cardioversion probably carries a transiently elevated stroke risk compared to a “steady state”. In contemporary anticoagulation trials, the monthly risk of stroke has been found to be approximately 0.1%-0.2% (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011), compared to the 30-day stroke risk of 0.4%-0.5% after elective cardioversion (Apos-

tolakis et al., 2013; Cappato et al., 2014; Klein et al., 2001). This highlights the importance of evaluating the need for cardioversion in asymptomatic patients, since in the clinical trials rhythm control has offered no additional benefit in patients with AF (Van Gelder et al., 2002; Wyse et al., 2002).

6.3 Postoperative strokes in patients with atrial fibrillation (III)

Study III showed that 6.0% of the strokes and 2.9% of the intracranial bleeds in patients with AF occurred after an invasive procedure or operation. The approach to perioperative anticoagulation varied significantly. The most common approach was to interrupt OAC before the procedure. Bridging with LMWH was common, especially in patients suffering postoperative intracranial bleeding.

Warfarin was the only relevant OAC for many years, and it has certain well-known problems in perioperative treatment. Because its mechanism of action relies on inhibition of the coagulation factor synthesis in the liver, the anticoagulation effect of warfarin starts slowly, and it takes many days after cessation of treatment for normal hemostasis to be achieved. Over the years, many complicated protocols have been developed for the use of anticoagulation perioperatively. Bridging with LMWH has been widely adopted, without evidence proving its benefits in patient care. From the current point of view, it seems clear that the combination of high-dose LMWH and fresh surgical trauma predisposes the patient to a significant risk of bleeding. It is also possible for such bleeding events to override the possible benefits of the anticoagulation effect, since active bleeding activates the hemostatic cascade, predisposing the patient to thrombosis.

There are three possible approaches to perioperative anticoagulation in patients using warfarin: 1) uninterrupted warfarin, 2) interrupted warfarin with the use of perioperative bridging, and 3) interrupted warfarin without bridging. According to the current evidence, it seems that bridging is associated with inferior outcomes compared to both interrupted and uninterrupted warfarin (Birnie et al., 2013; Douketis et al., 2015; Siegal et al., 2012). As mentioned above, there is little data about patients with mechanical heart valves, because they were excluded from the randomized trial (Douketis et al., 2015). Hopefully more information on this subject will be available when the results from the PERIOP-2 trial are published (ClinicalTrials.gov, Identifier NCT00432796). In the PERIOP-2 trial, patients with mechanical heart valves undergoing non-cardiac surgery are randomized to receive LMWH or placebo. Study completion is estimated for 2017.

The NOACs will significantly change the perioperative treatment, since in most cases there will be no need to switch to a different anticoagulant perioperatively,

and the onset and offset of action are relatively fast compared to warfarin. The advent of antidotes for NOACs, idarucizumab (Pollack et al., 2015) and andexanet alfa (Connolly et al., 2016), will further facilitate urgent operations in patients using NOACs.

In patients using warfarin, the simplest method also seems to be the safest: Uninterrupted warfarin is preferred in low-bleeding-risk operations, while in high-bleeding-risk operations interrupted warfarin without bridging seems to offer the best outcomes. There is little data to guide clinical decision making for patients with an extremely high risk of thrombosis or mechanical valves undergoing high-bleeding-risk surgery.

6.4 Mortality after stroke in patients with paroxysmal and chronic atrial fibrillation (IV)

In Study IV, we showed that patients with paroxysmal AF had lower mortality after stroke than patients with chronic AF. Also, more than 60% of patients with paroxysmal AF were in sinus rhythm at the onset of stroke, and these patients had a significantly better prognosis after stroke than patients who were in AF. While the patients with chronic AF were older and had more comorbidity, the difference remained significant after adjusting for potential confounding factors in the regression analysis and in the comparison of propensity score-matched pairs.

