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AISSA BAH

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ABSTRACT

Atrial fibrillation (AF) causes a five-fold increase in the risk of stroke and is responsible for 10 to 15% of ischemic strokes. Ageing, female sex and several comorbidities increase the risk of thromboembolic complications (TEC) in AF. Oral anticoagulation (OAC) reduces the thromboembolic risk by two thirds and is recommended for AF patients with risk factors for stroke.

The aim of this dissertation was to evaluate sex- and age-related differences in anticoagulation treatment strategies and TEC after cardiac procedures of AF patients. We investigated (1) the interaction of sex, age, and timing of electrical cardioversion (ECV) on the risk of TEC in patients with recent onset (<48 hours) AF not using periprocedural anticoagulation in the retrospective FinCV study from 2003 to 2010, (2) sex-related differences in the use of OAC in AF patients suffering a stroke or intracranial bleed in the retrospective FibStroke study from 2003 to 2012, and (3) the impact of sex and age on the outcome of AF patients undergoing percutaneous coronary intervention (PCI) in the prospective AFCAS study from 2008 to 2010.

The multicenter observational FinCV study (I) consisted of 4715 ECVs in 2313 non-anticoagulated patients with recent onset AF. TEC occurred in 0.8% of patients during a 30-day follow-up. The risk of stroke was especially

high (2.7%) in elderly women with time from symptom onset to cardioversion >12 hours. The multicenter observational FibStroke study (II) consisted of 1747 AF patients suffering their first cerebrovascular event. A total of 78.5% of women and 58% of men had a high stroke risk ($CHADS_2$/CHA_2DS_2-VASc ≥2) with a more pronounced difference in their CHA_2DS_2-VASc score. Only 49% of the female patients with a high stroke risk were on OAC in comparison to 57% of men. Of those patients who were not anticoagulated, as many as two thirds of women and half of men had a high stroke risk. Stroke risk stratification ($CHADS_2$/CHA_2DS_2-VASc) was suboptimally implemented and reasons for not using OAC were poorly reported, particularly for women. The multicenter observational AFCAS study (III) consisted of 925 AF patients undergoing PCI in 17 European centers. Approximately one fifth of patients were ≥80 years old, 41% of whom were women. Octogenarian women had higher CHA_2DS_2-VASc scores than octogenarian men. Although the indication for PCI was acute coronary syndrome (ACS) more often in octogenarians than in younger patients, octogenarian women presented with ACS less often than octogenarian men. There were no differences between octogenarians and younger patients with respect to procedural success or the use of antiplatelet therapy post-PCI. However, the incidence of major adverse cardiac and cerebrovascular events, especially myocardial infarctions, was higher among octogenarians at 12-month follow-up. Nevertheless, the rate of bleeding events was similar with no sex-related difference during one-year follow-up.

To conclude this dissertation showed that female sex and old age increase the risk of TEC after ECV for acute AF. Secondly, women at a high risk of stroke were unsatisfactorily treated with OAC. In AF patients undergoing PCI octogenarians experienced a higher incidence of major cardiac and cerebrovascular events at 12-month follow-up with no sex-related difference.

Keywords: acute coronary syndrome, age factors, anticoagulants, atrial fibrillation, brain ischemia, electric countershock, female, follow-up studies, ischemic stroke, male, myocardial infarction, percutaneous coronary

interevention, platelet aggregation inhibitors, risk assessment, risk factors, sex factors, stroke, thromboembolism

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TIIVISTELMÄ

Eteisvärinä viisinkertaistaa aivohaverin riskin ja aiheuttaa 10–15 % iskeemisistä aivohalvauksista. Korkea ikä, naissukupuoli ja muut samanaikaiset perussairaudet lisäävät tromboembolisten komplikaatioiden riskiä. Antikoagulaatiohoito vähentää tromboembolisten komplikaatioiden vaaraa eteisvärinäpotilailla noin kahdella kolmasosalla, ja sitä suositellaan tukosriskin omaaville eteisvärinää sairastaville potilaille.

Väitöskirjatyössä tutkittiin (1) sukupuolen, iän ja hoitoviiveen vaikutusta tromboembolisten komplikaatioiden ilmaantuvuuteen akuutin (alle 48 tuntia) eteisvärinäkohtauksen sähköisen rytminsiirron jälkeen (retrospektiivinen FinCV- tutkimus v. 2003-2010), (2) sukupuolten välisiä eroja antikoagulaatiolääkityksessä eteisvärinää sairastavilla potilailla, joilla todetaan aivohaveri (retrospektiivinen FibStroke- tutkimus v. 2003-2012), sekä (3) sukupuolen ja iän merkitystä eteisvärinäpotilailla, joille tehdään sepelvaltimoiden pallolaajennustoimenpide (prospektiivinen AFCAS-tutkimus v. 2008-2010).

FinCV -monikeskustutkimus (I) tarkasteli yhteensä 4715 ilman antikoagulaatiohoitoa 2313 potilaalle tehtyä sähköistä rytminsiirtoa alle 48 tuntia kestäneen eteisvärinäkohtauksen yhteydessä. Aivohaverin ilmaantuvuus oli 0.8% 30 päivän seuranta-aikana, ja tukosriski kasvoi 2.7%: iin yli 75 -vuotiailla naispotilailla, jos rytminsiirto tehtiin yli 12 tuntia

rytmihäiriön ilmaantumisesta. FibStroke -monikeskustutkimus (II) koostui 1747 eteisvärinäpotilaasta, jotka hakeutuivat hoitoon ensimmäisen aivohaverin ilmaantuessa. Naisista 78.5%:lla ja miehistä 58%:lla oli korkea tukosriski ($CHADS_2$/CHA_2DS_2-VASc ≥2), ja sukupuolierot olivat suuremmat CHA_2DS_2-VASc- tukoslaskurilla verrattuna $CHADS_2$ -tukoslaskuriin. Korkean tukosriskin omaavista potilaista vain 49% naisista ja 57% miehistä oli antikoaguloitu. Niistä potilaista, joilla ei ollut verenohennuslääkitystä, jopa kahdella kolmasosalla naisista ja puolella miehistiä oli korkea tukosriski. Analysoitaessa $CHADS_2$ /CHA_2DS_2-VASc-tukosriskilaskureiden käyttöä kävi ilmi, että verenohennuslääkitystä käytettiin liian vähän korkean tukosriskin potilailla, ja syyt verenohennuslääkityksestä pidättäytymiseen kirjattiin sairauskertomuksiin riittämättömästi etenkin naispotilaiden kohdalla. AFCAS- monikeskustutkimukseen (III) osallistui 925 eteisvärinäpotilasta, joille tehtiin sydämen pallolaajennustoimenpide yhteensä 17 eurooppalaisessa keskuksessa. Viidesosa potilaista oli ≥80- vuotiaita, ja heistä 41% oli naisia. Yli 80- vuotiailla naisilla oli korkeammat CHA_2DS_2-VASc-tukosriskipisteet samanikäisiin miehiin verrattuna. Vaikka iäkkäämpien potilaiden indikaatio pallolaajennustoimenpiteelle oli useammin sepelvaltimotautikohtaus nuorempiin verrattuna, iäkkäillä naisilla se oli harvinaisempaa kuin samanikäisillä miehillä. Iäkkäiden ja nuorempien potilaiden välillä ei todettu eroja toimenpiteen onnistumisen tai antitromboottisen lääkityksen välillä pallolaajennuksen jälkeen. Sen sijaan merkittävien sydän- ja verisuonitapahtumien, etenkin sydäninfarktien, määrä oli suurempi ≥80- vuotiailla 12 kuukauden seurannassa. Vuototapahtumat eivät siitä huolimatta eronneet iän tai sukupuolen mukaan seuranta-aikana.

Tässä väitöskirjassa osoitettiin, että naissukupuoli ja ikä lisäävät akuutin eteisvärinäkohtauksen rytminsiirtoon liittyviä tromboembolisia riskejä etenkin rytminsiirron viivästyessa, ellei antikoagulaatiohoitoa käytetä. Antikoagulaatiohoidon käyttö naisilla, joilla oli korkea halvausriski, oli epätyydyttävää. Sukupuoli ja ikä eivät vaikuttaneet eteisvärinäpotilaiden antitromboottiseen lääkitykseen, toimenpiteiden onnistumiseen tai vuototapahtumiin sepelvaltimoiden pallolaajennustoimenpiteissä, mutta

12 kuukauden seurannassa merkittävien sydän- ja verisuonitapahtumien määrä oli iäkkäillä suurempi.

Avainsanat: eteisvärinä, hoito, hyytymisenestohoito, ikä, komplikaatiot, leikkaushoito, lääkehoito, naiset, miehet, potilaat, rytmihäitiöt, sukupuoli, sydäntaudit, riskit

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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Bah A, Nuotio I, Grönberg T, Ylitalo A, Airaksinen K.E.J, Hartikainen J.E.K. Sex, age and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation. The FinCV Study. Annals of Medicine May;49(3): 254-259, 2017.

II Bah A, Nuotio I, Palomäki A, Mustonen P, Kiviniemi T, Ylitalo A, Hartikainen P, Airaksinen K.E.J, Hartikainen J.E.K. Inadequate oral anticoagulation with warfarin in women with cerebrovascular event and history of atrial fibrillation. The FibStroke Study. Annals of Medicine Jan;53(1): 287-294, 2021.

III Lahtela H*, Bah A*, Kiviniemi T, Nammas W, Schlitt A, Rubboli A, Karjalainen P, Proietti M, Lip G, Hartikainen J.E.K, Airaksinen K.E.J. Outcome of octogenarians with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry. Clinical Cardiology Dec;40(12): 1264-1270, 2017.
* = Lahtela and Bah contributed equally to this work.

CONTENTS

ABBREVIATIONS

ACS acute coronary syndrome

AF atrial fibrillation

AHRE atrial high rate episodes

AV atrioventricular node

BARC Bleeding Academic Research Consortium

CAD coronary artery disease

CHA_2DS_2-VASc Congestive Heart failure, hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)

$CHADS_2$ Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)

COPD chronic obstructive pulmonary disease

Covid-19 coronavirus disease 2019

DAPT dual antiplatelet therapy

DOAC direct oral anticoagulation

ECG electrocardiogram

ECV electrical cardioversion

HAS-BLED hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)

HF heart failure

HTA hypertension

ICH intracerebral hemorhhage

INR international normalized ratio

LAA left atrial appendage

MACCE	major adverse cardiac/cerebrovascular events
MI	myocardial infarction
NOAC	novel oral anticoagulation
NSTEMI	non-ST-elevation myocardial infarction
OAC	oral anticoagulation
OR	odds ratio
PCI	percutaneous coronary intervention
QoL	quality of life
RAA	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RF	risk factor
SCAF	subclinical atrial fibrillation
STEMI	ST-elevation myocardial infarction
TEC	thromboembolic complications
TEE	transesophageal echocardiogram
TIA	transient ischemic attack
TTE	transthoracic echocardiogram
VKA	vitamin-K antagonist
TTR	time in therapeutic range

1 INTRODUCTION

Globally atrial fibrillation (AF) is the most common cardiac arrhythmia in both women and men. Risk factors for AF include age, hypertension, heart failure (HF), obesity, alcohol use and sleep apnea (Hindricks et al., 2020). The prevalence of AF increases with age. AF symptoms range from mild to incapacitating. The etiology and AF types are heterogeneous. AF reduces cardiac output and leads to an irregular cardiac rhythm and palpitations (Bhatt et al., 2015; Goette et al., 2016a). AF impairs the quality of life (QoL) and causes hospitalizations (Hindricks et al., 2020).

AF is associated with an increased risk of comorbidities such as HF, dementia, stroke and other thromboembolic events, and mortality. AF independently increases the risk of stroke by five-fold (Wolf et al., 1996; Kannel et al., 1998). One third of cardiogenic strokes and 10-15% of ischemic strokes are caused by AF. Ageing and female sex are associated with an increased risk of thromboembolic complications (TEC) in paroxysmal and permanent AF but the risk related to recent onset AF is less clear (Rosamond et al., 2008; Kleemann et al., 2009; Olesen et al., 2011a and 2012; Bushnell et al., 2014).

Oral anticoagulation (OAC) reduces thromboembolic risk by two thirds or circa 66% (Hart et al., 2007) and strokes are less devastating if they occur during adequate OAC therapy (Gladstone et al., 2009). OAC is recommended for AF patients with risk factors for stroke (Kirchhof et al., 2016).

All patients with AF should undergo assessment of stroke risk using risk stratification scores (CHA_2DS_2-VASc score) (Hindricks et al., 2020). Until the end of 2009, guidelines recommended OAC for AF patients with an increased stroke risk but excluded female gender as a risk factor (Fuster et al. 2006). From 2010 onwards, female sex has been included in the risk stratification. Despite effective treatment recommendations, there is substantial heterogeneity in the use of OAC worldwide: OAC is often underused or discontinued and sex-related differences in OAC treatment

may result in different outcomes and prognosis between sexes (O'Donnell 2006; Palomäki et al., 2016a; Steinberg et al., 2017; Marzona et al., 2020).

Approximately 5% of patients undergoing PCI-stenting have an indication for long-term OAC due to AF (Rubboli et al., 2008). The number of patients ≥80 years of age undergoing PCI and stent implantation is increasing (Rajani et al., 2011). Women suffer bleeding events and hemorrhagic strokes more often after PCI compared to men (Chichareon et al., 2020). The elderly population and women are both underrepresented in clinical trials and knowledge concerning the efficacy and safety of their treatment is limited.

2 REVIEW OF THE LITERATURE

2.1 EPIDEMIOLOGY

AF is the most common cardiac arrhythmia with a rapidly increasing prevalence worldwide in both sexes (January et al., 2014; Hindricks et al., 2020). In 2010, there were approximately 21 million men and 13 million women with AF in the world, with a higher incidence and prevalence of AF in developed countries (Chugh et al., 2014). The current global prevalence of AF is estimated at 0.51% with an increase of AF by circa 30% in the last 20 years. The prevalence of AF is estimated to increase by >60% by 2050 (Lippi et al., 2021). In Western countries, the prevalence ranges between 1-4 % and affects white patients more often, whereas in Asian countries the prevalence is slightly lower (0.5 to 2%) (Zulkifly et al., 2018). Increasing age, the burden of AF risk factors as well as better detection of AF have increased the incidence of AF worldwide (Staerk et al., 2017). AF prevalence is higher in elderly patients and it has been estimated that by 2050 more than half of AF patients will be ≥80 years of age (Wolf et al., 1996; Go et al., 2001; Zulkifly et al., 2018). The lifetime risk of AF is related to various factors, such as age, genetics and other clinical factors, and is lower in women (Chugh et al., 2014). It is probable that early intervention of modifiable risk factors may prevent development of AF or delay AF onset (Hindricks et al., 2020).

The prevalence of AF in a medium-size Finnish town (Joensuu) in 2011 was 3.7% (4.1% for men and 3.4% for women) (Hallinen et al., 2014). In 2015, AF prevalence in patients aged ≥75 years was 10% and according to the 2021 Finnish national AF guidelines, the prevalence of AF in the whole population was around 230 000 patients (Atrial fibrillation: Current Care Guidelines 2015; Atrial fibrillation: Current Care Guidelines 2021). In Finland, approximately 8 000 patients suffered an ischemic stroke in 2007 of whom half were women. Nearly 1 300 of these patients had AF and 1 000 were on warfarin before having a stroke (Meretoja et al., 2011). The lifetime cost of a stroke per patient was estimated at 100 000 euros by

Finnish health and social care. Moreover, female patients cost approximately 16% more than their male counterparts with costs increasing in the female population after the age of 70-74 (Meretoja et al., 2011). The cost for elderly patients increased 0.7% to 0.9% per each year of age (Meretoja et al., 2011). Costs were related to existing comorbidities prior to stroke as well as stroke treatment in elderly patients. Permanent institutional care was the most expensive cost regardless of sex. Higher expenses in stroke treatment were also partly explained by the age structure of the Finnish population and a higher number of treated survivors (Meretoja et al., 2011).

Patients with AF are hospitalized more often than patients without AF and 10 to 30% of AF patients are hospitalized at least once a year. Although in-hospital mortality rates in the USA have decreased by a third from 2000 to 2010, approximately 1 to 2% of AF patients die in hospital compared to 0.1% of patients without AF (Patel et al., 2014). Additionally, mortality increases in hospitalized AF patients ≥80 years of age (2%) (Kim et al., 2011; Patel et al., 2014; Steinberg et al., 2014). Direct AF costs amount for 1% of total healthcare spending in the UK. In the USA, in 2008 AF costs ranged between 6 to 26 billion dollars including complications (e.g. stroke) and treatment costs (e.g. hospitalizations) (Stewart et al., 2004; Kim et al., 2011). These sums cannot be directly compared to the Finnish health care system.

2.2 DEFINITION OF ATRIAL FIBRILLATION

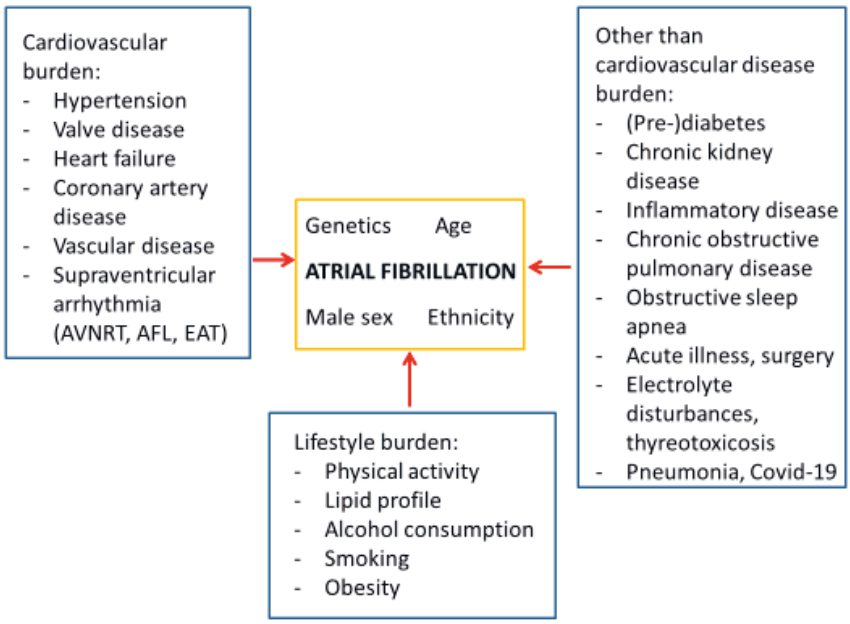
AF is a supraventricular arrhythmia, which is often associated with underlying heart disease, either by being the cause or consequence of heart disease, or because it directly worsens the underlying condition causing AF. Atrial activity is chaotic and results in poor atrial contraction. AF can be diagnosed if the electrocardiogram (ECG) presents a typical AF pattern for at least 30 seconds including (1) irregular R-R intervals, (2) the absence of distinct repeating P waves and (3) irregular atrial activity. ECG recording is easy and cost-effective in documenting permanent AF, and daily ECG recordings in patients over 75 years of age and prolonged monitoring of undiagnosed patients increase the likelihood of detecting

paroxysmal AF (Friberg et al., 2013; Gladstone et al., 2014). Contemporary detection methods include cardiac implantable electronic devices, such as pacemakers, implantable cardioverter defibrillators, cardiac resynchronization therapy devices, implantable loop recorders and wireless consumer electronics, such as smartwatches (Apple Watch) (Fung et al., 2015).

2.3 CLASSIFICATION OF ATRIAL FIBRILLATION

The clinical progression of AF usually evolves from short, infrequent paroxysms to longer, more frequent episodes that in time become permanent (Chugh et al., 2014). In patients without structural disease paroxysmal AF can last for decades (Jahangir et al., 2007).

AF is classified into five main types and more than one can coexist in the same individual (Table 1). Different types of AF do not correspond to the burden of the arrhythmia. AF should be characterized in a structured manner including classification of the type of AF by duration, assessment of stroke risk, symptoms, AF burden and evaluation of substrate to optimize treatment (Charitos et al., 2014; Hindricks et al., 2020).



Abbreviations: AVNRT = atrioventricular nodal reentry tachycardia; AFL = atrial flutter; EAT = ectopic atrial tachycardia; Covid-19 = coronavirus disease 2019.

Figure 1. Atrial fibrillation risk factor burden (adapted from ESC Guidelines on atrial fibrillation 2020)

Table 1. Classification of different AF types (adapted from ESC Guidelines on Atrial Fibrillation 2020)

AF type	Definition
First-ever diagnosed	Not diagnosed before, irrespective of duration of arrhythmia or symptom severity
Paroxysmal	Terminating spontaneously or by intervention within 7 days from onset. Episodes may recur with varying frequency.
Persistent	Continuous arrhythmia that is sustained > 7 days including episodes terminated by intervention after 7 days or more.
Long-standing persistent	Continuous arrhythmia lasting for > 1 year when it is decided to adopt rhythm control strategy.
Permanent	AF that is accepted by the patient and the clinician as permanent excluding any further rhythm control interventions.

2.3.1 Paroxysmal atrial fibrillation

Paroxysmal AF ends spontaneously in most cases within 48 hours and at lengthiest in seven days either independently or by intervention. Many paroxysmal AF episodes are missed due to lack of prolonged ECG monitoring.

2.3.2 Persistent atrial fibrillation

AF is considered persistent if the episode lasts over seven days including cardioverted AF. Distinction between paroxysmal and persistent AF should be based on long-term monitoring (Charitos et al., 2014). If the management strategy is rhythm control in patients with AF having lasted for more than a year, AF should be classified as “long-standing persistent”.

2.3.3 Permanent atrial fibrillation

Permanent AF refers to the arrhythmia that is accepted as such by the patient and the physician and excludes rhythm control therapy. Acceptance of permanent AF underscores a therapeutic attitude.

2.3.4 Lone atrial fibrillation

The term “lone AF” is historical and refers to AF patients without cardiopulmonary disease, hypertension or diabetes and should not be used (Hindricks et al., 2020).

2.4 PATHOGENESIS OF ATRIAL FIBRILLATION

The pathogenesis of AF is complex and not completely understood. Abnormal pathophysiological mechanisms and different disease pathways may result in AF. The causes of AF comprise of structural and/or electrophysiological abnormalities that alter atrial tissue and impulse formation and/or propagation. Physiological states and diseases (e.g. hypertension, atherosclerotic disease, amyloidosis, obesity, valvular heart disease) increase the risk of developing AF and AF progression is associated with the aggravation of these states by the arrhythmia itself (Table 2) (Hindricks et al., 2020 Supplement 1).