As mentioned in the literature review, the significance of the type of AF as a risk factor for stroke has long been debated, and the results of clinical studies have been mixed. There are number of factors explaining these differences. The definition of paroxysmal AF has varied over the years, meaning that these different populations might not be comparable. Also, it is likely that the modern trials have included patients who have been in the earlier phases of the disease process and atrial remodeling, because it is probable that the diagnosis of AF is more eagerly searched and diagnosed today because of the awareness of the stroke risk. It is well acknowledged that AF is a progressive disease, with the structural and electrical changes in the heart progressing over the course of years, with the increasing burden of AF paroxysms ultimately leading to chronic AF in many patients. For these reasons, it is most likely that patients in the early phases of AF have a lower risk of stroke, while patients with long-lasting paroxysmal AF are probably advancing towards the same stroke risk as patients with chronic AF.

It is increasingly recognized that factors other than the arrhythmia itself might contribute to the risk of thromboembolism, including endothelial dysfuntion, fi-

brosis, chamber dilatation and mechanical dysfunction in the left atrial appendage (Kamel et al., 2016). Therefore, a myriad of confounding factors that are not routinely measured in clinical practice might affect the independent thromboembolic risk in a patient, while the presence of AF can be seen as a signal of the underlying thrombogenic pathology.

There is some evidence that measurement of the AF burden with an implantable device can be used to quantify the risk of stroke (Glotzer et al., 2009). While measuring the exact amount of AF with an implantable device seems logical, it is impractical and laborious in clinical practice, and there is not much data to indicate what amount of AF would be safe for a patient.

The clinical guidelines have offered a practical approach, recommending antithrombotic therapy based on the CHA_2DS_2-VASc score irrespective of the type of AF (European Heart Rhythm Association et al., 2010; January et al., 2014). While this approach identifies high-risk patients, it is likely that some of these patients would in reality have only very rare paroxysms of AF and such a low risk of stroke that they would not benefit from OAC. However, until more precise systems for evaluating thromboembolic risk emerge, we have no better tool to identify these low-risk patients than the guideline-recommended scoring systems.

The lower mortality after stroke in patients with paroxysmal AF is probably multifactorial, but since the majority of the patients were in sinus rhythm at the onset of stroke, it is probable that many of the strokes were not thromboembolic but rather atherothrombotic, resulting in a less severe ischemic event with a more benign prognosis. It is well known that strokes are more severe and lethal in patients with AF than in patients without AF (McGrath et al., 2013; Wolf et al., 1998). Obviously, it is possible that some of the patients had spontaneous cardioversion before the onset of stroke, but these patients probably represent only a minority in this population. We also know that a significant proportion of the mortality in patients with AF is not directly associated with thromboembolism, as, for example, congestive heart failure and sudden cardiac death cause a significant proportion of the deaths in this population (Bassand et al., 2016). While some of these deaths might not be related to the stroke per se, it is probable that, during the 30 days after an ischemic event, the majority of the deaths are related to the cerebral thromboembolism.

How should these findings affect clinical judgment? At the moment, there is not enough evidence to alter clinical decision making. However, it seems clear that there is room for improvement in the risk stratification schemes, because it seems that there are certain patients with AF who have a lower risk of stroke and mortality than that predicted by the CHA_2DS_2-VASc score alone. Since measuring

the exact amount of AF in a given patient is impractical and such measurements are hard to interpret, a more practical surrogate marker might be better able to serve the same purpose. For example, the biomarker-assisted risk-scoring systems might offer a better "view" of the underlying heart pathology and thromboembolic risk than the scores that are solely based on clinical factors (Ruff et al., 2016). Additionally, one of the large prospective studies underway, e.g., the GARFIELD study; (Kakkar et al., 2012) or the ORBIT-AF registry (Piccini et al., 2011), might provide a more accurate risk-scoring system in the future.

6.5 Limitations

The FibStroke study carries all the inherent limitations of a retrospective observational study. The characterization of the patients could not be as accurate as in a prospective trial. On the other hand, we did have access to all electronic patient records of the participating hospitals, so we were not dependent on the data recorded during a single visit. Also, reporting of certain conditions might be affected by the clinical scenario; for example, the treating physician might be more eager to write down contraindications to anticoagulation when making the decision to withhold OAC. While we used logistic regression and propensity score matching to control for confounding factors, the non-randomized trial design cannot rule out residual confounding by unmeasured risk factors. While multicenter design is a strength of the study, it might also bring about variations in treatment decisions that are not visible in the patients' characteristics. Moreover, the definition of paroxysmal AF was the one used by the treating physician. While the exact definition might contain some inaccuracy, it is the one most closely reflecting the clinical practice at the moment.