Table 2. Pathogenesis of AF and clinical outcome (adapted from ESC Guidelines on Atrial Fibrillation 2016)

Pathophysiological alteration	**Clinical condition**	**Mechanism/functional change**
Fibrosis	High AF burden, HTA, HF, valvular heart disease (pressure, volume overload)	Electrical dissociation, conduction block, complex AF
Inflammation, fatty infiltration	Obesity	Profibrotic, proinflammatory, conduction block, complex AF
Amyloid deposition	Ageing, heart disease, CAD (scarring), genetic disposition	Conduction disturbances
Ion channel remodeling, Ca^{2+}-instability, gap-junction redistribution	High AF burden, genetic factors	Changes in AF cycle duration, heterogeneity of atrial repolarization
Myocyte apoptosis, necrosis, hypertrophy	CAD, HF (cardiomyocyte death, scarring), atrial dilatation, AF	Profibrotic, conduction disturbances
Microvascular and endocardial changes	Atherosclerosis, CAD, peripheral artery disease	Atrial ischemia, structural remodeling, prothrombotic milieu, heterogeneity of electrical function
Sympathetic hyperinnervation	HF, HTA	Propensity to ectopy

AF = atrial fibrillation; HTA = hypertension; HF = heart failure; CAD = coronary artery disease.

AF substrates, triggers, and modulators interact in a complex manner resulting in AF activation. AF requires both a trigger and a modulator for

initiation as well as an appropriate anatomic substrate for maintenance (January et al., 2014; Kirchhof et al., 2016).

2.4.1 Substrates of atrial fibrillation

AF susceptibility increases with any disturbance of atrial architecture as impulse formation and/or propagation is altered. Partly irreversible structural atrial remodeling frequently occurs before AF onset. Structural remodeling affects re-entry and perpetuation of the arrhythmia due to electrical dissociation and local conduction heterogeneities.

Pathophysiological changes in the atria include stretch-induced atrial fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodeling, ischemia, ion channel dysfunction and Ca^{2+}-instability due to different etiologies (diabetes, HF, obesity, coronary artery disease (CAD), hypertension, ageing and genetic predisposition) (Spach et al., 1995; Shinagawa et al., 2002; Kistler et al., 2004; Spach et al., 2007; Allessie et al., 2010).

2.4.2 Triggers of atrial fibrillation

Ectopic focal discharges often initiate AF. The most typical trigger sites are found in the pulmonary veins, but triggers can also arise elsewhere in the atria. At the beginning of the arrhythmia AF shortens the cycle length and refractory period of the atria due to changes in Ca^{2+}-inward current and inward rectifier K+-currents. Disturbances in calcium regulation may trigger delayed afterdepolarizations (Haïssaguerre et al., 1998; Dobrev et al., 2005; Voigt et al., 2014; Dridi et al., 2020).

2.4.3 Modulators of atrial fibrillation

Modulators, such as ischemia and autonomic (parasympathetic and/or sympathetic) activation, can provoke AF (Scherf et al., 1948; Park et al., 2012). Athletes usually suffer from paroxysmal AF, which is thought to arise from increased vagal tone, atrial enlargement as well as possible transient inflammation and increased wall stress during uncomplete recovery.

Nevertheless, physical exercise should not be reduced due to a potential risk of AF (Karjalainen et al., 1998; Guasch et al., 2018).

2.4.4 Risk factors for atrial fibrillation

Risk factors for AF can be static or dynamic (Figure 1). When modifiable, they should be treated aggressively to delay AF-onset (Hindricks et al., 2020). There is currently a shift towards reducing the disease burden before the diagnosis of AF. Modifiable risk factors, such as obesity, smoking, hypertension, alcohol abuse and obstructive sleep apnea, are not included in risk stratification scores (besides hypertension) but should be treated aggressively nevertheless (Staerk et al., 2018; Linde et al., 2018; Hindricks et al., 2020).

The REVERSE-AF trial showed a significant decrease in AF burden and the need for AF ablation after 10% weight loss (Middeldorp et al., 2018). Pathak et al. showed in the ARREST-AF trial that AF ablated patients who received aggressive risk factor management after the procedure, benefited more from ablation in the long-term than AF patients having undergone ablation without risk factor management during follow-up (Pathak et al., 2014). Indeed, patients who received risk factor management suffered less from AF symptoms and AF frequency and saw a decrease in the duration of AF during the 12-month follow-up (Pathak et al., 2014). These data in addition to the updated AF guidelines highlight the importance of treating modifiable risk factors actively (Pathak et al., 2014; Middeldorp et al., 2018; Hindricks et al., 2020).

Risk assessment should not only focus on high-risk patients but also on true low-risk patients with annual event rates <1% without OAC initiation in addition to optimization of other dynamic (modifiable) comorbidities (Lip et al., 2017; Hindricks et al., 2020). In elderly patients, treatment options should be discussed individually with the overall clinical context (Poposka et al., 2019). Recently, a CHA_2DS_2-VAScAFBurden score has been proposed, focusing on more individualized and efficient AF treatment. The focus of this is on a biological gradient of AF burden and stroke risk that considers clinical and non-clinical AF phenotypes (Tiver et al., 2021).

2.4.5 Genetics and atrial fibrillation

Genetic studies have showed an association between AF and heredity (Arnar et al., 2006; Lozano-Velasco et al., 2020). Monogenic and polygenic factors increase the risk of developing AF (Choi et al., 2020). Studies on selected gene variants may improve treatment of AF in the future (Roselli et al., 2020).

2.4.6 Sex-related cardiac differences and atrial fibrillation

There is some evidence on sex-related cardiac differences, which may influence pathophysiological mechanisms leading to AF. Heart rate and the size of ventricular myocytes differ between men and women (Utemi et al., 1998; Tadros et al., 2014). Sex hormones affect the expression of ion channel subunits and the modulation of channel function, and they also influence ADP and proteins involved in depolarization and trigger activity. Repolarization in female hearts is associated with fewer potassium channel subunits and sex hormones may affect Ca^{2+}-currents (Tadros et al., 2014; Odening et al., 2014a and b; Linde et al., 2018). Evidence on the effect of the menstrual cycle on cardiac electrophysiology, autonomic system and arrhythmia prevalence is inconsistent (Linde et al., 2018).

2.4.7 Coronavirus disease and atrial fibrillation

Recent literature shows that coronavirus disease 2019 (Covid-19) is associated with cardiac arrhythmias, such as AF (Bhatla et al., 2020; Inciardi et al., 2020; Wang et al. 2020). AF prevalence ranges from 20-40% in hospitalized Covid-19 patients and increases in patients with cardiovascular diseases and those patients who do not survive (Inciardi et al., 2020). Older age, prior AF diagnosis and comorbidities (such as hypertension and HF) were associated with more frequent AF (Bhatla et al., 2020; Taha et al., 2020). It has been suggested that Covid-19 patients with new-onset AF may have a pre-existing substrate for AF that is activated by the infection (Gawałko et al., 2020). Atrial arrhythmias increase morbidity and mortality of Covid-19. Covid-19 may contribute to the formation of a prothrombotic state as well as activate or worsen pre-existing AF.

Furthermore, AF significantly increases 30-day mortality irrespective of age, co-morbidities and pre-existing or new-onset AF in Covid-19 patients (Gawałko et al., 2020; Peltzer et al., 2020).

2.5 MORTALITY AND MORBIDITY IN ATRIAL FIBRILLATION

Despite progress made in treatment, AF is still a common cause of major cardiovascular events, such as myocardial infarction (MI), strokes and death. AF increases the risk of total and cardiovascular mortality as well as sudden cardiac death (Pedersen et al., 2006; Miyasaka et al., 2007; Soliman et al., 2014; Feng et al., 2020).

Cardiovascular deaths in patients with AF are common despite adequate treatment. The INTERSTROKE study (O'Donnell et al., 2016) pointed out the differences in treatment, diagnostics and stroke units, which were less available in low- and middle-income countries compared to high-income countries. In the UK, patients with a higher stroke risk received OAC less often (Cowan et al., 2013). Infrastructure and education do not explain such trends in higher income countries. Adverse outcomes may be better recorded in higher income countries but increasing comorbidities, such as obesity, diabetes and hypertension, may negatively affect stroke prevalence despite better treatment options. This may affect stroke incidence and mortality (Gale et al., 2019).

The disease burden of AF patients evolves over time. Hospitalization is frequent due to AF management, HF and MI. During the last decades, hospitalizations due to HF decreased in the USA whereas hospitalizations due to AF increased. Age and female sex are independent risk factors for HF-related AF and hospitalization, and both conditions often coexist, worsening the outcome (Soliman et al., 2014; Vasan et al., 2019; Reinhardt et al., 2021). There is a need for additional research to better target patients at risk of comorbidities and increased mortality.

AF is almost or totally asymptomatic in 20-40% of patients in comparison to half of patients having severe symptoms and 16% with disabling symptoms (Boriani et al., 2015; Freeman et al., 2015). AF results in a variety of symptoms, such as fatigue, palpitations and impaired physical

capacity. Symptom severity should be reported with the modified EHRA–scale (Table 3) (Modified European Heart Rhythm Association symptom) revised in 2014 (Wynn et al., 2014). AF is associated with an increased risk of dementia, cognitive impairment, decreased QoL and depressed mood (Ott et al., 1997; Marzona et al., 2012; Schnabel et al., 2013; Freeman et al., 2015). Patients with paroxysmal AF often report anxiety and palpitations (Lip et al., 2015; Arbelo et al., 2012) and patients with persistent AF report depressed mood, fatigue and poorer capacity for exercise (Lip et al., 2015; von Eisenhart et al., 2015). Therapy, be it pharmacological and/or interventional, aims at improvement of QoL (Hindricks et al., 2020).

Table 3. The modified Modified European Heart Rhythm Association symptom (EHRA) score (adapted from ESC Guidelines on Atrial Fibrillation 2020)

EHRA	Symptoms	Classification
1	None	-
2a	Mild	Normal daily activity, symptoms not troublesome to patient
2b	Moderate	Normal daily activity, troublesome symptoms to patient
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

2.6 RISK OF STROKE AND BLEEDING IN ATRIAL FIBRILLATION

AF, irrespective of duration or classification, contributes to a prothrombotic milieu due to myocardial structure, functional changes and stasis of blood in the atrium and especially in the left atrial appendage (Lim et al., 2013). AF promotes a hypercoagulable state: hypocontractility reduces local endothelial shear stress, which activates plasminogen activator inhibitor 1. Ischemia promotes inflammation, which activates endothelial adhesion molecules and promotes shedding of endothelial cells. This cascade results

in tissue factor exposure to the blood stream and creates a thrombogenic environment in the atria. As a result, AF significantly increases the risk of TEC (i.e. stroke and systemic embolism) (Kirchhof et al., 2016). There is increasing knowledge on the dynamic nature of certain risk factors or risk modifiers, which highlight the need to regularly assess stroke and bleeding risk with guideline-recommended stratification scores (Hindricks et al., 2020). Recent guidelines highlight treatment optimization for AF patients and propose the Atrial Fibrillation Better Care pathway (ABC or A: avoid stroke/anticoagulation, B: better symptom control, C: cardiovascular risk and comorbidity optimization) (Lip, 2017; Hindricks et al., 2020;). Elderly (≥75 years old) AF patients are undertreated, although AF prevalence and stroke risk increase with age. OAC therapy is beneficial for high stroke risk patients, such as the elderly, despite frailty, falls and comorbidities (Lloyd-Jones et al., 2004; Lip et al., 2015; Marzona et al., 2020).

2.6.1 Risk factors for stroke

Several patient characteristics have been identified to enhance risk stratification of stroke and thromboembolisms in AF patients. Contemporary clinical risk stratification scores are mainly based on risk factors identified from non- vitamin-K antagonist (VKA) arms of trial cohorts and one cohort study (Framingham) (Wolf et al., 1991). Clinical trials have limitations in the systematic documentation of all potential risk factors for TEC. Risk categorization differs between different scores (Wolf et al., 1991; Lip et al., 2010) and their value in predicting strokes is only modest (C-statistics circa 0.6) (Stroke in AF Working Group, 2007).

Hart et al. (2007) concluded in a systematic review of stroke risk factors that only four risk factors were consistent: prior stroke or transien ischemic attack (TIA), advancing age, hypertension, and diabetes. The Euro Heart Survey and other studies showed that female sex (Dagres et al., 2007), vascular disease (Conway et al., 2004) and age >65 years increased stroke risk (Lip et al., 2002).

2.6.2 Risk assessment of stroke

Stroke risk stratification was developed in small cohort studies in the late 1990s. It was then refined and validated in larger populations (SPAF III Writing Committee, 1998; Gage et al., 2001). Many risk scores have evolved from the now historical AF Investigators schema (AF Investigators, 1994), a placebo-controlled trial of warfarin vs. control, and the SPAF risk score (SPAF III Writing Committee, 1998), which included female sex as a risk factor. Birmingham/NICE, $CHADS_2$ and CHA_2DS_2-VASc scores have been developed from these (Hart et al., 1999; Gage et al., 2001; Lip et al., 2010). Biomarker-based risk scores are new promising tools and may be validated in the future to identify those at a truly low risk of stroke (Hijazi et al., 2016).

$CHADS_2$

The $CHADS_2$ score (one point for Cardiac failure, Hypertension, Age and Diabetes [CHAD] and two points for Stroke/TIA [S_2]) has been validated in several non-valvular AF cohorts. It was implemented in international guidelines in 2006 (Fuster et al., 2006). The stroke risk increases approximately 2.0% for each point (from 1.9% with a score of 0 to 18.2% with a score of 6) (Table 4). Its limitation is the score of 1 representing an "intermediate risk", which can result in not identifying those at lowest risk. A total of two thirds of subjects were classified as having an intermediate risk for a stroke, and TEC occurred in low-risk $CHADS_2$ subjects (Lip et al., 2010). A $CHADS_2$ score of 2 due to prior stroke may also indicate a greater burden than indicated (January et al., 2014).

CHA_2DS_2-VASc

The revised $CHADS_2$, namely CHA_2DS_2-VASc or Birmingham 2009 schema, (Congestive heart failure, Hypertension, Age ≥75 [two point], Diabetes, Stroke [two points], Vascular disease, Age 65–74, and Sex [female]) replaced the $CHADS_2$ score in international guidelines in 2010. The CHA_2DS_2-VASc score enhanced the classification of stroke risk with the addition of vascular disease, female sex and age of 65 to 74 years as new

risk factors (Table 4). The C-statistic of approximately 0.6 improved slightly with the revision of risk stratification in predicting TEC in low-risk patients and a smaller proportion of patients were categorized as intermediate-risk patients (Lip et al., 2010).

Table 4. $CHADS_2$ and CHA_2DS_2-VASc- scores and the adjusted annual stroke rate (adapted from ESC Guidelines on Atrial Fibrillation 2020)

$CHADS_2$	**Adjusted stroke rate (% per y)**	**CHA_2DS_2-VASc**	**Adjusted stroke rate (% per y)**
0	1.9	0	0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15.20

2.6.3 Subclinical atrial fibrillation and stroke risk

There are no current guidelines on OAC initiation in subclinical AF (SCAF) or atrial high-rate episodes (AHRE) and treatment decisions may vary significantly (Khan et al., 2013). The minimum duration of SCAF requiring initiation of OAC is unclear. SCAF duration is associated with strokes, HF and hospitalization (Wong et al., 2018; Kaplan et al 2019). Different devices have been validated for the detection of AF paroxysms (Kaleschke et al., 2009; Tieleman et al., 2014; Lowres et al., 2014). Patients with a previous stroke of unknown etiology or with stroke risk factors without a prior stroke might benefit from prolonged screening for AF or AHRE (Healey et al., 2019; Boriani et al., 2020).

Almost 85% of patients with implanted pacemakers have subclinical, short-lasting and asymptomatic AF (Healey et al., 2012; Healey et al., 2019).

The prevalence of asymptomatic paroxysmal AF in patients >75 years of age increases with duration of monitoring, and in elderly patients with other cardiovascular risk factors, long-term monitoring has demonstrated short-lasting (from 20 seconds to circa five minutes) AF in one third of patients (Ziegler et al., 2012; Engdahl et al., 2013). Device-monitoring at a single-time point shows approximately 1–3% of asymptomatic patients to have undiagnosed AF and that approximately 25–50% of emergency ward patients have paroxysmal AF (Ziegler et al., 2012; Oldgren et al., 2014). AF detected by single-screening-ECG can be considered permanent or persistent rather than paroxysmal as monitoring usually lasts for ≤30 seconds (Ziegler et al., 2012).

The relative and absolute stroke risks appear lower in SCAF compared to other (clinical) AF types (Gage et al., 2001; Healey et al., 2019). In patients >65 years old and a diagnosis of hypertension, SCAF >6 minutes was associated with stroke incidence. However, only 8% had SCAF 30 days prior to their stroke and the median time from SCAF diagnosis to stroke was 339 days (Brambatti et al., 2014). A recent 2017 consensus statement suggested OAC initiation for high-risk patients with SCAF episodes >5 minutes (Gorenek et al., 2017).

The risk of stroke and all-cause mortality is lower in paroxysmal AF compared to persistent or permanent AF (Steinberg et al., 2015). This may be due to hemodynamic or electromechanical differences, shorter (less than six months) duration of AF and a smaller AF burden in paroxysmal AF (Steinberg et al., 2015). Stroke risk may be affected by the general risk profile of patients with paroxysmal, persistent or permanent AF (Zhang et al., 2019; Paciaroni et al., 2019). However, in respect to stroke prevention, patients with paroxysmal, persistent and permanent AF are treated similarly.

2.6.4 Risk assessment of bleeding

Anticoagulant therapy increases the risk of bleeding. Risk factors for stroke and bleeding partly overlap. Bleeding risk is not exclusively static. It includes dynamic factors that should be assessed, corrected, and

reassessed, to allow OAC initiation also in patients with high bleeding scores because of the net clinical benefit. The ESC 2020 guidelines highlight precise and separate analysis of non-modifiable, potentially modifiable, and modifiable risk factors, including biomarkers, for bleeding with OAC and antiplatelet therapy (Hindricks et al., 2020).

HAS-BLED

The HAS-BLED score (systolic blood pressure >160 mm Hg, abnormal liver or renal function, history of stroke or bleeding, labile INRs, elderly age (>65 years), the use of drugs that promote bleeding or alcohol abuse) is useful in assessing treatable and more permanent bleeding risk factors (Pisters et al., 2010; Olesen et al., 2011b). The risk for bleeding is considered high with a score ≥3 and corresponds to an annual risk of serious bleeding of 4% or more (Pisters et al., 2010). As such it does not exclude OAC therapy but may necessitate closer observation, monitoring or different dose selection for antithrombotic treatment. OAC therapy should be initiated with HAS-BLED-scores ≤2, as the risk of serious bleeding is less than 2% per year, or if the CHA_2DS_2-VASc score is higher than the HAS-BLED score (Atrial fibrillation: Current Care Guidelines 2021).

Other bleeding risk scores

Other bleeding scores exist but have seldom been prospectively tested in RCTs. The ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) (O'Brien et al., 2015) and more recently the ABC (Age, Biomarkers [GDF-15, cTnT-hs, hemoglobin] and Clinical history [previous bleeding]) bleeding risk scores were validated in a large OAC-treated AF population and were shown to be superior to HAS-BLED (Hijazi et al., 2016). The new DAIGA score predicts the bleeding risk of AF patients with triple antithrombotic therapy after drug-eluting stent implantation (Kobayashi et al., 2016). Its predictive value is superior to HAS-BLED and the DAIGA-score includes a cut-off level for INR and the stopping of dual antiplatelet therapy (DAPT) (Kobayashi et al., 2016). To date, there is no information on the

target level of INR even though HAS-BLED includes labile INR as a risk factor for bleeding. However, these risk scores have not been implemented into routine use.

The RIETE score (Computerized Registry of Patients with Venous Thromboembolism: 2 points for recent bleeding, 1.5 points for abnormal creatinine levels or anemia and 1 point for each of the following: >75 years of age, cancer or pulmonary embolism) is a point-based score developed from a major venous thromboembolism cohort (Ruiz-Gimenez et al., 2008). The items of the ATRIA score (Anticoagulation and Risk Factors in Atrial Fibrillation: anemia 3 points, severe renal disease 3 points, >75 years of age 2 points, prior hemorrhage 1 point and hypertension 1 point) (Fang et al., 2008) and the HEMORR2HAGES score (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age [>75 years], Reduced platelet count or function, Rebleeding risk [prior bleed = two points], Hypertension [uncontrolled], Anemia, Genetic factors [CYP 2C9 polymorphisms], Excessive fall risk [including neuropsychiatric disease] and Stroke) (Gage et al., 2006) partly overlap with HAS-BLED risk factors. HAS-BLED has been found to be superior to the HEMORR2HAGES or ATRIA scoring systems but C indexes are below 0.70 for all three scores, which implies modest predictive value. The predictive accuracy of HAS-BLED, HEMORR2HAGES and ATRIA for patients ≥80 years of age is equal, however, HAS-BLED is slightly superior to HEMORR2HAGES and ATRIA for patients <80 years of age (Fauchier et al., 2016; Sani et al., 2016).

2.7 TREATMENT OF ATRIAL FIBRILLATION

The treatment of atrial fibrillation can be divided into rhythm vs. rate control and stroke prevention. Rhythm control therapy aims to restore and maintain sinus rhythm whereas rate control therapy accepts the presence of AF and aims to control ventricular rate at rest and during exercise as well as improve QoL despite AF. The objective of rhythm and rate control is to improve symptoms and preserve cardiac function. Earlier studies showed no difference in long-term morbidity or mortality between patients randomized to receive rhythm or rate control treatment (Van Gelder et al.,

2002; Al-Khatib et al., 2014). However, recent studies demonstrate that rhythm control decreases adverse outcomes and increases QoL and survival particularly in patients with HF (Kirchhof et al., 2020; Packer et al., 2021). The CABANA study showed that among AF patients with HF and preserved systolic left ventricular function, ablation reduced all cause-mortality, AF recurrence and AF burden, and improved QoL during a five-year follow-up (Packer et al., 2021). Treatment strategy assessment is based on the severity of symptoms as well as the possibility of maintaining sinus rhythm (Kirchhof et al., 2007; Grecu et al., 2020) demonstrated that sex differences prevail in rhythm control treatment as women undergo ablation less often, although women are more symptomatic and the success rate does not differ in comparison to men. Women suffer acute complications more frequently in less experienced centers, have more comorbidities and are more often overweight (Grecu et al., 2020).

A crucial element of AF treatment is the prevention of strokes and other TEC. Patient management should include the ABC pathway to avoid strokes, manage symptoms better and optimize cardiovascular and other comorbidities (Lip et al., 2017; Hindricks et al., 2020). Based on recent studies, the ESC 2020 guidelines recommend precise analysis of non-modifiable, potentially modifiable and modifiable risk factors, and include hypertrophic cardiomyopathy as a risk factor for stroke, highlighting the importance of the treatment of hypertension (Jung et al., 2019; Hindricks et al., 2020). AF burden should not influence the decision of an intervention that is purposeful for other reasons, and women and men should be offered equal treatment options (Kirchhof et al., 2016; Hindricks et al., 2020).

2.7.1 Rhythm control therapy

Restoring and maintaining sinus rhythm as long-term rhythm-control management is indicated to decrease symptoms and improve QoL (class IA). It can be achieved by cardioversion, antiarrhythmic drugs and/or catheter ablation (Hindricks et al., 2020). RCTs have failed to show a superiority of rhythm control on the mortality for either treatment strategy

in asymptomatic patients or patients with mild symptoms (EHRA 1-2). However, a recent study demonstrated the superiority of early rhythm control therapy with antiarrhythmic drugs or ablation in decreasing adverse cardiovascular outcomes during a five-year follow-up (studied in AF patients diagnosed ≤1 year ago in comparison to the usual care of AF symptoms) (Kirchhof et al., 2020). Furthermore, rhythm control with catheter ablation in selected AF patients with advanced HF reduces mortality (Marrouche et al., 2018; Packer et al., 2021). Short-term antiarrhythmic drug treatment prevents AF recurrence but is not as effective as long-term treatment. In patients with recent onset AF diagnosis (≤1 year), early rhythm-control therapy either with antiarrhythmic drugs or ablation therapy was beneficial and decreased adverse events in comparison to symptom-relieving therapy (Kirchhof et al., 2012; Kirchhof et al., 2020). However, a recent study showed that catheter ablation in asymptomatic patients with persistent AF resulted in symptomatic recurrent atrial tachycardia in almost 40% of previously asymptomatic patients (Wu et al., 2016).

Lifestyle interventions

Unhealthy lifestyle factors and borderline conditions increasing the risk of AF activation should be treated early to postpone AF development. Cardiovascular and other comorbidities should be managed also after AF diagnosis (ABC pathway) (Lip et al., 2017). Modifiable risk factors that increase the disease burden (e.g. obesity, hyperlipidemia, chronic obstructive pulmonary disease, obstructive sleep apnea, alcohol use or physical inactivity) should be targeted and optimized. Furthermore, opportunistic AF screening in hypertensive patients or patients with obstructive sleep apnea is recommended (class IIa-b) (Hindricks et al., 2020). In order to improve long-term procedural success, active lifestyle interventions should be addressed and modifiable risk factors (e.g. obesity, hypertension and tobacco) aggressively treated already prior to ablation (Packer et al., 2014; Middledorp et al., 2018).

Cardioversion of atrial fibrillation

In direct-current cardioversion, an electrical shock is delivered under general anesthesia. The shock is given in synchrony with the QRS complex to prevent ventricular fibrillation if the shock were to be given during ventricular repolarization on the T wave. Successful cardioversion is affected by technical factors, such as energy, waveform and electrode placement (Kerber et al., 1996; Kirchhof et al., 2002). A biphasic waveform is more effective than a monophasic waveform (Kerber et al., 1996). A high-energy shock at initiation is also more effective and may improve success of cardioversion and thus diminish the duration of sedation (Mittal et al., 2000; Gallagher et al., 2001). If cardioversion is unsuccessful, it may be reattempted after administering an antiarrhythmic medication (Oral et al., 1999).

The success of cardioversion decreases after the duration of AF surpasses ≥6 months (Frick et al., 2001). AF recurrence increases with elderly patients, women, prior history of cardioversions and comorbidities, such as chronic obstructive pulmonary disease (COPD), larger left atrial volume and HF (Ecker et al., 2018). The most serious complications of cardioversion are thromboembolisms, sedation-related complications, ventricular tachycardia and fibrillation and bradyarrhythmias. Minor side effects include skin burn or irritation from electrodes, muscle soreness and the reprogramming or altering of implanted cardiac device function.

In patients with hemodynamic instability, immediate cardioversion is the treatment of choice (Hindricks et al., 2020). With unstable acute coronary syndrome (ACS) patients with new-onset AF, urgent direct-current cardioversion should be performed to prevent ongoing ischemia or inadequate rate control (Kirchhof et al., 2003). A wait-and-see strategy may be opted for in stable recent onset AF patients instead of early cardioversion as paroxysmal AF often converts spontaneously into sinus rhythm within 24 hours (Pluymaekers et al., 2019).

Antiarrhythmic drugs can also be used to facilitate electrical cardioversion (Hindricks et al., 2020). If propafenone or flecainide treatment (in addition to a beta blocker or nondihydropyridine calcium

channel antagonist) have been proven successful in hospital settings, a peroral administration at home (pill-in-the-pocket) is a simple option for selected out-of-hospital patients (Alboni et al., 2004). Vernakalant, flecainide or propafenone are recommended for pharmacological cardioversion of recent onset AF (class IA) (Hindricks et al., 2020). Amiodarone is a potent antiarrhythmic drug commonly used in AF cardioversion and is also safe in the elderly AF population. It has a delayed onset of action in comparison to vernakalant and is comparable to placebo during the first hours of infusion (Camm et al., 2011). Amiodarone may require infusions for several hours to achieve conversion of AF into sinus rhythm (Khan et al., 2003). Ibutilide is an alternative to ECV but may also be used as pretreatment to increase the success rate of conversion of AF to sinus rhythm. It requires, however, close monitoring for several hours after drug infusion due to a risk of ventricular arrhythmias (Nair et al., 2011).

Guidelines recommend a follow-up for AF patients after cardioversion to optimize treatment and assess the efficacy of the rhythm control strategy. Follow-up should focus on the early recognition of AF recurrence, the evaluation symptoms and antiarrhythmic drugs' side-effects, QoL as well as comorbidities to optimize the maintenance of sinus rhythm (Hindricks et al., 2020).

Antiarrhythmic therapy to maintain sinus rhythm

Precipitating and reversible causes of AF should be treated before initiating antiarrhythmic drug therapy. Antiarrhythmic drug efficacy is modest and may result in partial symptom recovery and incomplete AF suppression. The indication for initiation of long-term antiarrhythmic therapy is the relief of symptoms and it should include an overview of symptom burden, drug side-effects and patient preference (Hindricks et al., 2020). Antiarrhythmic drug therapy may be continued after pulmonary vein isolation (catheter ablation) to prolong maintenance of sinus rhythm despite inadequate efficacy prior to ablation (Duytschaever et al., 2018). Safety considerations guide antiarrhythmic drug selection more than drug efficacy, and the increased risk for adverse effects should be considered (e.g. heart disease,

bradyarrhythmias, risk factors for excessive QT prolongation and torsades de pointes, patient age and renal or hepatic dysfunction). Antiarrhythmic drugs are usually not the recommended treatment option for patients with coronary artery disease (CAD), structural heart disease, significant left ventricle hypertrophy and HF (Hindricks et al., 2020).

Currently available and routinely used antiarrhythmic drugs are amiodarone, flecainide and propafenone (Dan et al., 2018). Amiodarone is the most potent drug and it is the only antiarrhythmic drug that can be used in patients with moderate or severe cardiac failure. However, amiodarone requires regular laboratory monitoring due to potentially toxic side effects and should not be used as first choice therapy. Other antiarrhythmic drugs should be either contraindicated or proved inefficient before initiating amiodarone (AFFIRM First Antiarrhythmic Drug Substudy Investigators, 2003; Singh et al., 2005). If the AF becomes permanent, the indication for antiarrhythmic drug therapy no longer exists (January et al., 2014; Kirchhof et al., 2016;).

Upstream drug therapy

There is emerging evidence on the benefits of upstream therapy, which refers to the primary and secondary prevention of AF and the treatment of concomitant cardiovascular conditions. It should be considered for AF patients in addition to antiarrhythmic drugs and catheter ablation (Goette et al., 2013; Hindricks et al., 2020; Kirchhof et al., 2020). Upstream therapy includes angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, statins, beta blockers and mineralocorticoid receptor antagonists (aldosterone) (Hindricks et al., 2020). Upstream therapy affects structural remodeling of the atria and may promote maintenance of sinus rhythm (Smit et al., 2009). However, primary prevention is not effective for patients without cardiovascular disease (Goette et al., 2013). Valsartan may be beneficial in secondary prevention (preventing AF recurrence) (De Vecchis et al., 2020). Currently, results are heterogeneous and more research is needed to validate treatment options.

Catheter ablation to maintain sinus rhythm

Pulmonary veins often serve as focal activators of AF and treatment with local pulmonary vein radiofrequency catheter ablation, cryoablation or isolation of the pulmonary veins suppress recurrent AF (Haïssaguerre et al., 1998; Pappone et al., 2001). The procedure is increasingly effective and safe (Calkins et al., 2012). Invasive treatment of AF should be considered for highly symptomatic patients and patients with a poor QoL, particularly those with failed antiarrhythmic therapy. Catheter ablation is most effective in young patients with paroxysmal AF and without structural heart disease (Leong-Sit et al., 2010). It is superior to antiarrhythmic medication in patients with rhythm-control strategy and who have had an unsatisfactory response to medication (IA) (Calkins et al., 2017).

The decision to pursue AF catheter ablation depends on variable factors, not the least being patient preference (Calkins et al., 2012). The procedure may lead to adverse effects especially in the presence of risk factors (older age, female sex, $CHADS_2 \geq 2$) (Shah et al., 2012). Complication rates range around 5-8%, major complications around 1.7% and readmission within 30 days circa 9% (Arbelo et al., 2012; Shah et al., 2012). Less severe complications include asymptomatic cerebral embolisms detectable on imaging that spontaneously resolve over time. However, greater microembolic lesions (10 mm) have been detectable by magnetic resonance imaging as far as three months post-procedure (Herrera Siklódy et al., 2011). Also, age and the number of microemboli have been shown by Kochhäuser et al. (2015), to have a negative influence on neuropsychological tests although no acute negative cognitive outcome was apparent (Kochhäuser et al., 2015). ECV failure after catheter ablation does not predict long-term outcome of ablation. Instead, AF history as well as procedure time and complexity are associated with AF recurrence in the long term (Ebert et al., 2017).

Catheter ablation results in symptom-free patients and better QoL although complications requiring intervention are more frequent compared to antiarrhythmic drug therapy (Calkins et al., 2017). Catheter ablation reduces all-cause mortality, the risk of stroke, major bleeding and cardiac arrest in comparison to antiarrhythmic drugs and may be

considered as first-line rhythm control therapy for selected patients (Marrouche et al., 2018; Noseworthy et al., 2019; Hindricks et al., 2020; Packer et al., 2021).

In some studies, the maintenance of sinus rhythm ranges around 80-90% during a three-year follow-up (Nademanee et al., 2015; Metzner et al., 2016) whereas other studies report a success rate of approximately 50% during a five-year follow-up (Schreiber et al., 2015; Poole et al., 2020). Catheter ablation also reduces AF recurrence during a five-year follow-up by approximately 50% in comparison to medical treatment (Poole et al., 2020). It is important to note that although catheter ablation has been in medical use for several decades, long-term (over 10-year) follow-up studies are still lacking. Atrial fibrosis decreases the response to catheter ablation (Akoum et al., 2011). There is increasing evidence that preprocedural cardiac magnetic resonance imaging is of clinical utility in identifying patients with left atrium fibrosis as fibrosis is independently associated with procedure outcome and AF recurrence (Chubb et al., 2019; Ghafouri et al., 2021). The CASTLE-AF trial showed that AF patients with HF benefited from catheter ablation: mortality, hospitalization and worsening HF rates decreased (Marrouche et al., 2018). Catheter ablation also lowered AF burden and improved ejection fraction but failed to prevent AF recurrence (Marrouche et al., 2018). Additionally, the CABANA trial demonstrated superiority of catheter ablation in patients with stable HF in survival (lack of primary outcomes, such as all-cause mortality, stroke, serious bleeding or cardiac arrest), AF recurrence and QoL (Packer et al., 2021). Further research is needed on the discontinuation of OAC therapy after catheter ablation.

In addition to the usual radiofrequency energy source, pulmonary vein isolation can be performed with cryoablation (Kuck et al., 2016). Cryoballoon ablation is safe, efficient and superior to antiarrhythmic drug therapy with recurrent paroxysmal AF patients (Andrade et al., 2021; Wazni et al., 2021). In a recent register study with a 12-month follow-up, cryoballoon ablation technique was quicker and decreased the need for re-ablation in comparison to radiofrequency ablation (Mörtsell et al., 2019).

More research, especially randomized clinical trials, are needed to confirm the findings.

Symptomatic or asymptomatic AF episodes are frequent during the first three months following catheter ablation (Hindricks et al., 2005; Calkins et al., 2012). Asymptomatic AF episodes may increase also in symptomatic patients and long-term monitoring is needed to assess genuine AF recurrence rates (Hindricks et al., 2005). Post-ablation AF episodes are associated with an increased risk of hospitalization and failure of treatment. However, they do not exclude success in the long term and AF paroxysms should be treated with cardioversions (Calkins et al., 2012). If AF paroxysms persist after three months, it may indicate the need to re-ablate or start antiarrhythmic medication (Gaztañaga et al., 2013).

2.7.2 Rate control therapy

Rate control aims to control heart rate during rest and exercise in order to maintain QoL and preserve cardiac function. In patients with mild symptoms (EHRA 1-2), the prognosis of patients on rate control treatment does not differ from those AF patients treated with rhythm control (Van Gelder et al., 2002). The optimal heart rate in AF patients is not known. Targets for optimal ventricular rate control differ and are affected by the degree of symptoms and comorbidities. Target rates are achieved in approximately half of patients when aiming for a heart rate of ≤80 beats per minute (resting) or averaging ≤100 beats per minute (Van Gelder et al., 2002; Olshansky et al., 2004). There is no significant difference in adverse outcomes (e.g. death, hospitalization for HF, TEC, bleeding or life-threatening arrhythmias) or superiority of either lenient (resting heart rate <110 bpm) or strict rate control (resting heart rate <80 bpm) (Hagens et al., 2004). Thus, lenient rate control may be an option for minimally symptomatic elderly patients, and it is effective and easier to achieve in patients with permanent AF compared to strict rate control (Van Gelder et al., 2010; Olshansky et al., 2010; Groenveld et al., 2013). Potential advantages of rate control include fewer adverse effects of drugs (Wyse et al., 2002). Finnish guidelines recommend rate control therapy to elderly AF

patients with mild symptoms (EHRA 1-2) (Atrial fibrillation: Current Care Guidelines 2021). Finnish guidelines suggest a mean daily heart rate of <110 bpm during rest for asymptomatic patients and a stricter target for more symptomatic patients of 60 to 80 bpm during rest and 90 to 115 bpm during light exercise (Atrial fibrillation: Current Care Guidelines 2021).

Pharmacological rate control

Commonly used beta blockers are potent in controlling heart rate in acute and permanent AF. They block sympathetic tone and reduce ventricular rate effectively and can be administered orally or intravenously. Beta blockers reduce the mortality of HF patients with sinus rhythm but not of HF patients with AF (Olshansky et al., 2004; Van Gelder et al., 2016)

Diltiazem and verapamil have direct atrioventricular (AV) nodal effects and can be used in acute and permanent AF. Intravenously administered diltiazem and verapamil are safe and effective in most patients with recent onset AF (Ellenbogen et al., 1991). Diltiazem may also be superior to metoprolol in rapid rate control (Martindale et al., 2015). Diltiazem has little effect on AF during daily activity (Farshi et al., 1999). Both nondihydropyridine calcium channel blockers have negative inotropic effects and are contraindicated for patients with systolic dysfunction, decompensated HF or pre-excitation (Gulamhusein et al., 1982; Jacob et al., 1985).

Intravenous digoxin (a second-line therapy) has slow onset of action (>1 hour) and a peak effect at approximately six hours after administration. It is not effective in recent onset AF in comparison to conversion to sinus rhythm (Jordaens et al., 1997). Oral digoxin slows the heart rate at rest but has minimal or no effect during exercise. Combined with atenolol, digoxin has a synergistic effect on the AV node (Farshi et al., 1999). It has no negative inotropic effects and thus can be used in patients with HF. Digoxin may be used in elderly patients who are physically inactive and have not benefited from other treatment options if used with caution (Van Gelder et al., 2016). Recently digoxin was found to be superior to beta blockers regarding proBNP (proB natriuretic peptide) and adverse events (Kotecha

et al., 2020). It should be considered for AF patients who do not respond to other medication, preferably at low doses. High serum concentrations of digoxin increase mortality irrespective of HF in AF patients (Lopes et al., 2018; Ferrari et al., 2020). Low serum concentrations reduce mortality and hospitalization due to HF also in elderly patients and may be used in elderly patients with chronic kidney disease with caution and careful monitoring (Yang et al., 2021).

Atrioventricular node ablation and pacemaker

AV nodal ablation with permanent pacemaker implantation in selected patients improves QoL and mitigates symptoms. It is recommended to insert a pacemaker four to six weeks prior to AV node ablation (Evans et al., 1991; Wood et al., 2000). It is effective in AF patients suffering from refractory atrial tachyarrhythmias and may be a treatment option when other treatments have failed (Willy et al., 2020). Brignole et al. (2018) showed that AV node ablation and biventricular pacing with cardiac resynchronization therapy is superior to pharmacological rate control in AF patients, decreases HF and hospitalization and improves QoL also in elderly patients (mean age 72 years ±10 years) (Brignole et al., 2018). In HF patients with implantable cardioverter-defibrillators, it is feasible and safe and has a high success rate. It also decreases incorrect shocks and improves left ventricular function (Wang et al., 2019). Serious complications include sudden cardiac death, which may be associated with the dispersion of ventricular refractoriness produced by the sudden slowing of the heart rate and ventricular pacing.

Management of atrial fibrillation in Covid-19 patients

Data is emerging on rhythm and rate control management of Covid-19 patients with AF. Urgent cardioversion should be considered for hemodynamically unstable Covid-19 patients with recent onset AF. Intravenous amiodarone is recommended for hemodynamically unstable patients and diltiazem may be considered for critically ill patients in general

(Delle Karth et al., 2001; Mujović et al., 2020). For hospitalized and stable patients with antiviral treatment and recent onset or recurrent AF, beta blockers should be considered and antiarrhythmic drugs discontinued to minimize drug interactions and risk of QT-prolongation (Gawałko et al., 2020; Hu et al., 2020). Drug interactions with antiarrhythmic drugs or anticoagulants can affect up to one in four AF patients with Covid-19 and the risk of bleeding is seven-fold (Momo et al., 2019). Interactions may lead to bradycardia, ventricular arrhythmias or severe bleeding (Rattanawong et al., 2020). Impairment of the coagulation system seems to increase the risk of TEC (Gawałko et al., 2020; Hu et al., 2020). Thromboprophylaxis is important. It seems that Chinese patients infected with Covid-19 have a lower risk for TEC in comparison to Caucasian patients (Fogarty et al., 2020). Decisions on OAC therapy with Covid-19 patients with AF are the same as for AF patients without Covid-19 (Rattanawong et al., 2020). Anticoagulation with heparin presents a survival benefit (Tang et al., 2019). OAC may be continued with direct oral anticoagulants (DOACs) after hospitalization considering drug interactions and TEC risk stratification (Rattanawong et al., 2020). VKAs should be avoided as recurrent INR-blood testing may spread the infection. Vitamin K seems to be part of Covid-19 pathogenesis and deficiency of vitamin K may be associated with worse outcomes (Dofferhof et al., 2020; Gawałko et al., 2020). Remote monitoring of heart rhythm and virtual health visits are recommended to minimize the spread of the infection and nevertheless ensure optimal follow-up of AF patients after Covid-19 infection (Hu et al., 2020). Ablation procedures should be postponed for three months or longer (Gawałko et al., 2020).

2.8 PREVENTION OF THROMBOEMBOLIC COMPLICATIONS

OAC therapy prevents two thirds of AF-related TEC (Hart et al., 1999). Strokes that occur during OAC medication are less devastating and less frequent than those that occur without OAC (Hylek et al., 2003; Gladstone et al., 2009). Guidelines recommend OAC for AF patients with a high risk for TEC (January et al., 2019; Hindricks et al., 2020). In the ESC guidelines 2020, high risk is defined as CHA_2DS_2-VASc ≥3 for women and ≥2 for men. OAC

should also be considered for patients with a moderate risk of stroke (CHA_2DS_2-VASc score of 2 for women and 1 for men) whilst considering the patients' additional stroke risk factors, the risk of major bleeding and patient preference. For AF patients with a low stroke risk (CHA_2DS_2-VASc 1 for women and 0 for men), OAC should not be used (Figure 2).

Absolute contraindications for OAC initiation are active major bleeding or a history of intracranial hemorrhage (Hindricks et al., 2020). The unadjusted annual rate of intracerebral hemorrhage (ICH) in anticoagulated AF patients ranges around 0.5-0.6% compared to 0.3% for AF patients not on OAC and the annual major hemorrhage rate of circa 1% (Fang et al., 2005; Fang et al., 2006; Singer et al., 2009).

There is significant heterogeneity in OAC therapy worldwide (Lewis et al., 2014; Steinberg et al., 2017; Freedman et al., 2018, Cowan et al., 2018, Piccini et al., 2019; Marzona et al., 2020). Despite guideline recommendations, OAC is often underused or discontinued after the first few years. Treatment gaps or discontinuation of OAC can be seen in 30% to 50% of warfarin-treated patients and 20% to 40% of DOAC-treated patients (Deitelzweig et al., 2013; Lip et al., 2014; Lip et al., 2018; García Rodríguez et al., 2020). In a Finnish retrospective registry study from 2014 analyzing warfarin use in AF patients in a medium-size Finnish city (Joensuu), warfarin treatment was suboptimally performed with one third of patients with a time in therapeutic range (TTR) of under 60% (Hallinen et al., 2014). The FinWAF registry suggested that optimal TTR should be at least 80% instead of 60-70% as optimal warfarin treatment was associated with better patient outcome (Lehto et al., 2017). Implemented programs targeted at improving guideline-adherence are efficient and increase adequate stroke prevention in AF patients (Piccini et al., 2019).

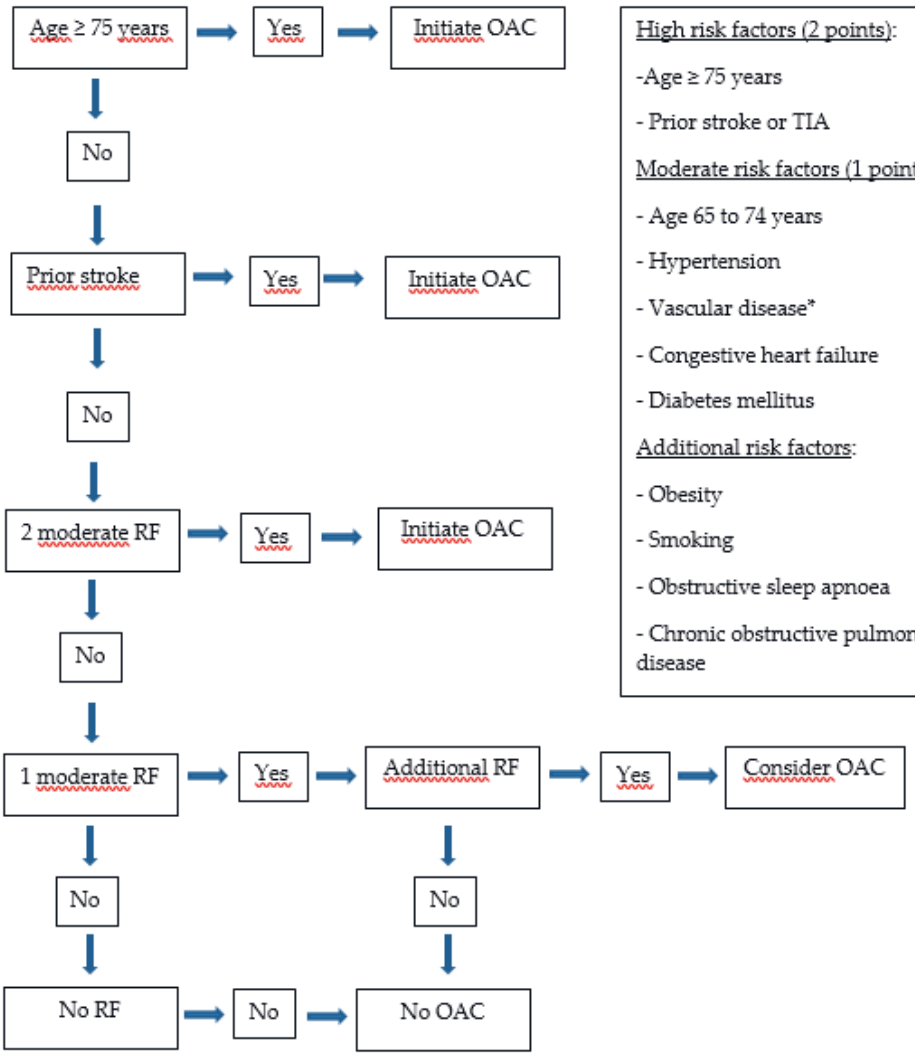


Figure 2. Initiation of oral anticoagulation for preventing thromboembolic complications in patients with atrial fibrillation. RF = risk factor; TIA = transient ischemic attack; OAC = oral anticoagulation. * = Myocardial infarction, peripheral arterial disease, aortic plaque.