Our study also has certain strengths. The retrospective design allowed for the inclusion of all consecutive patients and events, reflecting real-life clinical practice. In addition, because of the Finnish healthcare system and stability of the population, it is probable that almost all hospital treatment in the catchment areas of the participating hospitals was conducted in those hospitals, allowing for a comprehensive identification of the previous cardioversions and procedures.

6.6 Future implications

Cardiology is a rapidly advancing field of medicine, and significant advances have been made in the treatment of patients with AF in recent years.

It is likely that the use of catheter ablation procedures will increase in the future, providing a more powerful tool to achieve rhythm control. Whether or not these procedures can improve the prognosis of these patients or reduce the risk of thromboembolism has yet to be proven. Until now, stroke prevention with left atrial appendage occlusion devices has been used only in selected patients with a high risk of bleeding and thromboembolism. If the procedural safety is improved, the indications for these procedures might expand to patients with a more moderate risk profile.

The majority of patients will still be using OAC for stroke prevention in the coming years. It is likely that most new patients with AF will be started on NOAC in the future, while warfarin will still be used by patients with valve prostheses.

Perioperative treatment of patients with AF will be more straightforward in patients with NOAC compared to warfarin, and the role of LMWH bridging will most likely decrease. Exceptions include those patients who cannot take oral medications due to surgery and patients with valve prostheses. Hopefully, new trials will shed more light on the best perioperative treatment for patients receiving OAC.

More accurate risk stratifications schemes for thromboembolism will be developed in the future, incorporating more comprehensive patient characteristics and biomarkers. The role of cardiac imaging in risk stratification is still unclear but might carry a more significant role in the future. More complex evaluations may rely on computer-based algorithms.

While technological advances are being made, the final decision of whether to accept and adhere to the given treatment is still made by the individual patient. Patient education and participation in the treatment will be key elements in improving outcomes. The communication and the relationship between the physician and the patient will also remain highly important in the future.

7 CONCLUSIONS

Underuse of OAC is a highly important reason for stroke in patients with AF. (I)

Most post-cardioversion strokes occur after cardioversion of acute AF and to patients not using OAC. (II)

Postoperative ischemic strokes are often preceded by interruption of OAC for the operation. Bridging therapy with LMWH and a combination of anticoagulation with antiplatelet agents is common in patients with postoperative intracranial bleeding. (III)

Mortality after stroke is lower in patients with paroxysmal AF compared to patients with chronic AF. In particular, patients who are in sinus rhythm at the onset of stroke have a better prognosis. (IV)

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REFERENCES

Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, et al. (2016) The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointestinal Endoscopy* 83(1): 3-16.

ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. (2009) Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *The New England Journal of Medicine* 360(20): 2066-2078.

Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, et al. (2013a) Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *Journal of the American College of Cardiology* 62(13): 1187-1192.

Airaksinen KE, Korkeila P, Lund J, Ylitalo A, Karjalainen P, Virtanen V, et al. (2013b) Safety of pacemaker and implantable cardioverter-defibrillator implantation during uninterrupted warfarin treatment--the FinPAC study. *International Journal of Cardiology* 168(4): 3679-3682.

Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, et al. (2013) Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *European Heart Journal* 34(31): 2464-2471.

Annala AP, Karjalainen PP, Porela P, Nyman K, Ylitalo A and Airaksinen KE (2008) Safety of diagnostic coronary angiography during uninterrupted therapeutic warfarin treatment. *The American Journal of Cardiology* 102(4): 386-390.

Apostolakis S, Haeusler KG, Oeff M, Treszl A, Andresen D, Borggrefe M, et al. (2013) Low stroke risk after elective cardioversion of atrial fibrillation: an analysis of the Flec-SL trial. *International Journal of Cardiology* 168(4): 3977-3981.