2.8.1 Antiplatelet agents

Antiplatelet therapy is not recommended for stroke prevention in AF. It reduces stroke risk by 22% in comparison to 64% for OAC with warfarin or

DOACs, which are superior to warfarin by approximately 20% (Hart et al., 2007; Ruff et al., 2014; Hindricks et al., 2020). The use of aspirin (150–200 mg daily) in low-risk AF patients tends to increase adverse side effects (Sato et al., 2006).

DAPT with 100 mg of aspirin and 75 mg of clopidogrel taken daily by patients with nonvalvular AF is superior to aspirin alone but inferior to warfarin with no difference in major bleeding events (ACTIVE writing group et al., 2006). Aspirin is clearly inferior to apixaban in stroke or TEC prevention with no difference in bleeding events (Connolly et al., 2011). Combination therapy with OAC and antiplatelets is generally not recommended as it increases the risk for major bleeding events (Mant et al., 2007; Lip 2011).

2.8.2 Vitamin K antagonists

Warfarin is a VKA that has been used since the 1950s as OAC for preventing strokes in AF patients. Warfarin is superior to antiplatelet therapy in stroke prevention. When used at therapeutic levels (INR 2-3), warfarin reduces the risk by two thirds and decreases the risk of MI and vascular death in patients without prior TEC (Hart et al., 2007; Aguilar et al., 2005). In elderly AF patients (≥75 years old), warfarin is superior to aspirin in the prevention of strokes, intracranial hemorrhages and significant arterial embolisms, with a similar risk of bleeding events (Mant et al., 2007). TTR in patients using warfarin should be over 0.80 (Lehto et al., 2017) but is often found to be unsatisfactory in clinical trials (55% to 66%) and in communities (50%) (Connolly et al., 2009; Granger et al., 2011). When TTR is high (≥71%), stroke prevention with warfarin is equal to DOACs although bleeding risk is higher with warfarin (Själander et al., 2018).

AF patients on warfarin have an estimated annual stroke risk of 1.66% and stroke risk increases with age, female sex, prior stroke and VKA-naive patients. The risk for major annual bleeds ranges between 1.4% and 3.4% (Granger et al., 2011).

The SAMe-TT_2R_2 score (female sex, age <60 years, medical history of ≥2 comorbidities (hypertension, diabetes mellitus, coronary artery

disease/myocardial infarction, peripheral artery disease, HF, previous stroke, pulmonary disease and hepatic or renal disease disease), treatment [interacting drugs e.g. amiodarone], tobacco use and non-Caucasian ethnicity) can be used to guide OAC initiation with a VKA and program additional interventions to achieve beneficial TTR levels in patients at risk of poor INR control (SAMe-TT_2R^2 score >2) (Apostolakis et al., 2013).

2.8.3 Direct oral anticoagulants

Approved DOACS are either direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) (Table 5) (Connolly et al., 2009; Patel et al., 2011; Granger et al., 2011; Giugliano et al., 2013). Betrixaban has been approved by the United States Food and Drug Administration (FDA) for venous thromboembolism but is not in use for stroke prevention in AF patients (Giugliano et al., 2013; Chan et al., 2014). DOACs are pharmacologically predictable in large populations, have rapid onset of action, and less drug and dietary interactions compared to warfarin (Scaglione et al., 2013). Regular laboratory monitoring is not required (Eikelboom et al., 2017). Non-interruption or short discontinuation of DOACs before most invasive procedures is considered safe (Beyer-Westendorf et al., 2014).

DOACs are efficient and safe for use in different AF patient subgroups. They show a significant benefit over warfarin in stroke and TEC prevention, reduction of ICH and mortality. However, DOACs present an increased risk for gastrointestinal bleeding despite better safety regarding ICH (Ruff et al., 2014). Low dosage use of DOACs reduce bleeding events but ischemic strokes are more frequent in comparison with normal DOAC dosing (Ruff et al., 2014). Stroke and TEC risk reduction in DOACs is circa 20% higher than with warfarin (Ruff et al., 2014; Lip et al., 2017). The hazard ratio for reduction in stroke or TEC ranges around 0.61-0.80 for apixaban, dabigatran and rivaroxaban (Lip et al., 2017). The risk for ICH or major bleeds is lower with DOACs in comparison with warfarin and ranges around 0.40% for ICH (dabigatran), 2% for major bleeding and 0.24% for hemorrhagic stroke (apixaban) (Connolly et al., 2009; Granger et al., 2011).

High dose edoxaban (60 mg once daily) is equal to warfarin with respect to TEC and bleeding events. Low dose edoxaban (30 mg once daily) is noninferior to warfarin with respect to TEC but bleeding events are less frequent (Carnicelli et al., 2017). The Aristophanes study demonstrated that apixaban and dabigatran were safer than warfarin with respect to major bleeding and rivaroxaban had a higher rate for major bleeding (gastrointestinal bleeding) than warfarin (Lip et al., 2017). Apixaban, dabigatran and rivaroxaban had a lower risk for ICH than warfarin (Lip et al., 2017). When analyzing the cost-effectiveness of different DOACs with respect to high quality-adjusted life-years, apixaban ranks highest before dabigatran and rivaroxaban, and all three are superior to warfarin (Harrington et al., 2013; Sterne et al., 2017).

In addition to absolute contraindications that apply to all OAC therapy, all DOACs are contraindicated in AF patients with mechanical heart valves or (rheumatic or nonrheumatic moderate to severe) mitral stenosis (Hindricks et al., 2020). Apixaban, dabigatran and edoxaban can be used in AF patients with native (non-rheumatic mitral and/or aortic regurgitation or other) valvular heart disease and AF patients with bioprosthetic valves despite an increase in bleeding events (Jaffer et al., 2015; Carnicelli et al., 2017; Pan et al., 2017). Edoxaban may be considered for AF patients with aortic or mitral bioprosthetic valves implanted >30 days prior to OAC initiation.

Table 5: Dose selection for DOACs (ESC 2020 guidelines)

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Standard dose	150 mg x 2	20 mg x 1	5 mg x 2	60 mg x 1
Lower dose	110 mg x 2			30 mg x 1
Reduced dose		15 mg x 1	2.5 mg x 2	15–30 mg x 1
Dose-reduction criteria	Any of the following: Age ≥ 80 years Verapamil Increased bleeding risk	CrCl 15–49 mL/min	At least 2 criteria Age ≥ 80 years Weight ≤ 60 kg Serum creatinine ≥ 133 µmol/l	Any of the following: CrCl 30–50 mL/min Weight ≤ 60 kg Verapamil, quinidine or dronedarone

CrCl = creatine clearance

2.8.4 Left atrial appendage closure

Thrombus formation takes place primarily in the left atrial appendage (LAA) (Blackshear et al., 1996). It can be occluded using percutaneous devices to reduce TEC in AF patients (IIb) (Lip et al., 2017; Hindricks et al., 2020). LAA occlusion is especially indicated for AF patients with life-threatening bleeding during OAC or patients with recurrent stroke despite adequate OAC (Glikson et al., 2020). It is not known whether OAC with or without antiplatelet therapy or no therapy should be recommended after LAA occlusion, and postprocedural management is merely based on consensus (Lip et al., 2017). Dual antiplatelet therapy may be prescribed for three months after a LAA procedure in AF patients with a low risk for bleeding and a history of stroke during OAC, followed by single antiplatelet therapy up to six months. For patients with contraindications to warfarin - such as a history of bleeding during OAC - single antiplatelet therapy or no antithrombotic therapy may be the treatment of choice, but more evidence in required (Lip et al., 2017; Pouru et al., 2019).

Procedural success rates are high irrespective of device type (96% to 100%): risk reduction of TEC is significant (nearly 50%) and the rate of bleeding events decreases in the long-term follow-up (Holmes et al., 2014; Reddy et al., 2013; Tzikas et al., 2017; Reddy et al., 2017; Chen et al., 2019).

The LAA can also be sutured or tied off epicardially with a LARIAT or Atriclip device, which appears superior to one-time endocardial radiofrequency ablation (Caliskan et al., 2019; Parikh et al., 2020). Further research is required to define the stroke risk reduction. Surgical LAA occlusion decreases stroke risk in AF patients, but more evidence is needed on long-term benefits (Tsai et al., 2015; Atti et al., 2018; Whitlock et al., 2021).

2.9 ATRIAL FIBRILLATION AND PERCUTANEOUS CORONARY INTERVENTION

The incidence of CAD in hospitalized AF patients is approximately 21% and doubles with age after 70 years. Invasive cardiac procedures (PCI or coronary artery bypass grafting (CABG)) affect up to one fifth of AF patients (Kralev et al., 2011). AF incidence in ACS patients ranges from 5-8%, and particularly new-onset AF in patients with non-ST-elevation myocardial infarction (NSTEMI) increased in-hospital mortality (González-Pacheco et al., 2015). Strokes and bleeding events are more frequent in AF patients with ACS (Lopes et al., 2008; González-Pacheco et al., 2015). In addition to short-term (in-hospital) mortality, AF increases also long-term mortality in patients with acute coronary syndrome (Lopes et al., 2008; González-Pacheco et al., 2015).

2.9.1 Antithrombotic therapy in patients without atrial fibrillation undergoing stenting

Patients without AF undergoing percutaneous coronary intervention and stenting for chronic coronary syndrome should use DAPT (P2Y12, adenosine-receptor-blockade and aspirin), typically for six months (Collet et al., 2021). In patients with ACS without an increased risk of bleeding, DAPT is often continued for one year post-PCI. Subsequently a single antithrombotic therapy with aspirin (or clopidogrel) is continued for the rest of the patient's life. Discontinuation of aspirin or P2Y12 can be considered after one to three months in patients with a high bleeding risk

(Collet et al., 2021; Valgimigli et al., 2021). Low-dose rivaroxaban may be considered in patients with a high stroke risk but no prior stroke and non-fatal bleeding risk for approximately one year alongside DAPT (aspirin and clopidogrel) (Mega et al., 2012; Collet et al., 2021).

2.9.2 Antithrombotic therapy in patients with atrial fibrillation undergoing stenting

Approximately one third of all AF patients have coronary artery disease and 5-10% undergo PCI (Kralev et al., 2011; Golwala et al., 2018). Nearly 7% of PCI patients have an indication for permanent OAC (Choi et al., 2017). Traditionally warfarin used to be the drug of choice in AF patients undergoing PCI. However, current guidelines recommend DOACs as first-line OAC in preference to warfarin (Table 6) (Lopes et al., 2019).

In patients undergoing PCI due to chronic coronary artery disease and with a high stroke risk and an indication for OAC, triple antithrombotic therapy, consisting of OAC and DAPT, is recommended for one week (up to one month) after stenting. After this dual therapy (aspirin or clopidogrel with OAC) should be prescribed for up to 12 months (Collet et al., 2021). OAC monotherapy should continue in AF patients with CAD and stenting after 12- months of follow-up free of ischemic events as well as in AF patients with CAD and no stenting (Yasuda et al., 2019; Hindricks et al., 2020).

In AF patients undergoing PCI for ACS the default therapy is triple antithrombotic therapy (OAC and DAPT) up to one month after PCI followed by OAC and single antiplatelet therapy (aspirin or P2Y12) for 12 months continued with long-term OAC monotherapy (Hindricks et al., 2020).

Table 6. Considerations on antithrombotic medication after an acute coronary syndrome with aspirin, new-generation P2Y12 inhibitor (ticagrelor, prasugrel) or P2Y12 (clopidogrel) and DOACs (adapted from Rodriguez et al., 2021)

Follow-up after ACS	Normal strategy	High ischemic risk	High bleeding risk	AF patients
0–1 month	Aspirin + new-P2Y12	Aspirin + new-P2Y12	Aspirin + new-P2Y12	Aspirin + clopidogrel + DOAC
1–12 months	Aspirin + new-P2Y12	Aspirin + new-P2Y12	Any P2Y12	Clopidogrel + DOAC
>12 months	Any P2Y12	Aspirin + new-P2Y12 or aspirin + low-dose rivaroxaban	Any P2Y12 or Aspirin alone	DOAC

ACS = acute coronary syndrome; DOAC = direct oral anticoagulant

2.10 SEX, AGE, AND ATRIAL FIBRILLATION

It has been suggested that AF burden will increase >60% by 2050 with 6-12 million AF patients in the United States by 2050 and 18 million AF patients in Europe by 2060 (Lippi et al., 2021). AF prevalence is associated with age and increases successively for each decade except for the oldest age group (>89 years) (Benjamin et al., 1994; Lloyd-Jones et al., 2004; Heeringa et al., 2006; Wilke et al., 2013; Zoni-Berisso et al., 2014). AF is the most frequent arrhythmia in the elderly and AF rates increase from 5% to 17% in patients from 65 to 84 years old. Currently, a total of 70% of AF patients are >65 years old in Western countries (Zulkifly et al., 2018). It has been estimated that by 2050 more than half of AF patients will be ≥80 years of age (Wolf et al., 1996; Go et al., 2001; Zulkifly et al., 2018; Poposka et al., 2019). Approximately 10% of Finnish patients ≥75 years had an AF diagnosis in 2015 (Atrial fibrillation: Current Care Guidelines 2021).

Mortality due to AF increases by 1.5- fold in men and 1.9- fold in women (Benjamin et al., 1998). AF-related in-hospital mortality increases with age and is circa 2% in AF patients ≥80 years (Patel et al., 2014). High age and female sex are independent risk factors for HF-related AF and hospitalization and both conditions often coexist, contributing to an adverse outcome. During a 25-year follow-up in the USA, hospitalization and mortality due to HF decreased in contrast with increasing AF rates (Emdin et al., 2016; Vasan et al., 2019; Reinhardt et al., 2021).

Age-adjusted AF prevalence is lower in women in both developed and developing countries (Chugh et al., 2014; Emdin et al., 2016; Ko et al., 2016; Marzona et al., 2020). The male to female ratio of AF is approximately 1.2:1 in general, but although AF prevalence is higher in men, women are overrepresented in the elderly AF patient population due to longer survival (Zoni-Berisso et al., 2014; Marzona et al., 2020).

Female AF patients are older, have more comorbidities (hypertension, HF) and less CAD than men. In addition, at the time of AF diagnosis women are more symptomatic. It is of note that women live alone more often than men mostly due to widowhood and are more often lacking in tertiary education. AF type is paroxysmal more often than persistent or permanent in women in comparison with men (Potpara et al., 2012; Ball et al., 2013; Schnabel et al., 2017). For otherwise healthy women with new onset AF the risk of cardiovascular death is four times higher (Conen et al., 2011).

2.10.1 Sex, age, and guidelines

The strongest risk factors for AF-related stroke in non-anticoagulated AF patients are age and a history of stroke (Linde et al., 2018; Ball et al., 2013). The significance of female sex on stroke risk is still under debate. Some studies consider female sex as a risk factor for stroke particularly in elderly women (Mikkelsen et al., 2012; Wagstaff et al., 2014), while others consider female sex an independent risk factor irrespective of age (Marzona et al., 2020). Some guidelines consider sex as a risk modifier rather than a risk factor (Table 7) (Kirchhof et al., 2016; Stroke Risk in Atrial Fibrillation Working Group 2007; Mikkelsen et al., 2012; Linde et al., 2018; Nielsen et

al., 2018; Hindricks et al., 2020). Multiple studies have shown an interaction between female sex and other stroke risk factors such as age ≥65 years (Andersson et al., 2017; Olesen et al., 2012; Fang et al., 2005; Mikkelsen et al., 2012; Nielsen et al., 2017) although there are population-based findings that have not indicated a significant relation between the two (Renoux et al., 2017).

In female patients AF presented a more important risk factor for stroke and cardiovascular mortality and independently increased all-cause mortality and morbidity by approximately 2 to 2.5- fold in women in comparison to men (Wolf et al., 1991; Friberg et al., 2004; Emdin et al., 2016). In one study the risk of stroke doubled in women aged 65 when compared to women aged 55 years (Rosamond et al., 2008). Another study showed that stroke incidence in women with permanent AF and no other stroke risk factors was slightly higher (0.7% vs. 0.5%) in women <65 years in comparison to men (Friberg et al, 2012). In permanent AF, female sex was an independent risk factor with a hazard ratio of 1.6 during 1 year follow-up, but not in patients <65 years (Olesen et al., 2011a).

The $CHADS_2$ score launched in the 2006 international guidelines did not list sex as a risk factor (Fuster et al., 2006). The 2010 international guidelines introduced the CHA_2DS_2-VASc- score and included female sex in risk stratification (CHA_2DS_2-VASc- score) (Kirchhof et al., 2010). The 2010 and 2012 European guidelines defined high stroke risk as CHA_2DS_2-VASc ≥2 for both women and men. Recommendations were not strict on OAC therapy for women and men with an intermediate stroke risk (CHA_2DS_2-VASc 1) and decisions were left to the physicians' discretion. For women <65 years with no other risk factors (CHA_2DS_2-VASc 1) the 2010 and 2012 European guidelines recommended no OAC (Kirchhof et al., 2010; Camm et al., 2012).

The 2014 AHA/ACC/HRS and the 2016 European guidelines included sex differences in risk stratification and OAC initiation for high stroke risk patients: women at high risk had CHA_2DS_2-VASc ≥3 and men had CHA_2DS_2-VASc ≥2 but clear recommendations on OAC therapy for the intermediate-risk group (CHA_2DS_2-VASc 2 for women and 1 for men) were lacking (January et al., 2014; Kirchhof et al., 2016). Current European and American

guidelines consider high stroke risk as CHA_2DS_2-VASc ≥3 for women and CHA_2DS_2-VASc ≥2 for men (January et al., 2019; Hindricks et al., 2020). The 2019 updated American guidelines recommend consideration of OAC therapy for intermediate-risk AF patients (CHA_2DS_2-VASc 2 for women and 1 for men) and underscore that female sex matters in CHA_2DS_2-VASc risk stratification for AF patients aged >65 years or having ≥2 non-sex-related stroke risk factors. The 2016 and 2020 European AF guidelines state that OAC should be considered for intermediate-risk AF patients (CHA_2DS_2-VASc 2 for women and 1 for men) (class IIa) (Kirchhof et al., 2016; January et al., 2019; Hindricks et al., 2020).

A CHA_2DS_2-VA score was proposed in a Danish observational cohort excluding sex as a risk factor for stroke (Nielsen et al., 2018). The AF management guidelines of Australia and New-Zealand also propose a sexless risk stratification score guiding initiation of OAC (Brieger et al., 2018). Korean national guidelines recommend OAC for women only with CHA_2DS_2-VASc ≥3 as female sex seems to present a lower stroke risk in the Korean population (KHRS Korean Heart Rhythm Society 2018) (Joung et al., 2018). In the recently updated Finnish guidelines, female sex scores one risk point only in women ≥75 years and the threshold for OAC initiation is CHA_2DS_2-VASc ≥2 for both women and men (Atrial fibrillation: Current Care Guidelines 2021).

The age-related stroke risk has been more constant in guideline updates. Age ≥65 years is considered a risk factor that continuously increases stroke risk and potentiates other risk factors (Nielsen et al., 2018). In the 2006 American guidelines age ≥75 years was considered a moderate risk factor (one risk point) for AF patients favoring OAC initiation ($CHADS_2$ score) (Fuster et al., 2006). The 2010 ESC guidelines included age 65-74 as a moderate risk factor (one risk point) in risk stratification and considered ≥75 years a strong risk factor (two risk points) for stroke (CHA_2DS_2-VASc score) (Kirchhof et al., 2010), which is still the norm (January et al., 2019; Hindricks et al., 2020). Literature demonstrates that the ages of 65 to 74 years are more significantly associated with stroke risk than other items scoring one point in the CHA_2DS_2-VASc score (HF, hypertension, diabetes mellitus, vascular disease, sex) (Friberg et al., 2012; Chao et al., 2015;

Andersson et al., 2017; Tomasdottir et al., 2019). This has penetrated the Canadian AF guidelines, which have recommended OAC treatment for AF patients ≥65 years since 2016 (Macle et al., 2016). However, there is also emerging evidence that younger age may increase stroke risk in the presence of AF. A modified CHA_2DS_2-VASc may be used in Asian patients with respect to age as the stroke risk seems to rise in Asian people from ages 50 to 55 onwards (Kim et al., 2018).

Table 7. Guideline recommendations with respect to female sex as a stroke risk factor in AF patients (Boriani et al., 2019)

Guideline	Risk stratification	Female sex (FS) as risk factor
ACC/AHA/ESC 2006	$CHADS_2$	Not considered (FS: weak risk factor)
ESC 2010, 2012, 2016, 2020	CHA_2DS_2-VASc	Considered (FS: seems not to increase stroke risk without other risk factors)
CCS 2012	$CHADS_2$	Not considered
CCS 2014, 2016, 2018	CHADS-65	Not considered (FS: low stroke risk, non-significant hazard ratio)
AHA/ACC/HRS 2014, 2019, CCG 2021	CHA_2DS_2-VASc	Considered (FS: age-dependent risk modifier)
APHRS 2017	CHA_2DS_2-VASc	Considered (OAC for Asian patients with 1 additional risk factor beyond sex)
NHFA/CSANZ 2018	CHA_2DS_2-VA	Not considered
ACCP 2018	CHA_2DS_2-VASc	Considered (FS: risk modifier for women > 65 years)
KHRS 2018	CHA_2DS_2-VASc	Considered (FS: lowers stroke risk in Korean population, OAC for women with score ≥ 3)

ACC American College of Cardiology; ACCP American College of Chest Physicians; AHA American Heart Association; APHRS Asia Pacific Heart Rhythm Society; CCS Canadian Cardiovascular Society; CSANZ Cardiac Society of Australia and New Zealand; ESC European Society of Cardiology; HRS Heart Rhythm Society; NHFA National Heart Foundation of Austria; KH 2021 Atrial fibrillation: Current Care Guidelines 2021 (KH = Käypä hoito suositus); KHRS Korean Heart Rhythm Society; OAC = oral anticoagulation

2.10.2 Sex and oral anticoagulation

Female AF patients have a more significant stroke risk despite OAC therapy, although individual stroke risk is heterogeneous and associated with other stroke risk factors, particularly older age (Fang et al., 2005; Andersson et al., 2014; Pancholy et al., 2014). The long-term outcome and prognosis of acute stroke are worse in women in comparison to men and the OAC-related risk reduction in TEC and recurrent stroke is greater for women than for men (Lane et al., 2009; Vinereanu et al., 2015; Lang et al., 2017). Despite this, AF-related strokes are more severe than non-AF-related strokes and non-anticoagulated women are at a greater risk of TEC in comparison to men (Jorgensen et al., 1996; Marini et al., 2005). However, several studies also show that if OAC therapy with warfarin or DOACs is adequate, female sex in itself is not a risk factor for adverse events (Connolly et al., 2009; Patel et al., 2011; Giugliano et al., 2013; Granger et al., 2011; Penttilä et al., 2019). The residual TEC risk is nevertheless higher in women treated with warfarin but there is no sex-related difference in residual stroke risk on DOACs (Sullivan et al., 2012; Pancholy et al., 2014).

There is evidence that when adequately anticoagulated, the bleeding risk in women is similar to that in men (Jorgensen et al., 1996; Marini et al., 2005). Several studies indicate that the risk for ICH and major hemorrhage events in anticoagulated women with AF is equal to men but bleeding events are less frequent and cardiovascular and all-cause mortality are lower in warfarin-treated women in comparison to men. Minor bleeds affect women more frequently, but major bleeding is lower than in men, even when the elderly patient population (≥75 years) is considered (Fang et al., 2005; Gomberg-Maitland et al., 2006; Pancholy et al., 2014; Penttilä et al., 2018; Marzona et al., 2020). A recent study demonstrated that women with acute ischemic stroke have a better outcome than men due to higher disability at the index event, lower in-hospital mortality, and beneficial functional outcome (Bonkhoff et al., 2021).

Findings on OAC use and sex-related differences are controversial. Register-based studies show similar OAC use between women and men when analyzing overall anticoagulant use (Dagres et al., 2007; Lip et al.,

2015; Piccini et al., 2016; Schnabel et al., 2017). Other studies demonstrate clear sex-related differences in OAC therapy with respect to suboptimal treatment especially among female AF patients ≥75 years old (Kassim et al., 2017; Marzona et al., 2020) but also at all CHA_2DS_2-VASc levels (Thompson et al., 2017). Suboptimal treatment in women with AF and a high stroke risk is heterogeneous: aspirin may be prescribed instead of OAC (Shantsila et al., 2015; Hsu et al., 2016; Marzona et al., 2020), OAC therapy with warfarin may be inadequate with low TTR and INR-levels (Van Spall et al., 2012), DOAC dosing may be insufficient (Lee et al., 2018).

2.10.3 Age and oral anticoagulation

Age is a predictable and dynamic risk factor for stroke that affects patients globally irrespective of sex. A total of 12-14% of low-risk AF patients (CHA_2DS_2-VASc 1 for women and 0 for men) develop one new risk factor annually and one third develop more stroke risk factors during two-years of follow-up (Chao et al., 2018; Chao et al., 2019; Choi et al., 2020). A recent study analyzed a dynamic Delta CHA_2DS_2-VASc score indicating the difference between CHA_2DS_2-VASc scores at the time of AF diagnosis and the highest recorded score before stroke or death. With Delta CHA_2DS_2-VASc scores >1 the slope of change of the CHA_2DS_2-VASc score was high and indicated a significantly increased risk of stroke. Most AF patients had higher stroke risk scores during follow-up, which highlights the dynamic process of AF and interactions with age and other comorbidities, such as hypertension, which is the most common comorbidity (Chao et al., 2018).

Recent data suggest that OAC therapy might be beneficial for low-risk AF patients >65 years old or ≥55 years old with 0 or 1 non-sex risk factors (Friberg et al., 2019; Andersson et al., 2021; Abdel-Qadir et al., 2021). Some risk factors seem to affect stroke risk in association with age more significantly than others, although they are rated one point in the CHA_2DS_2-VASc score (Chao et al., 2019). Some low-risk AF patients benefit from lower age thresholds for OAC initiation than guideline recommendations suggest. DOACs reduced stroke risk in low-risk AF patients with

hypertension or diabetes mellitus at age 50, and with vascular disease at age 55, and with HF at age 35 (Chao et al., 2019). In addition, recent findings suggest a new grey zone for OAC initiation ranging between 55 and 59 years or 60 and 65 years (Friberg et al., 2019; Andersson et al., 2021). Friberg et al. (2019) proposed that age 65 be substituted as the OAC cut-off age instead of age 75 years). The overall necessity of risk scores in AF patients >65 years old has been questioned as these AF patients appear to benefit from OAC irrespective of stroke risk scores. However, risk scores are useful in assessing stroke risk in AF patients <60 years (Friberg et al., 2019).

Age independently increases the risk for hemorrhage in AF patients by approximately 1.2 to 1.5% every 10 years from age 60 onwards irrespective of OAC use (Granger et al., 2011). ICH rates are higher in anticoagulated patients ≥80 years underscoring the need for close monitoring to ensure safe OAC therapy (Fang et al., 2006). Despite a higher risk of bleeding, elderly AF patients should be anticoagulated according to guideline recommended risk stratification. OAC therapy in the elderly should favor DOACs versus VKA and avoid antiplatelet agents (Schäfer et al., 2020).

Warfarin was underused in AF patients, especially in patients ≥75 years with a high stroke risk and who significantly benefit from OAC (Fang et al., 2009; Kim et al., 2018). Adequately monitored warfarin therapy (TTR ca. 70%) provides up to 50% stroke risk reduction in the elderly population (Mant et al., 2007). In comparison with ICH the net clinical OAC benefit is highest for AF patients >85 years (Singer et al., 2009).

DOACs are effective and safe in the elderly (≥75 years old) AF population even with moderate renal impairment (CrCl <50 ml/min) with appropriate dose reduction (Kim et al., 2018). Apixaban and edoxaban are the safest DOACs in the elderly population irrespective of dose reduction with lower TEC, ICH, and major bleeding rates (Ng et al., 2016; Kato et al., 2016; Schäfer et al., 2020). Dabigatran and rivaroxaban can be considered alternatives to warfarin in elderly patients, but no significant benefit has been shown in this subgroup (Halperin et al., 2014; Lauw et al., 2017; Schäfer et al., 2020). DOACs increase gastrointestinal bleeding in comparison to VKA therapy in patients ≥75 years old and proton-pump-

inhibitors are suggested in addition to OAC (Eikelboom et al., 2011; Halperin et al., 2014; Halvorsen et al., 2014; Kato et al., 2016; Schäfer et al., 2020).

2.10.4 Sex and treatment

Women are more actively treated for cardiovascular disease in primary prevention but not in secondary prevention and they respond to cardiovascular treatment with less adverse outcomes than men (Walli-Attaei et al., 2020). Women with AF tend to be treated differently than men although outcomes are comparable between sexes. Women are less often referred to specialist care, rhythm control therapy and invasive cardiac procedures (Schnabel et al., 2017; Lee et al., 2018; Linde et al., 2018). These differences exist also in Finland: women with strokes are more commonly treated in general hospitals than in stroke centers and this affects the outcome of treatment negatively (Meretoja et al., 2010).

Paroxysmal AF or sinus rhythm is more common in AF in women than persistent or permanent AF (Potpara et al., 2012; Ball et al., 2013; Piccini et al., 2016; Schnabel et al., 2017). Women are generally older and have a higher symptom burden and heart rate during AF paroxysms than men (Dagres et al., 2007). Piccini et al. (2016), showed that only one third of women are asymptomatic in comparison with 40% of men. Women report palpitations and anxiety more often than dyspnea, chest pain and fatigue which are common symptoms in men (Potpara et al., 2012). EHRA scores are higher in women ranging around III and IV (Potpara et al., 2012; Lip et al., 2015). Women have a lower QoL, refer to hospital care later and have a longer AF history, and their functional capacity as well as their psychological and physical health is poorer when compared to men (Dorian et al., 2002; Anselmino et al., 2015; Lip 2015; Piccini et al., 2016).

In spite of this, AF patients are treated differently depending on sex: women are treated less aggressively and mostly by rate-control strategy and even symptomatic female AF patients receive rhythm control therapy and non-pharmacological (invasive) treatment less often than men (Dagres et al., 2007; Lip et al., 2015; Schnabel et al., 2017). Transesophageal

echocardiogram (TEE), coronary angiography, and exercise testing are less commonly performed in AF women (Lip et al., 2015). Atrioventricular node ablation and permanent pacemaker implantation are more frequent in women, although adverse effects with respect to pacemaker implantation occur more commonly in women than in men (Rienstra et al., 2005; Piccini et al., 2016; Kassim et al., 2017; Schnabel et al., 2017).

The use of antiarrhythmic medication is similar in women and men (Piccini et al., 2016; Schnabel et al., 2017). However, women with persistent AF have more adverse effects due to antiarrhythmic therapy (Rienstra et al., 2005). When rhythm control strategy is opted for in the treatment of AF, pharmacological therapy increases the risk for adverse events in female patients in comparison with the male population (Anselmino et al., 2015). Women are referred to catheter ablation and maze surgery less often in comparison to male patients (Anselmino et al., 2015; Kassim et al., 2017). Although the duration of AF paroxysms before ECV predicts immediate ECV success and ECV success is considered similar between sexes, women undergo ECV less often than men and are more often referred to pharmacological cardioversion (Fumagalli et al., 2002; Alegret et al., 2015; Fumagalli et al., 2015; Lip et al., 2015; Piccini et al., 2016; Kassim et al., 2017; Schnabel et al., 2017, Weberndörfer et al., 2019; Volgman et al., 2020). Machine learning can at best modestly predict successful cardioversion with no differences between women and men (C-index circa 0.60 for women and men) (Vinter et al., 2020). On the other hand, women undergoing cardioversion suffer from AF recurrence more frequently in comparison to men (Gurevitz et al., 2006; Vinter et al., 2020).

Women are also under-represented in catheter ablation trials (Avgil et al., 2015). Female AF patients have more comorbidities and a longer history of AF at the time of the procedure (Anselmino et al., 2015). Ablated women are usually older and AF recurrence and complications occur more frequently (Zylla et al., 2016). This may in part be related to older age in women and this emphasizes the necessity to offer ablation for symptomatic women with paroxysmal or persistent AF early enough when not contraindicated (Lip et al., 2015; Linde et al., 2018). However, the

CABANA trial did not find treatment and sex-related differences in adverse events (Russo et al., 2021).

2.10.5 Age and treatment

Elderly AF patients are inadequately studied and treated, and patients >80 years old are seldom enrolled in trials (Fumagalli et al., 2012). The prevalence of persistent or permanent AF increases with age whereas paroxysmal AF prevalence decreases (Hiasa et al, 2020). Elderly (≥75 years) AF patients have more comorbidities, they are more symptomatic and report palpitations more often than younger patients. Furthermore, prior hemorrhagic and ischemic events are more common in this subgroup (Fumagalli et al., 2012; Fumagalli et al., 2015, Hiasa et al., 2020). Elderly AF patients receive specialist care and extensive diagnostic testing less often than younger patients, and even common diagnostic tests are underused (Fumagalli et al., 2012; Fumagalli et al., 2015). During one-year follow-up elderly AF patients suffer MI and new-onset HF more often and mortality increases in comparison to younger AF patients (Fumagalli et al., 2012).

Rate control is recommended as first line therapy in patients >75 years old (Poposka et al., 2019). Rate control in septuagenarians is associated with lower all-cause mortality than rhythm control. This results primarily from a decrease in non-cardiac deaths. All-cause mortality and cardiovascular hospitalization is lower for patients in rate control (Shariff et al., 2013). Rhythm control therapy is challenging in the elderly (Fumagalli et al., 2012). Conversion to sinus rhythm after ECV is less common in elderly patients (Fumagalli et al., 2002). Catheter ablation and antiarrhythmic drug treatment are less frequently used in the elderly (Fumagalli et al., 2015). A study analyzing long-term (three years) efficacy and safety of catheter ablation in the elderly (≥75 years) with AF showed that patients with paroxysmal AF benefited from the procedure with respect to long-term outcome (sinus rhythm) in comparison to patients with persistent or long-standing persistent AF (Metzner et al., 2016). In addition, safety was comparable to younger patients (Metzner et al., 2016).

AF is associated with a more rapid decline in physical capacity in all patients, particularly in those ≥70 years old. Physical capacity measured with the Physical Performance Battery, a test validated for older adults, decreases significantly during a four-year follow-up in septuagenarians with AF (in comparison with septuagenarians without AF: grip strength, 400-meter walking time and two-minute walking distance diminish (Magnani et al., 2016). Frailty increases after age 60 years and affects approximately one third of female AF patients and 10% of the male AF population. There is no significant sex-related difference in prefrailty, which affects up to half of AF patients. Frail women are older than men, they live alone, suffer more often from cognitive impairment, and have a higher bleeding risk whereas frail men are less educated, have a lower monthly income and high stroke and bleeding risks (Son et al., 2019). AF treatment differs among elderly (≥75 years) women and men: women receive OAC therapy and rhythm control treatment less frequently and suffer from heart failure more often than men during rhythm control (Subramanaya et al., 2021).

2.10.6 Sex, age, and stroke risk after cardioversion of recent onset atrial fibrillation

There is only limited data on TEC risk associated with cardioversion of AF, particularly recent onset AF. Before 2010 it was a common practice to cardiovert patients with recent onset (duration <48 h) AF without periprocedural (or postcardioversion) OAC because the risk of TEC related to cardioversion was considered low (Weigner et al., 1997). The time-limit of <48 h in recent onset AF was based on consensus rather than solid evidence (Airaksinen et al., 2013). Older studies show that the risk of post-procedural TEC after elective cardioversion was approximately 5% (ranging between 3% and 7%) without OAC but OAC lowered the risk to 0.3-1% (Bjerkelund et al., 1969; Moreyra et al., 1995). Prior TEE did not increase safety in non-anticoagulated patients undergoing elective cardioversion with respect to TEC (Moreyra et al., 1995).

In previous studies left atrial thrombi were present in 4-14% of non-anticoagulated patients with recent onset AF (Stoddard et al., 1995; Kleeman et al., 2009). For cardioverted patients with recent onset AF the TEC risk is around 0.7% when performed without anticoagulation and increases in the presence of other risk factors for stroke (Weigner et al., 1997; Airaksinen et al., 2013; Grönberg et al., 2016; Själander et al., 2016). Most TECs occur within 10 days after cardioversion with highest TEC risk occurring two to three days after the intervention (Stoddard et al., 1995; Berger et al., 1998; Airaksinen et al., 2013; Hansen et al., 2015; Brandes et al., 2020). Age, prior stroke, re-hospitalization for AF and high risk stratification scores in AF patients undergoing cardioversion without effective OAC indicate an increased TEC risk (Hansen et al., 2015; Grönberg et al., 2016). It also appears that OAC and timing of cardioversion are associated with the risk of TEC (Nuotio et al., 2014; Jaakkola et al., 2018). Nuotio et al. (2014), observed that the risk of TEC increased significantly already after 12 hours of arrhythmia in non-anticoagulated patients with recent onset AF. TEE is an option for OAC when considering cardioversion in patients with uncertain duration of arrhythmia or use of OAC, but OAC must be initiated if the risk of TEC is increased even in the absence of left atrial thrombus in TEE (Hindricks et al., 2020). This underscores the need for proper stroke risk stratification and initiation of OAC in most patients. OAC is often omitted in AF patients who are younger, have a low CHA_2DS_2-VASc score, and short duration of an AF attack (Hansen et al., 2015).

When using DOACs, the risk of TEC is 0.4% and the risk of bleeding is 1.3% during a 30-day follow-up after elective ECV (Andò et al., 2016). Considering that the monthly ischemic stroke risk with DOACs ranges around 0.08-0.12%, the additional circa four-fold risk of TEC 30 days after ECV despite DOACs seems to indicate that ECV predisposes to an increase in TEC risk (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013; Jaakkola et al., 2018).

Current American and European guidelines recommend long-term OAC, preferably with DOACs, for cardioverted AF patients with a high risk of stroke (CHA_2DS_2-VASc ≥3 for women and ≥2 for men) irrespective of AF duration (January et al., 2019; Hindricks et al., 2020). OAC should be

initiated also for patients at high risk for strokes without prior OAC and who present with recent onset AF and continued long-term even after conversion to sinus rhythm (January et al., 2019; Hindricks et al., 2020). In anticoagulated AF patients TECs occurring after acute cardioversion are usually due to suboptimal OAC stressing the need for uninterrupted postprocedural OAC therapy for at least one month after acute cardioversion (Garg et all, 2016). Furthermore, a high risk for stroke predicts recurrence of AF during 30-days of follow-up (Vitali et al., 2019). Finnish guidelines recommend long-term OAC therapy for high-risk patients (CHA_2DS_2-VASc ≥ 2) after acute cardioversion (Atrial fibrillation: Current Care Guidelines 2021).

The use of OAC after acute cardioversion in low-risk AF patients is left to the clinicians' discretion (January et al., 2014; Kirchhof et al., 2016). OAC may be considered overtreatment in AF patients with low risk scores (CHA_2DS_2-VASc 0–2 for women and 0–1 for men) due to an extremely low TEC event rate irrespective of OAC use (Nuotio et al., 2014; Garg et al., 2016; Tampieri et al., 2018; Jaakkola et al., 2020). European guidelines highlight the reliable time limit of AF duration as less than 24 h in low stroke risk AF patients if no cardioversion related OAC is prescribed (Hindricks et al., 2020).

The management of patients with AF duration of ≤48 h is heterogeneous in clinical practice. In less than one fifth of European centers cardioversion was performed after TEE to exclude left atrial thrombus (Hernández-Madrid et al., 2013). In one fifth of centers cardioversion is performed without prior low-molecular-weight heparin and in one third low-molecular-weight heparin precedes cardioversion. Approximately 30% of centers prescribe OAC to low stroke risk AF patients for one month after cardioversion. ECV is the method of choice in circa 40% of centers.

2.10.7 Sex, age, outcomes, and percutaneous coronary intervention in patients with atrial fibrillation

Approximately 5% of patients undergoing PCI-stenting have an indication for long-term OAC due to AF and the number of patients ≥80 years undergoing PCI and stent implantation is increasing (Rubboli et al., 2008; Rajani et al., 2011). Moreover, female AF patients undergoing PCI are older than men (Sambola et al., 2019). The evidence concerning efficacy and safety of treatment options in the elderly and female AF population is limited as both groups are underrepresented in clinical trials (Kirchhof et al., 2016).

AF patients undergoing PCI suffer from stroke and bleeding more frequently and their mortality is increased (Morita et al., 2020). Female sex is a predictor of acute cardiovascular complications after PCI, such as ischemic and hemorrhagic stroke as well as major bleeding (Barywani et al., 2015; Kytö et al., 2015; Sambola et al., 2019; Chichareon et al. 2020), and is also an independent risk factor for cardiovascular death (Sambola et al., 2019).

After PCI, OAC use at discharge is comparable between sexes, but warfarin therapy is more often suboptimal in female AF patients (Sambola et al., 2019). Dual therapy (DOAC and a P2Y12 inhibitor) is comparable in efficacy with warfarin triple therapy with respect to TEC risk and there are no sex-related differences in safety using reduced-dose dabigatran. However, the risk of bleeding decreases with dual therapy in comparison to triple therapy (Eccleston et al., 2021). In-hospital ischemic stroke after PCI and AMI is rare but the risk increases with AF, female sex, and age (Patil et al., 2021).

Literature is controversial on the role of sex and the interaction of AF and MI or CAD. MI is a risk factor for AF (Kannel et al., 1998; Benjamin et al., 1994; Schmitt et al., 2009) but AF also independently increases the risk of MI (Chao et al., 2014; O'Neal et al., 2014; Soliman et al., 2014). Soliman et al. (2014) observed an independent association limited to an increased risk of non-STEMI that was higher in AF women in comparison to AF men. Instead, O'Neal et al. (2014) noted that AF patients had a higher risk of MI compared

to non-AF patients and AF women had a higher risk of coronary heart disease in comparison to AF men (O'Neal et al., 2014). Additionally, Chao et al. (2014) showed that in low risk (CHA_2DS_2-VASc 0–2) AF patients the risk for MI was higher in men in comparison to women. Perdoncin et al. (2017) showed that mortality was higher in women suffering from CAD and pointed out that sex-related treatment differences may affect the outcome in women and men. However, there is also evidence that although early bleeding events after PCI are more common in women, there is no sex-related difference in outcome during two-years of follow-up (Chichareon et al. 2020).

In a study by Kralev et al. (2011), the incidence of CAD in elderly (>70 years) AF patients was approximately 40%, and one fifth of all AF patients underwent PCI or CABG surgery. Octogenarian non-AF-women with acute coronary syndrome are frail and suffer worse outcomes than octogenarian men (Vicent et al., 2019). Sambola et al. (2016) observed that AF patients >75 years undergoing PCI had an increased risk of TEC within a 30-day follow-up whereas the risk of bleeding complications decreased continuously over time. Early and short-term use of triple therapy was beneficial with respect to TEC and all-cause mortality in the elderly. However, this study underscored that OAC medication should rely on guideline-recommended risk stratification and that triple therapy exceeding four weeks does not seem reasonable in the elderly with an increased risk for bleeding (Sambola et al., 2016).

There is increasing evidence indicating that dual therapy is non-inferior to triple therapy with respect to thromboembolic complications and is advantageous regarding bleeding events in elderly AF patients after PCI during a one to three-month follow-up (Mishra et al., 2019; Schäfer et al., 2020). There is no strong evidence on the ideal duration of acetylsalicylic acid and antithrombotic therapy should be individually prescribed in the very old (Schäfer et al., 2020). It seems reasonable for elderly AF patients referred to PCI to use acetylsalicylic acid peri-procedure and in hospital followed by dual therapy with clopidogrel and OAC. Dual therapy should favor DOACs in elderly patients, providing comparable efficacy in comparison with warfarin but being superior to warfarin with respect to

bleeding events (Granger et al., 2011; Giugliano et al., 2013; Schäfer et al., 2020).

3 AIMS OF THE STUDY

The overall aim of this study was to evaluate sex and age- related differences in anticoagulation therapy strategy and thromboembolic outcomes after cardiac procedures in AF patients. The specific emphasis was:

1. To investigate the interaction of sex, age and timing of cardioversion on the risk of TEC after ECV in patients with recent onset AF without periprocedural anticoagulation.

2. To evaluate whether there are sex differences in the use of OAC in AF patients suffering a stroke or intracranial bleed and to examine the reasons for omitting OAC in women and men with AF.