Arnold AZ, Mick MJ, Mazurek RP, Loop FD and Trohman RG (1992) Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. *Journal of the American College of Cardiology* 19(4): 851-855.

Bajkin BV, Popovic SL and Selakovic SD (2009) Randomized, prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. *Journal of Oral and Maxillofacial Surgery : Official Journal of the American Association of Oral and Maxillofacial Surgeons* 67(5): 990-995.

Bassand J, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KAA, et al. (2016) Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *European Heart Journal* 37(38): 2882-2889.

Bilato C, Corti MC, Baggio G, Rampazzo D, Cutolo A, Iliceto S, et al. (2009) Prevalence, functional impact, and mortality of atrial fibrillation in an older Italian population (from the Pro.V.A. study). *The American Journal of Cardiology* 104(8): 1092-1097.

Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, et al. (2013) Pacemaker or defibrillator surgery without interruption of anticoagulation. *The New England Journal of Medicine* 368(22): 2084-2093.

Bjerkelund CJ and Orning OM (1969) The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. *The American Journal of Cardiology* 23(2): 208-216.

Bjorck S, Palaszewski B, Friberg L and Bergfeldt L (2013) Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke; a Journal of Cerebral Circulation* 44(11): 3103-3108.

Bonhomme F, Hafezi F, Boehlen F and Habre W (2013) Management of antithrombotic therapies in patients scheduled for eye surgery. *European Journal of Anaesthesiology* 30(8): 449-454.

Burton JH, Vinson DR, Drummond K, Strout TD, Thode HC and McInturff JJ (2004) Electrical cardioversion of emergency department patients with atrial fibrillation. *Annals of Emergency Medicine* 44(1): 20-30.

Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *European Heart Journal* 33(21): 2719-2747.

Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al. (2014) Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *European Heart Journal* 35(47): 3346-3355.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine* 361(12): 1139-1151.

Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. (2016) Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England Journal of Medicine* 375(12): 1131-1141.

Connolly SJ, Eikelboom J, Joyner C, Diener H, Hart R, Golitsyn S, et al. (2011) Apixaban in patients with atrial fibrillation. *The New England Journal of Medicine* 364(9): 806-817.

Culebras A, Messe SR, Chaturvedi S, Kase CS and Gronseth G (2014) Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(8): 716-724.

Daniels PR (2015) Peri-procedural management of patients taking oral anticoagulants. *BMJ (Clinical Research Ed.)* 351: h2391.

de Bruijn, Renée F A G, Heeringa J, Wolters FJ, Franco OH, Stricker BHC, Hofman A, et al. (2015) Association Between Atrial Fibrillation and Dementia in the General Population. *JAMA Neurology* 72(11): 1288-1294.

Diener H (2006) Stroke prevention using the oral direct thrombin inhibitor ximelagatran in patients with non-valvular atrial fibrillation. Pooled analysis from the SPORTIF III and V studies. *Cerebrovascular Diseases (Basel, Switzerland)* 21(4): 279-293.

Disertori M, Franzosi MG, Barlera S, Cosmi F, Quintarelli S, Favero C, et al. (2013) Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: data from the GISSI-AF trial. *BMC Cardiovascular Disorders* 13: 28.

Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. (2012) Perioperative Management of Antithrombotic Therapy. *Chest* 141(2 Suppl): e326s.

Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. (2015) Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *The New England Journal of Medicine* 373(9): 823-33.

Engdahl J, Andersson L, Mirskaya M and Rosenqvist M (2013) Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation* 127(8): 930-937.

European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European Heart Journal* 31(19): 2369-2429.

Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. (2010) Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circulation.Cardiovascular Quality and Outcomes* 3(6): 624-631.

Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. (2007) Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *The American Journal of Medicine* 120(8): 700-705.

Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK and Singer DE (2008) Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *Journal of the American College of Cardiology* 51(8): 810-815.

Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, et al. (2014) Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *Journal of the American College of Cardiology* 63(11): 1082-1087.

Friberg L, Rosenqvist M and Lip GY (2012) Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 125(19): 2298-2307.

Friberg L, Hammar N and Rosenqvist M (2010) Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *European Heart Journal* 31(8): 967-975.

Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *European Heart Journal* 27(16): 1979-2030.

Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW and Radford MJ (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama* 285(22): 2864-2870.

Gallagher MM, Hennessy BJ, Edvardsson N, Hart CM, Shannon MS, Obel OA, et al. (2002) Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. *Journal of the American College of Cardiology* 40(5): 926-933.

Gandolfo C, Balestrino M, Burrone A, Del Sette M and Finocchi C (2008) Stroke due to atrial fibrillation and the attitude to prescribing anticoagulant prevention in Italy. A prospective study of a consecutive stroke population admitted to a comprehensive stroke unit. *Journal of Neurology* 255(6): 796-802.

Garcia D, Alexander JH, Wallentin L, Wojdyla DM, Thomas L, Hanna M, et al. (2014) Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood* 124(25): 3692-3698.

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. (2013) Edoxaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine* 369(22): 2093-2104.

Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. (2009) Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke; a Journal of Cerebral Circulation* 40(1): 235-240.

Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. (2009) The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circulation.Arrhythmia and Electrophysiology* 2(5): 474-480.

Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, et al. (2003) Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA : The Journal of the American Medical Association* 290(20): 2685-2692.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine* 365(11): 981-992.

Granger CB, Lopes RD, Hanna M, Ansell J, Hylek EM, Alexander JH, et al. (2015) Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *American Heart Journal* 169(1): 25-30.

Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE, et al. (1993) Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. *Journal of the American College of Cardiology* 22(5): 1359-1366.

Haim M, Hoshen M, Reges O, Rabi Y, Balicer R and Leibowitz M (2015) Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *Journal of the American Heart Association* 4(1): e001486.

Hansen ML, Jepsen, Rikke Malene H G, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, et al. (2015) Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 17(1): 18-23.

Hart RG, Pearce LA and Aguilar MI (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine* 146(12): 857-867.

Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW and Halperin JL (2000) Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *Journal of the American College of Cardiology* 35(1): 183-187.

Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, et al. (2012a) Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation* 126(3): 343-348.

Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. (2012b) Subclinical atrial fibrillation and the risk of stroke. *The New England Journal of Medicine* 366(2): 120-129.

Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H, Hacke W, et al. (2015) Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 17(10): 1467-1507.

Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. (2016) The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *European Heart Journal* 37(20): 1582-1590.

Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, et al. (2007) Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *Journal of the American College of Cardiology* 50(22): 2156-2161.

Holmes DR, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. (2015) Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. *Journal of the American College of Cardiology* 65(24): 2614-2623.

Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. (2014) Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *Journal of the American College of Cardiology* 64(1): 1-12.

Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. (2003) Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *The New England Journal of Medicine* 349(11): 1019-1026.

Israel CW, Grönefeld G, Ehrlich JR, Li Y and Hohnloser SH (2004) Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *Journal of the American College of Cardiology* 43(1): 47-52.

Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, et al. (2007) Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 115(24): 3050-3056.

Jamula E, Lloyd NS, Schwalm JD, Airaksinen KE and Douketis JD (2010) Safety of uninterrupted anticoagulation in patients requiring elective coronary angiography with or without percutaneous coronary intervention: a systematic review and metaanalysis. *Chest* 138(4): 840-847.

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland J, Joseph C, et al. (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology* 64(21): 1.

Kakkar AK, Mueller I, Bassand J, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. (2012) International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *American Heart Journal* 163(1): 13-19.

Kamel H, Okin PM, Elkind MSV and Iadecola C (2016) Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. *Stroke; a Journal of Cerebral Circulation* 47(3): 895-900.

Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). *European Heart Journal* 37(38): 2893-2962.

Kiviniemi T, Airaksinen KE, Rubboli A, Biancari F, Valencia J, Lip GY, et al. (2015) Bridging therapy with low molecular weight heparin in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation: the AFCAS study. *International Journal of Cardiology* 183: 105-110.