3. To study the impact of sex and age on the outcome of AF patients undergoing PCI.

4 MATERIALS AND METHODS

4.1 STUDY POPULATION

4.1.1 Study I

The FinCV-study (Study I) included patients ≥18 years with recent onset AF (ICD code I48) undergoing cardioversion (NOMESCO Classification of Surgical Procedures code TFP20) and admitted to two university hospitals from 2003 through 2010 and one central hospital during year 2010 within the first 48 hours of AF and residing in the hospital catchment area. This substudy population consisted of 2313 patients undergoing 4715 ECVs due to recent onset AF (ICD-10 code I48) without pre-, peri- or postprocedural anticoagulation.

4.1.2 Study II

The FibStroke-study (Study II) population consists of patients admitted to two university hospitals and two central hospitals from 2003 through 2012 with a diagnosis of AF (ICD-10 code I48) and stroke, TIA or intracranial bleeding (ICD-codes I62). This substudy included 1747 patients ≥18 years with a history of AF and suffering their first intracerebral thromboembolic or bleeding event after the diagnosis of AF and residing in the hospital catchment area.

4.1.3 Study III

The AFCAS-registry (Study III) enrolled 925 patients with AF (ICD code I48) who underwent PCI and stenting from 2008 to 2010 in 17 centers in five European countries (Finland, Germany, Italy, Spain, and the United Kingdom). The inclusion criterion was a history of ongoing AF (paroxysmal, persistent, or permanent). The only exclusion criteria were unwillingness or inability to participate in the study or to give informed consent.

4.2 PATIENT CARE AND DATA COLLECTION

Studies I and III were retrospective multi-center observational studies and study II was a prospective multi-center observational study.

4.2.1 Study I

In the FinCV-study each participating hospital was the only referral hospital responsible for the acute care of patients with cardiac and neurologic events in their catchment area. Patients' clinical characteristics, date of AF diagnosis, other medical history and medication, laboratory values during admission, details about the care of the index event as well as outcome during 30-day follow-up were retrospectively collected from the individual medical reports.

ECV was performed according to contemporary guidelines under general anesthesia. During and after the procedure ECG, blood pressure and oxygen saturation were monitored. Paddles or pads were positioned in antero-posterior or antero-lateral configuration. The energy was set from 70 to 150 J with biphasic defibrillator devices and from 70 to 360 J with monophasic devices. A 12-lead ECG was controlled before and after ECV.

4.2.2 Study II

In the FibStroke-study the data was collected from medical records and included clinical characteristics, date of AF diagnosis, other medical history and medication, laboratory values during admission, details about the care of the index event as well as outcome during 30-day follow-up and the use of stroke risk scores. Reasons for not being on OAC were divided into valid, relative, non-valid or undocumented contraindications. Each participating hospital was the only referral hospital responsible for the acute care of patients with cardiac and neurologic events in their catchment area.

4.2.3 Study III

In the AFCAS-study PCI was performed in each participating center according to local practice, and patients were followed for 12 months. Peri- and post-procedural antithrombotic regimens were at the operator's discretion. Follow-up was performed by telephone calls or clinic visits scheduled at one, three, six, and 12 months after PCI. Patients were enquired about clinical outcome endpoints, hospitalization, and medications. CHA_2DS_2-VASc and HAS-BLED scores were calculated before PCI to evaluate the individual risks for stroke and bleeding events, respectively.

4.3 DEFINITIONS

All AFs were confirmed by a 12-lead ECG. Atrial flutter was excluded. Thrombotic events were defined as (1) a stroke documented clinically and considered definite by a neurologist and confirmed to be caused by cerebral infarction ascertained by imaging (computerized tomography or magnetic resonance imaging) or (2) a transient ischemic attack diagnosed clinically by a neurologist. Bleeding events included intracerebral hemorrhage, subdural hematoma, and subarachnoidal bleeding. Estimated glomerular filtration rate (eGFR) was calculated with the simplified Modification of Diet in Renal Disease (MDRD) formula.

4.3.1 Study I

In the FinCV-study cardioversion was successful if the patient was discharged from the emergency unit in sinus rhythm. AF recurrence was defined as a 12-lead ECG documented recurrence of AF within 30 days after index ECV. Net harm was defined as an adverse outcome or no benefit for the patient from the selected treatment strategy (failure of ECV, bradyarrhythmic complications, AF recurrence, or TEC).

4.3.2 Study II

In the FibStroke-study the $CHADS_2$ risk stratification score was used to assess thromboembolic risk until 31.12.2009 and the CHA_2DS_2-VASc score from 01.01.2010 onwards according to international guidelines. The index cerebrovascular event was not included in risk stratification scores. A modified HAS-BLED score omitting labile INR was used to analyze the bleeding risk. Reasons for not being on OAC were defined as valid ($CHADS_2$ or CHA_2DS_2-VASc score <2 or a history of ICH), relative (dementia, prior gastrointestinal bleed, excess alcohol intake, a history of frequent falls), non-valid (anemia, patient refusal, small stroke risk, paroxysmal AF, and restoration of sinus rhythm after electrical cardioversion) or undocumented.

4.3.3 Study III

In the AFCAS-study major adverse cardiac/cerebrovascular events (MACCE) were defined as the first occurrence of all-cause death, MI, repeat revascularization, stent thrombosis, stroke or TIA. Bleeding events were defined according to the BARC criteria and included events adjudicated as minor (BARC 0, 1 and 2) and major (BARC 3a, 3b, 3c, and 5) (Mehran et al., 2011). BARC from 0 to 2 was defined as no bleeding, bleeding that does not need medical assistance and overt bleeding leading to medical evaluation and an increased level of care. BARC 3a, 3b and 3c were defined as overt bleeding with hemoglobin drop necessitating transfusion, surgical intervention or intravenous vasoactive agents. BARC type 5 was defined as fatal bleeding. The endpoint event was the first occurrence of all-cause death, MI, repeat revascularization, stent thrombosis or stroke/TIA.

4.4 STATISTICAL ANALYSIS

Comparisons between groups were performed with the Chi-square or Fisher's exact test for categorical variables and the Student's t-test and Mann-Whitney U-test for analysis of continuous data. Time-specific calculations were made with the Mann-Whitney U-test and interquartile

ranges and reported as the median. Two-sided differences at $p < 0.05$ were considered statistically significant. Statistical analyses were performed using version Statistics 22 of IBM SPSS (IBM Corporation and Others 1989, 2013) (Study I), version 9.2 of the SAS software (SAS Institute Inc., Cary, NC, USA) (Study II) and SPSS software, version 20 (IBM SPSS Inc., Chicago, IL, USA) (Study III).

Clinical features were used for analyses of multivariate logistic regression with repeated measures option to assess the predictors of TEC and the GENMOD procedure with repeated measures option was used in univariate and multivariate analyses for repeated cardioversions of same individuals (Study I). Kaplan–Meier estimates of MACCE and all bleeding events were used to construct time-to-event curves (Study III).

4.5 ETHICAL CONSIDERATIONS AND STUDY REGISTRATION

All three studies were conducted according to the guidelines of the 1964 Declaration of Helsinki as revised in 2013. The study protocol was approved by the ethics committees of the participating centers and the National Institute for Health and Welfare. Informed consent was not required because of the register-based nature of the study for studies I and II. Informed written consent was obtained from every patient after full explanation of the study protocol of study III. Patient data was analyzed anonymously for all three studies. The FinCV-study is registered under http://www.ClinicalTrials.gov at NCT01380574, the FibStroke-study at NCT00596570 and the AFCAS-study at NCT00596570.

5 RESULTS

5.1 SEX, AGE AND RISK OF STROKE AFTER ELECTRICAL CARDIOVERSION OF RECENT ONSET ATRIAL FIBRILLATION

The FinCV- study population consisted of 1455 women and 3260 men. In this study women were older, had more comorbidities (e.g. hypertension, HF) and a higher CHA_2DS_2VASc score (Table 8). Women used beta-blockers more often and antiarrhythmic drugs less often than men. Heart rate on admission was higher for women who also presented with first-ever index AF more often than men. Time to ECV was shorter for women (50.9% vs. 45.1% <12 hours, p<0.001).

During a 30-day follow-up TEC was diagnosed in 40 patients (0.8%) of which 30 were strokes, seven were systemic embolisms, and four were TIAs. One patient had both stroke and systemic embolism. Three patients died of a fatal stroke. The incidence of TEC was significantly higher in women than in men (1.51% vs. 0.55%, p<0.001). Female sex was an independent predictor of TEC in multivariate analysis (OR 2.12, CI 1.09–4.11, p=0.03) as well as age (OR 1.04, CI 1.01–1.07, p=0.003), time to cardioversion (OR 3.70, CI 1.69–8.20, p=0.001) and history of vascular disease (OR 2.04, CI 1.06–3.91, p=0.03) (Table 9).

Table 8. Clinical characteristics on admission in patients undergoing electrical cardioversion

	Women (n=1455)	**Men (n=3260)**	**P-value**	**< 12 h (n=2211)**	**➢ 12h (n=2504)**	**P-value**
Age	66.7 ± 10.8	59.1 ± 12.3	<.0001	61.6 ± 12.2	61.4 ± 12.5	0.34
Women				741 (33.5)	714 (28.5)	<0.001
Hypertension	785 (53.0)	1377 (42.2)	<0.001	1019 (46.1)	1143 (45.7)	0.76
Heart failure	66 (4.5)	119 (3.6)	0.15	73 (3.3)	112 (4.5)	0.04
Diabetes	127 (8.7)	261 (8.0)	0.40	194 (8.8)	194 (7.8)	0.20
Vascular disease	369 (25.4)	740 (23.0)	0.05	533 (24.1)	578 (23.1)	0.41
$CHA_2DS_2VAS_{c-}$ score	2.9	1.3	<0.001	1.8	1.7	0.09
Kidney disease	16 (1.1)	65 (2.0)	0.03	45 (2.0)	36 (1.4)	0.12
Permanent pacemaker	50 (3.5)	106 (3.3)	0.80	68 (3.1)	88 (3.5)	0.39
Alcohol overuse	9 (0.6)	129 (4.0)	<0.001	65 (2.9)	73 (2.9)	0.96
Beta blocker on admission	1097 (75.4)	2320 (71.2)	0.003	1558 (70.5)	1859 (74.2)	0.004
AAD on admission	208 (14.3)	671 (20.6)	<0.001	371 (16.8)	508 (20.3)	0.002
First-ever AF episode	445 (30.6)	773 (23.7)	<0.001	540 (24.4)	723 (28.9)	<0.001
AF within 30 days	158 (10.9)	361 (11.1)	0.80	240 (10.9)	279 (11.2)	0.75
Time to cardioversion <12h	741 (51.0)	1470 (45.1)	<0.001			
Heart rate during AF	117 ± 23	108 ± 25	<0.001	114.0 ± 25.1	107.7 ± 24.6	<0.001

Abbreviations: CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/transient ischaemic attack/systemic embolism (2 points), associated Vascular disease, Age 65–74 years, and female sex category; AF = atrial fibrillation; AAD = antiarrhythmic drugs. The values denote mean ± SD or n (%).

Table 9. Multivariate predictors of thromboembolic complications within 30-day follow-up after electrical cardioversion of acute AF

	OR	95% CI	P-value
Age	1.04	1.01–1.07	0.003
Vascular disease	2.04	1.06–3.91	0.03
Female sex	2.10	1.09–4.11	0.03
Time to cardioversion	3.70	1.69–8.20	0.001
Heart failure	2.50	0.88–7.15	0.09
Diabetes	2.33	0.92–5.41	0.08
Aspirin or clopidogrel	1.13	0.51–2.53	0.77

The values denote odds ratio (OR) and 95% confidence interval (CI).
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The population was divided into three age categories (< 65 years, 65-75 years, and >75 years). In patients cardioverted within 12 hours from AF onset, the incidence of TEC in women and men aged < 75 years was low and did not differ between sexes (p=1.00) (Figure 3). However, for patients >75 years the risk of TEC increased in both sexes and was significantly higher in women (1.4% vs. 0.9%, p=0.03 respectively). When ECV was performed after 12 hours the risk of TEC in women was two- to four-fold higher compared to men in all age groups (1.9% vs. 0.5%, p=0.034, 3.5% vs.1.2%, p=0.052 and 2.7% vs. 1.4%, p=0.469 in the youngest, middle, and oldest age groups respectively). The clinical characteristics of patients cardioverted within or after 12 hours did not explain the risk of stroke.

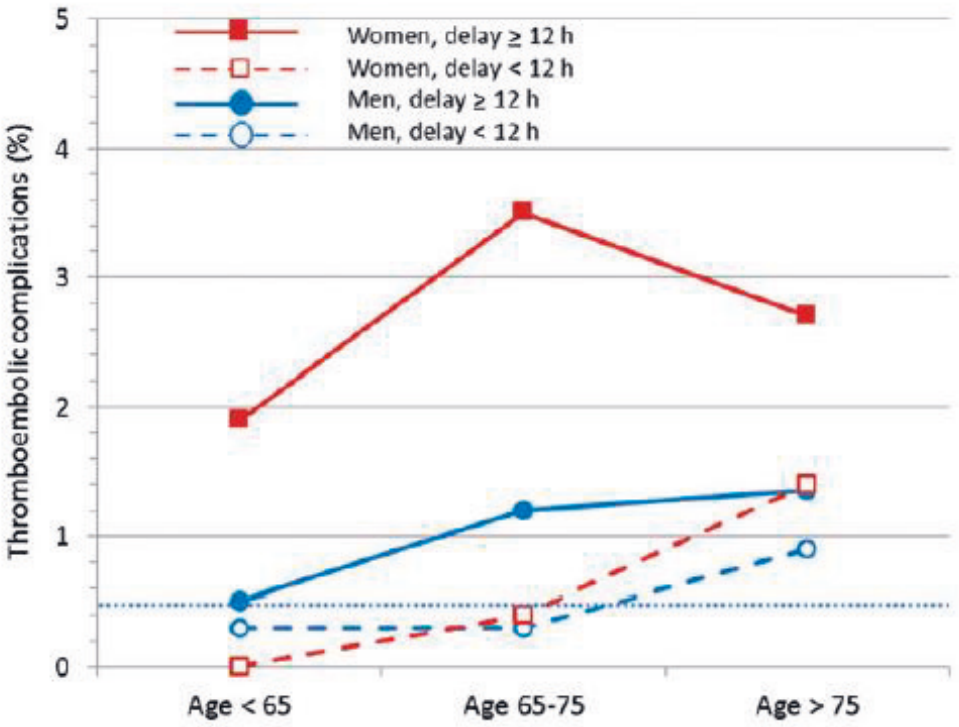

Figure 3. Thromboembolic complications according to sex, age and time to cardioversion. Reproduced with the permission of copyright holder (Bah et al., 2016)

To identify patients who did not benefit from ECV or experienced adverse outcomes we calculated a combined endpoint of net harm (failure of ECV, bradyarrhythmic complications, AF recurrence, or TEC) (Figure 4). The failure of cardioversion (6.7% vs. 4.0%, p<0.001), the incidence of bradyarrhythmic (heart rate < 40 bpm) complications (1.86 vs. 0.43%, p<0.001) as well as the incidence of TEC (1.51% vs. 0.55%, p<0.001) were higher in women than in men. The recurrence of AF within 30 days in patients with successful cardioversion tended to be higher in women than in men (13.7% vs. 11.7%, p=0.055). Altogether 17.82% of the patients undergoing ECV of their acute AF experienced an adverse outcome or did not benefit from the selected treatment strategy (net harm). The net harm was higher in women than in men (21.86% vs. 16.01%, p<0.001).

Particularly, net harm exceeded 20% in women >65 years of age and in men >75 years of age.

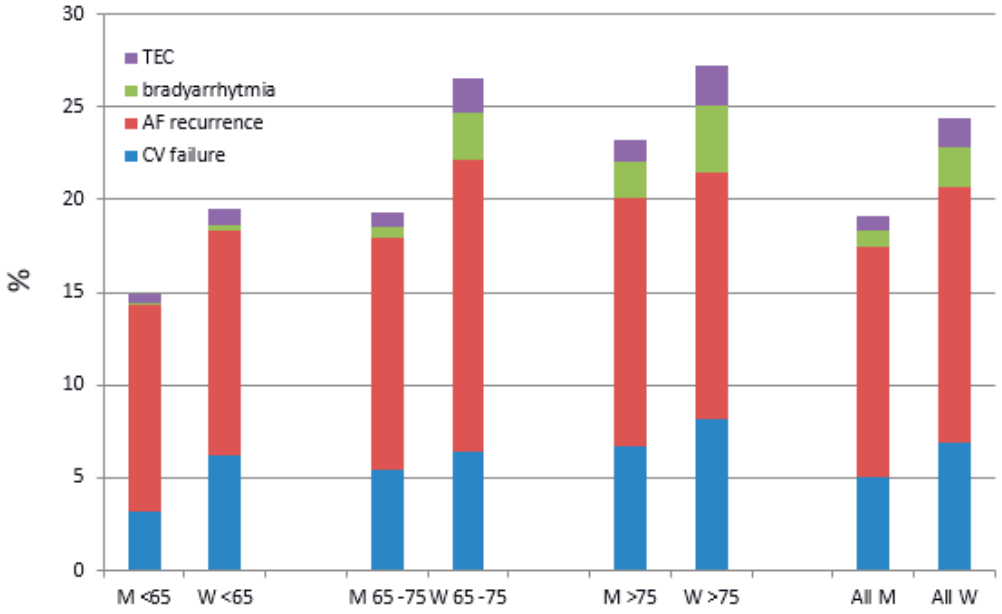

Figure 4. Net harm of patients with recent onset AF after index ECV within 30-day follow-up according to sex and age. M = men; W = women

In multivariate analysis the predictors of net harm were sex, age, other than first-ever AF, AF during the month preceding the index AF, use of antiarrhythmic drugs, vascular disease, HF, and renal insufficiency (Table 10).

Table 10. Multivariate predictors of net harm after electrical cardioversion for atrial fibrillation

	OR	95% CI	P-value
AF during the preceding month	3.45	2.71–4.38	<.0001
Renal insufficiency	1.99	1.19–3.33	0.0009
AAD on admission	1.88	1.53–2.32	<.0001
Heart failure	1.65	1.18–2.33	0.0039
Vascular disease*	1.45	1.16–1.81	0.001
Female sex	1.40	1.15–1.72	0.0009
Age	1.02	1.01–1.03	<.0001
First ever AF	0.71	0.58–0.88	0.0014

Abbreviations: AAD = antiarrhythmic drugs, AF = atrial fibrillation. * = coronary artery disease and atherosclerotic disease.

5.2 SEX AND ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION (II)

The FibStroke-study population consisted of 960 women and 787 (Table 11). Women were older than men and almost three quarters of women and half of men were at least 75 years old. Women had more comorbidities (e.g. hypertension, HF, a cardiac pacemaker, renal dysfunction) whereas men had more frequently a history of MI, alcohol overuse and liver disease in comparison with women. The index cerebrovascular event was stroke more often for women. Intracranial bleeds were more frequent among men.

Table 11. Clinical characteristics of the patient population with a history of atrial fibrillation at the time of cerebrovascular event

	Women (n=960)	**Men (n=787)**	**All (n=1747)**	**P-value**
Age	79.8 ± 8.5	73.5 ± 10.6	77.0 ± 10.0	<0.001
Age 65-75 years	190 (19.8)	240 (30.5)	430 (24.6)	<0.001
Age ≥ 75 years	716 (74.6)	381 (48.3)	1096 (62.7)	<0.001
Hypertension	674 (70.3)	492 (62.5)	1166 (66.8)	0.001
Heart failure	220 (22.9)	136 (17.3)	356 (20.4)	0.004
Severe renal impairment*	43 (4.6)	18 (2.3)	61 (3.5)	0.012
Anemia (haemoglobin <10g/dL)	34 (3.6)	14 (1.8)	48 (2.8)	0.024
Chronic liver disease	2 (0.2)	16 (2.0)	18 (1.0)	<0.001
Alcohol overuse	17 (1.8)	103 (13.1)	120 (6.9)	<0.001
Prior myocardial infarction	134 (14.0)	163 (20.7)	297 (17.0)	<0.001
Prior bleeding	70 (7.3)	47 (6.3)	117 (6.7)	0.270
Permanent pacemaker	95 (9.9)	55 (7.0)	150 (8.6)	0.032
Biological valve prostehesis	11 (1.1)	11 (1.4)	22 (1.5)	0.068
Paroxysmal AF	448 (46.7)	324 (41.2)	772 (44.2)	0.021
Permanent or persistent AF	411 (42.8)	359 (45.6)	770 (44.1)	0.240
Stroke	653 (68.0)	461 (58.6)	1114 (63.8)	<0.001
TIA	162 (16.9)	160 (20.4)	322 (18.4)	0.062
Intracranial haemorrhage	147 (15.3)	169 (21.5)	316 (18.1)	0.004
Warfarin	445 (46.4)	379 (48.2)	824 (47.2)	0.437
Aspirin	328 (34.4)	295 (37.5)	623 (35.8)	0.173

	Women (n=960)	Men (n=787)	All (n=1747)	P-value
INR (on admission)	2.0 ± 1.1 1.9 [1.3-2.5]	2.1 ± 1.1 2.0 [1.4-2.6]	2.1 ± 1.1 1.9 [1.3-2.6]	0.146
INR 2-3 (of those on OAC)	206 (45.0)	189 (48.6)	395 (46.6)	0.446
$CHADS_2$ (until end 2009)	1.8 ± 1.0	1.4 ± 1.0	1.6 ± 1.0	<0.001
$CHADS_2$ ≥2	364 (64.7)	198 (43.1)	562 (55.0)	<0.001
CHA_2DS_2-VASc (from 2010)	4.2 ± 1.3	2.7 ± 1.4	3.5 ± 1.5	<0.001
CHA_2DS_2-VASc ≥2	390 (98.2)	258 (78.7)	648 (89.4)	<0.001
$CHADS_2$/CHA_2DS_2-VASc ≥2	754 (78.5)	456 (57.9)	1210 (69.3)	<0.001
HAS-BLED	2.3 ± 0.9	2.1 ± 1.0	2.2 ± 0.9	0.001

Abbreviations: AF = atrial fibrillation; TIA=transient ischemic attack. $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/transient ischaemic attack/systemic embolism (2 points), associated Vascular disease, Age 65–74 years, and female Sex category; HAS-BLED* (labile INR omitted) = Hypertension, Abnormal liver or kidney function, prior Stroke, Bleeding history or predisposition, Labile INR (omitted), Elderly, and concomitant Drugs. Severe renal dysfunction*= estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration) < 30 ml/min/1.73m^2. The values denote mean (standard deviation), median [interquartile range] or n (%). p-value refers to women vs. men. Reproduced with the permission of copyright holder (Bah et al., 2021)

At the time of cerebrovascular event, both the $CHADS_2$ score (until end 2009) and the CHA_2DS_2-VASc score (from 2010 onwards) were higher in women. Correspondingly, a high risk ($CHADS_2$/CHA_2DS_2-VASc ≥2) was found in 78.5% of women and 57.9% of men (p<0.001). During the $CHADS_2$ era, a high $CHADS_2$ score ≥2 was present in 64.7% of women and in 43.1% of men. The difference was even more pronounced after 2010 for the CHA_2DS_2-VASc score: CHA_2DS_2-VASc score ≥2 was present practically in all (98.2%) women in comparison with 78.7% of men. Women had also slightly higher HAS-BLED scores.