Kleemann T, Becker T, Strauss M, Schneider S and Seidl K (2009) Prevalence of left atrial thrombus and dense spontaneous echo contrast in patients with short-term atrial fibrillation < 48 hours undergoing cardioversion: value of transesophageal echocardiography to guide cardioversion. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography* 22(12): 1403-1408.

Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, et al. (2001) Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *The New England Journal of Medicine* 344(19): 1411-1420.

Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. (2015) Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *Jama* 313(8): 824-836.

Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN and Lip GYH (2016) Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ (Clinical Research Ed.)* 353: i3189.

Lip GY, Frison L, Grind M and SPORTIF Investigators (2008) Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *Journal of Internal Medicine* 264(1): 50-61.

Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. (2014) A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 16(3): 308-319.

Lip GYH, Frison L, Halperin JL and Lane DA (2010a) Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke; a Journal of Cerebral Circulation* 41(12): 2731-2738.

Lip GYH, Nieuwlaat R, Pisters R, Lane DA and Crijns, Harry J G M (2010b) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 137(2): 263-272.

Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. (2004) Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 110(9): 1042-1046.

LOWN B, PERLROTH MG, KAIDBEY S, ABE T and HARKEN DE (1963) "Cardioversion" of atrial fibrillation. A report on the treatment of 65 episodes in 50 patients. *The New England Journal of Medicine* 269: 325-331.

Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. (2007) Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 370(9586): 493-503.

McGrath ER, Kapral MK, Fang J, Eikelboom JW, O'Conghaile A, Canavan M, et al. (2013) Association of atrial fibrillation with mortality and disability after ischemic stroke. *Neurology* 81(9): 825-832.

McGrath ER, Kapral MK, Fang J, Eikelboom JW, o Conghaile A, Canavan M, et al. (2012) Which risk factors are more associated with ischemic stroke than intracerebral hemorrhage in patients with atrial fibrillation? *Stroke; a Journal of Cerebral Circulation* 43(8): 2048-2054.

Michael JA, Stiell IG, Agarwal S and Mandavia DP (1999) Cardioversion of paroxysmal atrial fibrillation in the emergency department. *Annals of Emergency Medicine* 33(4): 379-387.

Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. (2011) Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 123(2): 131-136.

Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, et al. (2005) Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *European Heart Journal* 26(22): 2422-2434.

Nuotio I, Hartikainen JE, Gronberg T, Biancari F and Airaksinen KE (2014) Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *Jama* 312(6): 647-649.

O'Brien EC, Simon DN, Allen LA, Singer DE, Fonarow GC, Kowey PR, et al. (2014a) Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *American Heart Journal* 168(4): 487-494.

O'Brien EC, Holmes DN, Ansell JE, Allen LA, Hylek E, Kowey PR, et al. (2014b) Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *American Heart Journal* 167(4): 601-609.

O'Donnell M, Oczkowski W, Fang J, Kearon C, Silva J, Bradley C, et al. (2006) Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. *Lancet Neurology* 5(9): 749-754.

Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG and Emdin CA (2016) Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ (Clinical Research Ed.)* 354: i4482.

Ogilvie IM, Welner SA, Cowell W and Lip GY (2011) Characterization of the proportion of untreated and antiplatelet therapy treated patients with atrial fibrillation. *The American Journal of Cardiology* 108(1): 151-161.

Olesen JB, Torp-Pedersen C, Hansen ML and Lip GYH (2012) The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thrombosis and Haemostasis* 107(6): 1172-1179.

Page RL, Wilkinson WE, Clair WK, McCarthy EA and Pritchett EL (1994) Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation* 89(1): 224-227.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England Journal of Medicine* 365(10): 883-891.

Piccini JP, Fraulo ES, Ansell JE, Fonarow GC, Gersh BJ, Go AS, et al. (2011) Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *American Heart Journal* 162(4): 606-612.

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ and Lip GY (2010) A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 138(5): 1093-1100.

Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. (2015) Idarucizumab for Dabigatran Reversal. *The New England Journal of Medicine* 373(6): 511-520.

Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, et al. (2013) Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *Journal of the American College of Cardiology* 61(25): 2551-2556.

Reynolds MR, Shah J, Essebag V, Olshansky B, Friedman PA, Hadjis T, et al. (2006) Patterns and predictors of warfarin use in patients with new-onset atrial fibrillation from the FRACTAL Registry. *The American Journal of Cardiology* 97(4): 538-543.

Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. (2008) Rhythm control versus rate control for atrial fibrillation and heart failure. *The New England Journal of Medicine* 358(25): 2667-2677.

Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 383(9921): 955-962.

Ruff CT, Giugliano RP, Braunwald E, Murphy SA, Brown K, Jarolim P, et al. (2016) Cardiovascular Biomarker Score and Clinical Outcomes in Patients With Atrial Fibrillation: A Subanalysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial. *JAMA Cardiology* 1(9): 999-1006.

Schulman S, Beyth RJ, Kearon C, Levine MN and American College of Chest Physicians (2008) Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 133(6 Suppl): 257S.

Seidl K, Rameken M, Drogemuller A, Vater M, Brandt A, Schwacke H, et al. (2002) Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. *Journal of the American College of Cardiology* 39(9): 1436-1442.

Sherwood MW, Douketis JD, Patel MR, Piccini JP, Hellkamp AS, Lokhnygina Y, et al. (2014) Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation* 129(18): 1850-1859.

Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W and Spyropoulos AC (2012) Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 126(13): 1630-1639.

Sjalander S, Sjalander A, Svensson PJ and Friberg L (2014) Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 16(5): 631-638.

Spyropoulos AC and Douketis JD (2012) How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood* 120(15): 2954-2962.

Srivastava A, Hudson M, Hamoud I, Cavalcante J, Pai C and Kaatz S (2008) Examining warfarin underutilization rates in patients with atrial fibrillation: Detailed chart review essential to capture contraindications to warfarin therapy. *Thrombosis Journal* 6: 6.

Staerk L, Lip GYH, Olesen JB, Fosbøl EL, Pallisgaard JL, Bonde AN, et al. (2015) Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ (Clinical Research Ed.)* 351: h5876.

Steinberg BA, Peterson ED, Kim S, Thomas L, Gersh BJ, Fonarow GC, et al. (2015a) Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation* 131(5): 488-494.

Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, et al. (2015b) Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *European Heart Journal* 36(5): 288-296.

Stewart S, Hart CL, Hole DJ and McMurray JJV (2002) A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *The American Journal of Medicine* 113(5): 359-364.

Stiell IG, Clement CM, Perry JJ, Vaillancourt C, Symington C, Dickinson G, et al. (2010) Association of the Ottawa Aggressive Protocol with rapid discharge of emergency department patients with recent-onset atrial fibrillation or flutter. *Cjem* 12(3): 181-191.

Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Unoki T, Ishii M, et al. (2015) Incidence of Stroke or Systemic Embolism in Paroxysmal Versus Sustained Atrial Fibrillation: The Fushimi Atrial Fibrillation Registry. *Stroke; a Journal of Cerebral Circulation* 46(12): 3354-3361.

Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. (2002) A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *The New England Journal of Medicine* 347(23): 1834-1840.

Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, et al. (2015) Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *European Heart Journal* 36(5): 7a.

Weigner MJ, Caulfield TA, Danias PG, Silverman DI and Manning WJ (1997) Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Annals of Internal Medicine* 126(8): 615-620.

Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, et al. (2014) Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Annals of Cardiothoracic Surgery* 3(1): 45-54.

Wolf PA, Abbott RD and Kannel WB (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke; a Journal of Cerebral Circulation* 22(8): 983-988.

Wolf PA, Mitchell JB, Baker CS, Kannel WB and D'Agostino RB (1998) Impact of atrial fibrillation on mortality, stroke, and medical costs. *Archives of Internal Medicine* 158(3): 229-234.

Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. *The New England Journal of Medicine* 347(23): 1825-1833.

Xavier Scheuermeyer F, Grafstein E, Stenstrom R, Innes G, Poureslami I and Sighary M (2010) Thirty-day outcomes of emergency department patients undergoing electrical cardioversion for atrial fibrillation or flutter. *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine* 17(4): 408-415.

Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, et al. (2016) Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. *Journal of the American Heart Association* 5(6).