At the time of the cerebrovascular event approximately half of the patients were on OAC therapy (warfarin) and about half of the patients had an INR within the therapeutic range (2.0-3.0). When risk stratification was considered, women with a high-risk score ($CHADS_2$/CHA_2DS_2-VASc ≥2) were significantly less often on OAC than men: 49.2% of women and 56.7% of men were on OAC (OR 0.80, 95% CI 0.50–0.93, p=0.011) (Figure 5). During the $CHADS_2$ era 44.8% of women and 48.0% of men with a high stroke risk were on OAC (OR 0.88, 95% CI 0.62–1.25, p=0.011). During the CHA_2DS_2-VASc era 53.3% of women with high risk were on OAC compared to 63.4% of men (OR 0.66, 95% CI 0.48–0.91, p=0.011). Most importantly, of patients without OAC, 74.4% of women and 49.5% of men had a high stroke risk ($CHADS_2$/ CHA_2DS_2-VASc ≥2, p<0.001) and should have been on OAC (Figure 6). During the $CHADS_2$ era, 61.5% of women and 38.1% of men not on OAC had a high risk score (p<0.001) and during the CHA_2DS_2-VASc era a high risk score was present in 96.8% of women and 66.2% of men (p<0.001). Paradoxically the use of OAC treatment was inconsistent in patients with low or moderate stroke risk: 34.8% of men and 17.5% of women on OAC had a low or moderate risk ($CHADS_2$/CHA_2DS_2-VASc 0-1, p<0.001) (Figure 7).

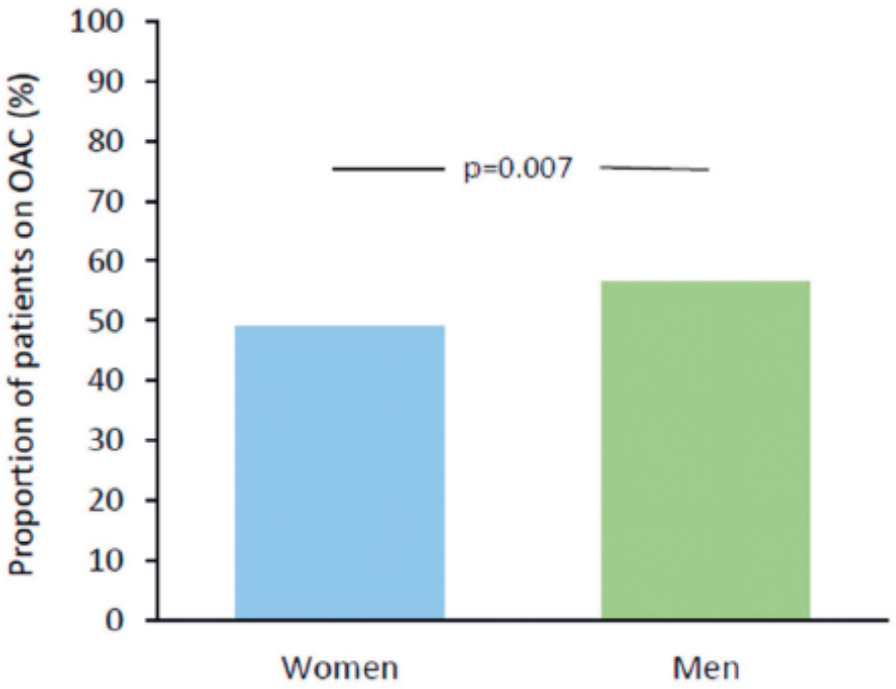

Figure 5. Oral anticoagulation in patients with high stroke risk ($CHADS_2$/CHA_2DS_2-VASc ≥ 2). Reproduced with the permission of copyright holder (Bah et al., 2021)

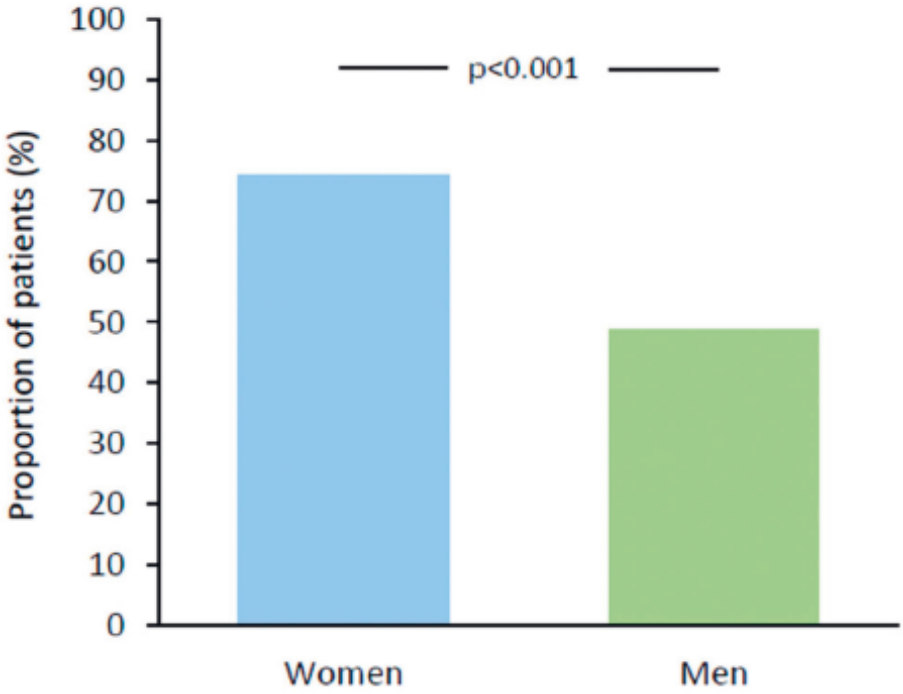

Figure 6. Proportion of high-risk patients ($CHADS_2$/CHA_2DS_2-VASc ≥ 2) among those not on oral anticoagulation. Reproduced with the permission of copyright holder (Bah et al., 2021)

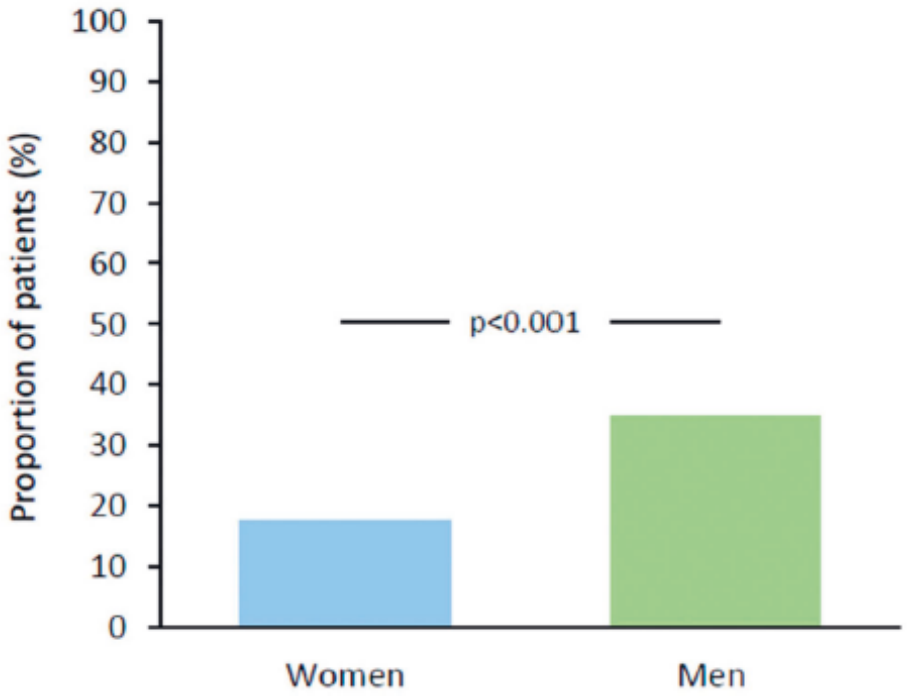

Figure 7. Proportion of low and moderate risk patients ($CHADS_2$/CHA_2DS_2-VASc 0-1) among those on oral anticoagulation. Reproduced with the permission of copyright holder (Bah et al., 2021)

A valid reason to omit OAC was reported in 38.6% of patients with a marked difference between sexes (Table 12). Approximately one quarter of women had a valid reason not to be prescribed OAC compared to half of men. If only a $CHADS_2$/CHA_2DS_2-VASc score 0 and intracranial hemorrhage were accepted as valid reasons to withhold OAC, 8.9% of women and 19.6% of men had a valid reason.

Table 12. Reasons for not being anticoagulatied in patients with atrial fibrillation diagnosed before cerebrovascular event

	Women (n=515)	**Men (n=408)**	**All (n=923)**	**P-value**
Valid reason	139 (27.0)	217 (53.2)	356 (38.6)	<0.001
$CHADS_2$/CHA_2DS_2-VASc 0-1	132 (25.6)	210 (51.5)	342 (37.1)	<0.001
$CHADS_2$ 0	33 (6.4)	57 (14.0)	90 (9.8)	<0.001
$CHADS_2$ 1	93 (18.1)	104 (25.5)	197 (21.3)	0.005
CHA_2DS_2-VASc 0	6 (1.2)	16 (3.9)	22 (2.4)	0.004
CHA_2DS_2-VASc 1	0 (0.0)	33 (8.1)	33 (3.6)	<0.001
Intracranial hemorrhage	7 (1.4)	7 (1.7)	14 (1.5)	0.657
Relative reason	35 (6.8)	37 (9.1)	72 (7.8)	0.197
Non-valid reason	82 (15.9)	57 (14.0)	139 (15.1)	0.755
Undocumented reason	259 (50.3)	97 (23.8)	356 (38.6)	0.898

Abbreviations: $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/transient ischaemic attack/systemic embolism (2 points), associated Vascular disease, Age 65–74 years, and female Sex category; Valid reason = $CHADS_2$/CHA_2DS_2-VASc<2 or intracranial hemorrhage; Relative reason = dementia, prior gastrointestinal bleed, excess alcohol intake, frequent falls; Non-valid reason = anemia, patient refusal, small stroke risk, paroxysmal AF and restoration of sinus rhythm after electrical cardioversion. The values denote n (%). P-value refers to women vs. men. Reproduced with the permission of copyright holder (Bah et al., 2021)

When evaluating patients with a high stroke risk ($CHADS_2$/CHA_2DS_2-VASc score ≥2) and not on OAC, women were older than men, had more often a high HAS-BLED score and were more often on aspirin. In addition, sex differences were significant (Table 13). Most patients not on OAC had a

history of paroxysmal AF and about half of them were ≥ 75 years old with no sex-related difference.

Table 13. Clinical characteristic of patients with a history of atrial fibrillation and $CHADS_2$ and CHA_2DS_2-VASc ≥2 and not on oral anticoagulation

	Women	**Men**	**All**	**P-value**
Age	82.2 ± 8.2	78.6 ± 8.4	81.0 ± 8.4	0.008
Age ≥ 75 years	335 (51.5)	150 (45.7)	485 (49.5)	0.091
HAS-BLED ≥ 3	234 (73.1)	132 (64.7)	366 (69.8)	0.041
Paroxysmal AF	215 (68.3)	108 (65.1)	323 (67.2)	0.478
Aspirin use	219 (86.2)	139 (74.7)	358 (81.4)	0.002

Abbreviations: AF = Atrial fibrillation; $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/transient ischaemic attack/systemic embolism (2 points), associated Vascular disease, Age 65–74 years, and female Sex category. The values denote mean ± SD (age) or n (%). p-value refers to women vs. men. Reproduced with the permission of copyright holder (Bah et al., 2021)

5.3 SEX AND AGE AND OUTCOMES IN ATRIAL FIBRILLATION PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION (III)

The AFCAS registry included a total of 275 women and 650 men (Table 14). A total of 195 (21.1%) patients were octogenarian (≥80 years) and 41.5% of octogenarians were women. Octogenarians had higher CHA_2DS_2-VASc and HAS-BLED scores.

Octogenarian women had hypercholesterolemia (p=0.011) and lower glomerular filtration rate (p<0.001) more often than octogenarian men but with respect to other comorbidities such as hypertension, body mass index, or smoking there was no significant sex-related difference.

Octogenarian women had also higher CHA_2DS_2-VASc scores than octogenarian men (5.8 ± 1.1 vs. 4.7 ± 1.1, $p<0.001$). HAS-BLED scores did not differ between sexes in octogenarian patients. Octogenarian women had a history of CABG surgery less frequently than men (2.5% vs. 16.7%, $p<0.001$).

Table 14. Clinical baseline characteristics of octogenarians and younger patients with atrial fibrillation undergoing percutaneous coronary intervention (Abbreviations next page)

	Whole Cohort (n=925)			Males (n=650)			Females (n=275)		
Variable	**OG (n=195)**	**Younger (n=730)**	**P-Value**	**OG (n=114)**	**Younger (n=536)**	**P-Value**	**OG (n=81)**	**Younger (n=194)**	**P-Value**
Age ± SD, median [IQR]	82.9 ± 2.6 82 [3]	70.4 ± 6.7 72 [8]	<0.001	83.0 ± 2.8 82 [4]	69.7 ± 7.1 71 [9]	<0.001	82.9 ± 2.4 83 [3]	72.3 ± 5.3 74 [6]	<0.001
Female gender	81 (41.5)	194 (26.6)	<0.001						
BMI	26.2 ±3.5	28.8 ± 4.7	<0.001	26.2 ± 23.2	28.7 ± 4.5	<0.001	26.2 ± 3.9	29.1 ± 5.1	<0.001
Periprocedural GFR	53 ± 19	80 ± 35	<0.001	55.3 ± 19.4	84.1 ± 35.9	<0.001	49.5 ± 18.5	69.3 ± 28.0	<0.001
LVEF (%)	49 ± 14	50 ± 14	0.41	48.4 ± 14.8	48.5 ± 14.0	0.95	49.2 ± 11.9	53.3 ± 13.6	0.041
Diabetes	63 (32.3)	274 (37.5)	0.18	36 (31.6)	189 (35.3)	0.45	27 (33.3)	85 (43.8)	0.11
Hypertension	160 (82.1)	616 (84.4)	0.43	88 (77.2)	447 (83.4)	0.12	72 (88.9)	169 (87.1)	0.68
Hyperlipidemia	114 (58.5)	502 (68.8)	0.007	62 (54.4)	361 (67.4)	0.008	52 (64.2)	141 (72.7)	0.16
Smoking	9 (4.6)	83 (11.4)	0.005	7 (6.1)	73 (13.6)	0.027	2 (2.5)	10 (5.2)	0.32
Prior MI	57 (29.2)	179 (24.5)	0.18	35 (30.7)	140 (26.1)	0.32	22 (27.2)	39 (20.1)	0.20
Prior PCI	25 (12.8)	135 (18.5)	0.063	16 (14.0)	99 (18.5)	0.26	9 (11.1)	36 (18.6)	0.13
Prior CABG	21 (10.8)	113 (15.5)	0.097	19 (16.7)	97 (18.1)	0.72	2 (2.5)	16 (8.2)	0.08
Prior heart failure	43 (22.1)	142 (19.5)	0.42	29 (25.4)	110 (20.5)	0.25	14 (17.3)	32 (16.5)	0.87
Prior stroke	26 (13.3)	85 (11.6)	0.52	16 (14.0)	64 (11.9)	0.54	10 (12.3)	21 (10.9)	0.72
Prior TIA	9 (4.6)	37 (5.1)	0.80	4 (3.5)	30 (5.6)	0.36	5 (6.2)	7 (3.6)	0.34
Prior hemorrhage	9 (4.6)	29 (4.0)	0.70	6 (5.3)	22 (4.1)	0.59	3 (3.7)	7 (3.6)	0.98
CHA_2DS_2-VASC	5.1 ± 1.2	4.2 ± 1.5	<0.001	4.7 ± 1.1	3.8 ± 1.4	<0.001	5.8 ± 1.1	5.1 ± 1.3	<0.001
CHA_2DS2-VASC ≥ 2	195 (100)	716 (98.1)	<0.001	114 (100)	522 (97.4)	0.081	81 (100)	194 (100)	1.0
HAS-BLED	3.1 ± 0.7	2.9 ± 0.7	<0.001	3.1 ± 0.8	2.9 ± 0.8	0.007	3.2 ± 0.6	3.0 ± 0.7	0.030
HAS-BLED ≥ 3	167 (85.6)	540 (74.0)	0.001	92 (80.7)	384 (71.6)	0.047	75 (92.6)	156 (80.4)	0.012

Abbreviations (Table 14): OG = octogenarian; BMI = body mass index; GFR= estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration) < 30 ml/min/1.73m^2; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA=transient ischemic attack. CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/transient ischaemic attack/systemic embolism (2 points), associated vascular disease, Age 65–74 years, and female Sex category; HAS-BLED (labile INR omitted) = Hypertension, Abnormal liver or kidney function, prior Stroke, Bleeding history or predisposition, Labile INR (omitted), Elderly, and concomitant Drugs. The values denote mean (standard deviation, SD), median [interquartile range, IQR] or n (%). P-value refers to women vs. men. Reproduced with the permission of copyright holder (Bah et al., 2021)

The indication for PCI in octogenarians was more often ACS in comparison to younger patients (Table 15). However, octogenarian women presented ACS as an indication for PCI less frequently than octogenarian men (67.5% vs. 71.1%, p<0.001). Instead, octogenarian women presented with NSTEMI more often (39.5% vs. 31.6%, p=0.005). There was no significant sex-related difference for octogenarians with STEMI (p=0.51). Neither was there any sex-related difference for octogenarian patients and the use of drug-eluting stents (22.2% vs. 18.3%, p=0.29) or radial access (22.2% vs. 34.2, p=0.30). Procedural success did not differ between female and male octogenarians (98.8% vs. 96.5%, p=0.17). Nevertheless, there was a trend towards longer hospital stay for female octogenarians (6.7 days ± 4 vs. 5.4 ± 3, p=0.056).

Approximately 19.5% of octogenarians and 16.8% of non-octogenarians did not have OAC despite AF (p=0.39) (Table 16). Octogenarians did not differ with younger patients with respect to antithrombotic therapy post-PCI. Triple therapy (OAC + clopidogrel + aspirin) was the most common antithrombotic regimen for octogenarians prescribed at discharge followed by DAPT (clopidogrel + aspirin). Octogenarians were prescribed lipid-lowering agents less frequently than non-octogenarians.

There was no significant sex-related trend in the octogenarian population with respect to DAPT (22.2% vs. 17.5%, p=0.33 for octogenarian women and men respectively), the combination of VKA and clopidogrel (12.3% vs. 7.4%, p=0.15 for octogenarian women and men respectively), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (89.6% vs. 81.7%, p=0.26 for octogenarian women and men respectively), beta blockers (80.2% vs. 86.0%, p=0.53 for octogenarian women and men respectively) or lipid-lowering agents (80.2% vs. 78.1%, p=0.14 for octogenarian women and men respectively).

Table 15. Procedural data and hospital stay in octogenarians and younger patients with atrial fibrillation undergoing percutaneous coronary intervention

	Whole Cohort (n=925)			Males (n=650)			Females (n=275)		
Variable	**OG (n=195)**	**Younger (n=730)**	**P-Value**	**OG (n=114)**	**Younger (n=536)**	**P-Value**	**OG (n=81)**	**Younger (n=194)**	**P-Value**
ACS	135 (69.6)	392 (53.7)	<0.001	81 (71.1)	276 (51.5)	<0.001	54 (67.5)	116 (59.8)	0.23
STEMI	32 (16.5)	93 (12.7)	0.18	17 (14.9)	68 (12.7)	0.52	15 (18.5)	25 (12.9)	0.23
Lesions per patient	1.2 ± 0.4	1.2 ± 0.4	0.64	1.2 ± 0.5	1.2 ± 0.4	0.15	1.1 ± 0.3	1.2 ± 0.4	0.30
Drug-eluting stents	38 (20.3)	181 (25.8)	0.12	20 (17.9)	138 (26.3)	0.061	18 (22.8)	44 (23.0)	0.96
Total stent length (mm)	24.6 ± 16.8	25.0 ± 16.3	0.75	26.4 ± 19.1	25.1 ± 16.9	0.47	22.2 ± 12.7	25.0 ± 14.3	0.13
Procedural success	190 (97.4)	707 (96.8)	0.67	110 (96.5)	515 (96.1)	0.84	80 (98.8)	192 (99.0)	0.88
Radial access	57 (29.2)	201 (27.5)	0.64	39 (34.2)	149 (27.8)	0.17	18 (22.2)	52 (26.8)	0.43
Hospital stay (days), mean ± SD median [IQR]	5.9 ± 7.8 4 [5]	4.8 ± 7.5 2 [5]	0.050	5.4 ± 6.9 3 [5]	5.0 ± 8.2 2 [5]	0.61	6.7 ± 8.9 4 [6]	4.0 ± 4.6 2 [5]	0.001
TTR (%)	68 ± 34	68 ± 34	0.87	71 ± 33	68 ± 32	0.38	64 ± 34	68 ± 33	0.46

Abbreviations: OG = octogenarian; ACS = acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; TTR = time in therapeutic range. The values denote mean (standard deviation, SD), median [interquartile range, IQR] or n (%). P-value refers to women vs. men. Reproduced with the permission of copyright holder (Lahtela, Bah et al., 2017)

Table 16. Antithrombotic and cardiac medications in octogenarians and younger patients with atrial fibrillation at discharge after percutaneous coronary intervention

	Whole Cohort (n=925)			Males (n=650)			Females (n=275)		
Variable	**OG (n=195)**	**Younger (n=730)**	**P-Value**	**OG (n=114)**	**Younger (n=536)**	**P-value**	**OG (n=81)**	**Younger (n=194)**	**P-value**
Periprocedural INR, SD	1.9 ± 0.6	1.9 ± 0.7	0.98						
GPI	41 (21.0)	139 (19.0)	0.53	25 (21.9)	107 (20.0)	0.64	16 (19.8)	32 (16.5)	0.52
VKA + Clop + Aspirin	137 (70.3)	541 (74.1)	0.28	80 (70.2)	401 (74.8)	0.31	57 (70.4)	140 (72.2)	0.76
VKA + Clop/ASA	20 (10.3)	66 (9.0)	0.60	14 (12.3)	51 (9.5)	0.37	6 (7.4)	15 (7.7)	0.93
Clop + Aspirin	38 (19.5)	123 (16.8)	0.39	20 (17.5)	84 (15.7)	0.62	18 (22.2)	39 (20.1)	0.69
Clop duration median [IQR]	5.7 ± 4.8 3 [11]	5.7 ± 4.7 3 [11]	1.0	5.7 ± 4.7 3 [11]	5.7 ± 4.7 3 [11]	1.0	5.8 ± 5.0 3 [11]	5.8 ± 4.7 3 [11]	0.96
Beta blockers	163 (83.6)	640 (87.7)	0.19	98 (86.0)	468 (87.3)	0.51	65 (80.2)	172 (88.7)	0.18
Lipid lowering agents	154 (79.0)	637 (87.3)	0.013	89 (78.1)	465 (86.8)	0.059	65 (80.2)	172 (88.7)	0.18
ACEI / ARB	158 (84.9)	573 (80.5)	0.16	89 (81.7)	419 (80.1)	0.71	69 (89.6)	154 (81.5)	0.10

Abbreviations: OG = octogenarian; INR = international normalized ratio; GPI = glycoprotein IIb/IIa inhibitor; VKA = vitamin K antagonist; Clop = clopidogrel; ASA = acetylsalic acid (aspirin); ACEI = angiotensin-converting enzyme inhibitor; ATRB = angiotensin receptor blocker. The values denote mean (standard deviation, SD), median [interquartile range, IQR] or n (%). P-value refers to women vs. men. Reproduced with the permission of copyright holder (Lahtela, Bah et al., 2017)

The cumulative incidence of MACCE in octogenarians was comparable during hospital stay and at 30-day follow-up but significantly higher at 12-month follow-up (p=0.02) in comparison to non-octogenarians (Table 17). This was driven by a higher incidence of MI in octogenarians but there was a tendency towards higher all-cause mortality (p=0.06) at 12-month follow-up for octogenarians. The rate of repeat revascularization did not differ significantly between octogenarians and younger patients.

When comparing octogenarian women and men, the cumulative incidence of MACCE in octogenarians did not differ between sexes. For both octogenarian women and octogenarian men MACCE incidence tended to be higher at 12-month follow-up (27.2% vs. 28.1%, p=0.12) when compared to MACCE incidence during hospital stay (3.7% vs. 3.5%, p=0.93) and at 30-day follow-up (6.2% vs. 7.9%, p=0.93). There was no significant sex-related difference in the incidence of MI during hospital stay or 12-month follow-up. All-cause mortality and repeat revascularization rates were alike between octogenarian women and men. Importantly, there was no age- or sex-related difference in BARC > 2 bleeds.

Table 17. Clinical outcome at 12-month follow-up in octogenarians and younger patients with atrial fibrillation after percutaneous coronary intervention (Abbreviations next page)

	Whole Cohort (n=925)			Males (n=650)			Females (n=275)		
Variable	**OG (n=195)**	**Younger (n=730)**	**P-Value**	**OG (n=114)**	**Younger (n=536)**	**P-Value**	**OG (n=81)**	**Younger (n=194)**	**P-Value**
MACCE									
12 months	54 (27.7)	147 (20.1)	0.023	32 (28.1)	112 (20.9)	0.09	22 (27.2)	35 (18.0)	0.09
30 days	14 (7.2)	51 (7.0)	0.93	9 (7.9)	36 (6.7)	0.65	5 (6.2)	15 (7.7)	0.65
In-hospital	7 (3.6)	31 (4.3)	0.67	4 (3.5)	24 (4.5)	0.64	3 (3.7)	7 (3.7)	0.99
Death									
12 months	29 (14.9)	74 (10.1)	0.06	18 (15.8)	56 (10.4)	0.10	11 (13.6)	18 (9.3)	0.29
30 days	6 (3.1)	26 (3.6)	0.74	4 (3.5)	17 (3.2)	0.85	2 (2.5)	9 (4.6)	0.40
In-hospital death	5 (2.6)	14 (1.9)	0.58	2 (1.8)	10 (1.9)	0.93	3 (3.7)	4 (2.1)	0.44
Myocardial infarction									
12 months	18 (9.2)	36 (4.9)	0.023	11 (9.6)	23 (4.3)	0.020	7 (8.6)	13 (6.7)	0.57
in-hospital	6 (3.4)	9 (1.3)	0.062	3 (2.9)	6 (1.2)	0.20	3 (4.0)	3 (1.6)	0.25
Repeat revascularization	59 (8.1)	14 (7.2)	0.68	8 (7.0)	43 (8.0)	0.72	6 (7.4)	16 (8.2)	0.82
Stent thrombosis	5 (2.6)	10 (1.4)	0.24	3 (2.6)	7 (1.3)	0.30	2 (2.5)	3 (1.5)	0.60
Stroke/TIA	8 (4.1)	15 (2.1)	0.10	4 (3.5)	12 (2.2)	0.42	4 (4.9)	3 (1.5)	0.10
All thromboembolism	10 (5.1)	20 (2.7)	0.09	5 (4.4)	16 (3.0)	0.44	5 (6.2)	4 (2.1)	0.08
All bleeding									
12 months	51 (26.2)	154 (21.1)	0.13	31 (27.2)	102 (19.0)	0.050	20 (24.7)	52 (26.8)	0.72
In-hospital	26 (13.3)	77 (10.5)	0.27	14 (12.3)	55 (10.3)	0.53	12 (14.8)	22 (11.3)	0.43
BARC >2									
12 months	24 (12.3)	71 (9.7)	0.29	15 (13.2)	44 (8.2)	0.10	9 (11.1)	27 (13.9)	0.53
in-hospital	9 (4.6)	31 (4.2)	0.82	4 (3.5)	22 (4.1)	0.77	5 (6.2)	9 (4.6)	0.60

Abbreviations (Table 17): OG = octogenarian; MACCE = major adverse cardiac and cerebrovascular event; TIA = transient ischemic attack; BARC = Bleeding Academic Research Consortium. The values denote mean (standard deviation, SD), median [interquartile range, IQR] or n (%). P-value refers to women vs. men. Continuous variables are presented as mean ± SD, whereas categorical variables are presented as frequency (percentage). Reproduced with the permission of copyright holder (Lahtela, Bah et al., 2017)

6 DISCUSSION

6.1 SEX, AGE AND RISK OF STROKE AFTER ELECTRICAL CARDIOVERSION OF RECENT ONSET ATRIAL FIBRILLATION (I)

The main findings of study I are that in patients <75 years undergoing ECV of recent onset (duration <48 h) AF within 12 h from the onset of AF symptoms the risk of TEC is very low (0.4%) and no significant sex-related difference exists. When delay to cardioversion exceeds 12 h, the risk of TEC increases markedly, particularly in women. Secondly, cardioversion failed more often in women and recurrence of AF tended to occur more commonly during a 30-day follow-up increasing the net harm in female AF patients undergoing ECV. Thirdly, women had higher heart rate, sought medical attention earlier than men and were cardioverted with shorter delay after index AF attack suggesting an increased burden of symptoms in female AF patients.

It is important to identify the risk factors of TEC in recent onset AF patients to perform cardioversion safely with minimum delay and to run emergency clinics efficiently (Airaksinen et al., 2013; Jaakkola et al., 2018). Female sex, age, HF, diabetes and time before performed cardioversion are independently associated with an increased TEC risk after cardioversion of recent onset AF. Patients at highest risk are those with HF and diabetes (TEC risk 9.8%) (Airaksinen et al., 2013; Nuotio et al., 2014). In patients <60 years without HF and in patients cardioverted without OAC within 12 hours from AF onset TEC risk is low (0.2-0.3%) but TEC risk increases when delay to cardioversion exceeds 12 h (Airaksinen et al., 2013; Nuotio et al., 2014).

The data of this study was collected at a time when it was common practice to cardiovert patients with recent onset AF without OAC. A total of 70% of patients were not on OAC when admitted to hospital (Airaksinen et al., 2013). Current guidelines recommend OAC to cardioverted patients with recent onset AF and stroke risk factors. However, OAC may be omitted in low-risk AF patients (Hindricks et al., 2020). In this study, the overall risk of TEC was low (0.8%) but increased in elderly women when delay to

cardioversion was >12 hours. Also, in women <65 years the risk of TEC was unacceptably high, up to 1.9%.

At the time of this study, it was not known whether peri- and postprocedural OAC is needed after cardioversion of an acute AF attack to prevent TEC, which typically occurs two to three days after cardioversion. Warfarin therapy does not reach a therapeutic level within the first days after initiation and may even increase the risk of stroke in the first month of use (Azoulay et al., 2014). Remodeling of the heart due to AF is minimal within 24 h although activation of platelets and coagulation factors can be seen already after 12 h of paroxysmal AF (Sohara et al., 1997, Linhart et al., 2006). TEE is useful if duration of AF or adequacy of prior OAC is uncertain when aiming for early cardioversion (Jaakkola et al., 2018).

In conclusion, the risk of TEC in patients cardioverted within 12 hours and age <75 years was very low (<0.4%) with no significant difference between sexes. In elderly patients (≥75 years), and as time before cardioversion exceeded 12 hours, the risk of TEC increased substantially in both sexes. Most importantly, women were at an undeniably increased risk of TEC. Time before cardioversion ±12 hours is useful in risk stratification in patients undergoing cardioversion of recent onset AF and cardioversion should be performed rather earlier than later if considered necessary (Linhart et al., 2006; Jaakkola et al., 2018).

Before proceeding to ECV, the possibility of early treatment failure and antiarrhythmic therapy options to prevent AF recurrence should be evaluated in elderly patients with milder symptoms to avoid futile cardioversions (Jaakkola et al., 2018). The AF-CVS score is useful in this respect but has not been implemented in routine use. Scores >5 predict a 40% rate of ECV failure and scores <3 predict a 10% rate of ECV failure (Jaakkola et al., 2017).

6.2 SEX AND ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION AND A CEREBROVASCULAR EVENT (II)

The main finding of study II was that stroke risk evaluation in AF patients was performed poorly resulting in underuse of OAC particularly in women.

Three quarters of women and half of men not using OAC at the time of the cerebrovascular event had a guideline-based indication for OAC ($CHADS_2$/CHA_2DS_2-VASc ≥2). Secondly, futile use of OAC was frequent in younger men with a low or moderate stroke risk. Finally, reasons for omitting guideline based OAC were poorly reported, particularly for women.

The 2006 ESC guidelines were the first to recommend routine use of risk stratification scores to guide OAC initiation (Fuster et al., 2006). In the current ESC 2020 guidelines all women are given one risk point and OAC is recommended with CHA_2DS_2-VASc ≥3 for women and ≥2 for men (Hindricks et al., 2020). This was not applied in our study, but the adherence to risk stratification was based on the ESC 2006 and 2010 guidelines that were valid at the time of the cerebrovascular event (Fuster et al., 2006; Camm et al., 2010). In line with literature, the implementation of these recommendations was inadequate also in AF patients suffering a cerebrovascular event and only half of the patients on OAC had an INR within the therapeutic target (Gladstone et al., 2009; Shantsila et al., 2015; Xian et al., 2017; Hohnloser et al., 2019).

The global trend for OAC use is problematic and there is a lot of heterogeneity despite guidelines (Cowan et al., 2018; Steinberg et al., 2017). Recent studies have demonstrated that despite higher CHA_2DS_2-VASc scores women have similar rates of OAC than men (Piccini et al., 2016). Moreover, female sex is associated with a lower use of OAC at each CHA_2DS_2-VASc score level (Thompson et al., 2017) although there are reports on similar use of OAC irrespective of sex (Lip et al., 2015). In the present study there were also sex-related differences in the use of guideline-based OAC. Almost three quarters of women not using OAC at the time of the index cerebrovascular event had a high risk score for stroke. The sex difference in OAC use became even more marked after 2010, when the CHA_2DS_2-VASc score was implemented and women aged 65-75 years were reclassified from low-risk to high-risk category (from 0 to 2) (Camm et al., 2010). During the CHA_2DS_2-VASc era almost all women (98%) in our study should have been on OAC. However, only 53% of them were anticoagulated.

The impact of age on risk evaluation is more pronounced in the CHA_2DS_2-VASc score differentiating between age 65-74 (1 point) and age ≥75 years (2 points). In the present study women were older than men. Although older age increases stroke risk, this was not reflected in the use of OAC in elderly women. Earlier studies have reported that not only OAC, but also rhythm control strategy is less often used for women in comparison to men (Piccini et al., 2013; Schnabel et al., 2017; Linde et al., 2018; Marzona et al., 2020).

Valid reasons for not prescribing OAC (ICH and $CHADS_2$/CHA_2DS_2-VASc 0-1) were identified in half of men but only in a quarter of women. The risk of stroke in patients with $CHADS_2$/CHA_2DS_2-VASc 0 is very low, and these patients do not need OAC. Patients with $CHADS_2$/CHA_2DS_2-VASc 1 are at a moderate risk of stroke and the current ESC guidelines (2020) recommend considering OAC in these patients particularly if additional risk factors such as smoking or obesity are present (Hindricks et al., 2020). If ICH and $CHADS_2$/CHA_2DS_2-VASc 0 are justifiable reasons to omit OAC, only 14% of patients had a valid reason to omit OAC in our study. These findings are in line with Xian et al. (2017), who reported that the reason for not using OAC therapy was documented only in one-third of high-risk AF patients.

In the present study the most common non-valid reason to omit OAC was paroxysmal AF. Two thirds of both women and men not on OAC had a history of paroxysmal AF. Paroxysmal AF is associated with an increased stroke risk and the risk is considered similar to permanent or persistent AF (Friberg et al., 2010). One possible explanation for omitting OAC is older age and frailty (Graham et al., 2015). In our study OAC was deferred particularly in elderly women. Although old age increases the risk of bleeding it is also a strong predictor of stroke (Hijazi et al., 2016). Women – who are often seen as fragile – are frequently left with reduced treatment. In addition, they have more comorbidities and worse prognosis after stroke than men (Bushnell et al., 2014; Kirchhof et al., 2016). Therefore, the benefits of stroke prevention usually overweigh the risk of bleeding also in older patients (Ruff et al., 2014).

The risk of stroke and bleeding often overlap and almost three quarters of women not on OAC have a HAS-BLED score >3 (Friberg et al., 2012),

which is in line with the findings of the FibStroke study, where most non-anticoagulated patients, especially women, had a HAS-BLED score ≥3. A high bleeding risk should not automatically result in withholding OAC, but in the elimination of modifiable bleeding risk factors such as hypertension, the use of non-steroidal anti-inflammatory drugs and alcohol use (Hindricks et al., 2020). Potential reasons leading to the patient discontinuing OAC are warfarin side effects, poor INR control and minor bleeds, which may not be recorded in the patient files. In the Re-LY trial, the incidence of minor bleeds in the warfarin group was 16.2% per year and 10.2% of patients discontinued warfarin therapy at one-year follow-up (Connolly et al., 2009).

Withholding OAC seems to result in frequent prescription of aspirin. Most patients not on OAC were using aspirin although the bleeding risk is similar to OAC particularly in the elderly with minimal effect on TEC risk (Mant et al., 2007).

An important finding of this study was also the frequent use of OAC in low and moderate risk patients, particularly in men, which has been reported in previous studies (Admassie et al., 2017; Pritchett et al., 2019). One third of men using OAC were at low or moderate risk ($CHADS_2$/CHA_2DS_2-VASc score 0-1). Unfortunately, data regarding reasons for initiation of OAC in low and moderate risk patients was not collected.

6.3 SEX, AGE AND OUTCOMES IN ATRIAL FIBRILLATION PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION (III)

The main findings of study III were that (1) octogenarians were treated with a similar antithrombotic treatment regimen as younger patients, (2) octogenarians had more MACCE events at one-year follow-up driven by MI with no significant sex-related differences and (3) there was no significant age- or sex-related difference in bleeding events.

There is scarce data on the optimal antithrombotic regimen in elderly patients with AF who need lifelong OAC and undergo PCI. A regimen of dual therapy with OAC and a P2Y12 inhibitor is associated with lower rates

of clinically significant bleeding compared with triple therapy (OAC + P2Y12 inhibitor + aspirin) (Dewilde et al., 2014; Gibson et al., 2016).

Unanswered questions include the duration of each antithrombotic medication and the change of the antithrombotic regimen over time. In real-life practice the duration of intensified antithrombotic therapy after PCI is often shortened in elderly patients because of a presumed higher bleeding risk. In the AFCAS study the prescribed antithrombotic regimens (medications, dosage, and duration) were widely heterogeneous because they were based on local practice and on the operators' discretion. Antithrombotic treatment was, however, comparable between octogenarians and younger patients but octogenarian women seemed to be prescribed DAPT more often than octogenarian men.

In the AFCAS study the incidence of MACCE was higher in octogenarians at 12-months of follow-up compared to younger patients, which is in line with a study by Caballero et al. (2013) focusing on an unselected cohort of AF patients undergoing PCI. Their finding was that octogenarians experienced more MACCE and major bleeds in comparison to younger patients and that OAC prescribed at discharge for octogenarian patients was associated with lower rates of MACCE. Sambola et al. (2016) demonstrated that AF patients >75 years undergoing PCI and who prescribed triple therapy or DAPT at discharge had survival curves for thromboembolic events that diverged within a 30-day follow-up and remained parallel thereafter. There was no significant difference between triple therapy and DAPT concerning all-cause mortality and they suggested early and short-term use of triple therapy also in elderly patients shortly after PCI based on CHA_2DS_2-VASc risk stratification (Sambola et al., 2016).

A previous study showed that octogenarians presented more often with ACS (Yazji et al., 2016). Octogenarians had higher rates of mortality and restenosis at 12-month follow-up in comparison with younger patients. In the AFCAS study the indication for PCI in octogenarians was most often ACS. This may partly explain the higher incidence of MI and consequently of MACCE at 12-month follow-up in octogenarians in study III. On the other hand, MACCE and its components did not differ between octogenarian women and men. Octogenarians treated with PCI have more comorbidities

compared to younger patients (Hassani et al., 2006; Yazji et al., 2016) and this may affect non-cardiac causes of mortality as well. Furthermore, women have comorbidities more frequently than men (Linde et al., 2018; Hindricks et al., 2020). Yet, in a cohort of octogenarians who underwent PCI for ACS, cardiovascular death was responsible for most (71%) deaths at five-year follow-up (Barywani et al., 2015).

Increasing age is a well-known risk factor for mortality after PCI. The proportion of patients aged ≥80 years (21.1%) in the AFCAS registry was higher than in reports on patients who underwent primary PCI for STEMI (10.3% and 11.6%) (Antonsen et al., 2011; Bromage et al., 2016). This is comprehensible because the prevalence of AF increases progressively with age. As expected, the risk for MACCE and all-cause mortality was higher for octogenarians although the AFCAS study did not show a sex-related difference in octogenarians.

As expected, octogenarians in the AFCAS cohort had a higher HAS-BLED score. The higher bleeding risk did not, however, lead to a less intensive antithrombotic treatment. The total and clinically significant bleeding event rates did not differ with respect to sex or age. Octogenarian women, who are often considered frail patients, had bleeding rates comparable with octogenarian men as well as younger women in Study III. The comparable 12-month bleeding rates, despite a higher bleeding risk in octogenarians, might be viewed similar in time spent in therapeutic range as well as the duration of clopidogrel usage in both age groups. Elderly patients on triple therapy have a higher stroke and bleeding risk and studies have shown that they benefit from early thromboembolic risk reduction post-procedurally although major bleeding rates increase over time (Karjalainen et al., 2007; Sambola et al., 2016). A study by Sambola et al. (2016) on elderly AF patients on either triple therapy or DAPT post-PCI proposed that the risk-benefit ratio of antithrombotic therapy was time-dependent. In this study most TEC events appeared within a 30-day follow-up post-PCI, but bleeding events were distributed more evenly over time (Sambola et al., 2016).

In conclusion, study III showed that octogenarians had a higher risk of thrombotic events, especially MI, at 12-month follow-up. Conversely, the

occurrence of bleeding events did not differ between octogenarians and younger patients nor octogenarian women and men. Given the higher rates of thrombotic events, the comparable rates of bleeding events in octogenarians, and the comparable distribution of prescribed antithrombotic medications between the two age groups, this study supports the view that octogenarians should be treated as comprehensively as younger patients and longer antithrombotic treatment might be considered in octogenarians with ACS. The assumption, however, needs to be confirmed in adequately powered randomized trials.

6.4 LIMITATIONS

The retrospective design of the studies always carries some limitations with the accuracy of data collection. The collected data are dependent on data recorded by the physicians responsible for cardiac procedures but on the other hand, only patients living in the catchment area of the hospitals were selected. Thus, the data regarding patient outcomes can be considered reliable. Accuracy of the data collection in this setting is of utmost importance especially when data collection was performed by several reviewers and in several centers. Reviewers underwent a training program and were given written structured instructions about interpretation of the clinical data similarly to a protocol used in multicenter prospective clinical trials. Outcome events were verified by senior members of the study group.

All three studies were observational and thus include the inherent limitations of an observational study design such as unmeasured confounders, individual decision-making in treatment choice and procedural routines. Study III may reflect the heterogeneity of international cohorts among the participating centers. The strength of the registry is enrollment of consecutive patients with the only exclusion unwillingness or inability to participate. In this sense, the registry cohort represents well real-world patients with AF referred for PCI.

The data in Study II were derived from secondary care medical hospital records. Thus, there is no data from primary care for example on

discontinuation of OAC and reasons leading to discontinuation. Prescription of OAC was always at the treating physician's discretion and may have been affected by factors not written in the patient records. This, however, is one of the main results of the study and indicates the need for assessing valid reasons for initiation or omission of OAC in clinical practice. In Study II warfarin was the predominant OAC during the study period while DOACs are currently the dominant form of OAC therapy. However, the fundamental question, when to start OAC, remains also in the DOAC era. At present, there is no evidence to suggest that DOACs or new guidelines have changed the sex- and age-gap between women and men in the treatment of AF. Suboptimal DOAC adherence in one third of anticoagulated AF patients (Ozaki et al., 2020) underscores the need to improve patient commitment collaboratively especially in high stroke risk patients.

6.5 FUTURE PERSPECTIVES

The findings of Study I emphasize that time before performed cardioversion ≥12 hours should be considered in risk stratification of patients undergoing cardioversion for recent onset AF. In addition, OAC treatment should be initiated especially in elderly female AF patients before cardioversion or as soon as possible periprocedurally. International guidelines have already taken this into account (Andrade et al., 2018; Hindricks et al., 2020). More research is needed on cardioversion of recent onset AF, anticoagulation strategies and the significance of female sex as a risk factor for thromboembolic complications.

The results of Study II underline the need to improve risk stratification and evidence based OAC initiation especially in women with AF.

Study III suggested that longer antithrombotic therapy might be considered in octogenarians, especially in those with ACS, but this assumption needs to be studied in adequately powered randomized trials. Increasing life expectancy together with an increase in AF highlight the need for further studies in this patient group. The proportion of women

and men should be better balanced in future studies and more women should be included in RCTs.

7 CONCLUSIONS

This dissertation explored sex- and age-related differences in anticoagulation treatment and thromboembolic outcomes with respect to routine procedures in patients with atrial fibrillation. This dissertation showed the interaction between sex, age and time on stroke risk after electrical cardioversion in recent onset atrial fibrillation. Cardioversion failed more frequently in women, and bradyarrhythmic complications and recurrence of atrial fibrillation were more common in women than in men. Importantly, the risk for thromboembolic complications in women was twice as high as for men and the risk increased with age and delay to cardioversion. This dissertation also demonstrated that stroke risk stratification was suboptimally performed, especially in women, resulting in underuse of anticoagulation despite a high risk for stroke. Reasons for omitting appropriate oral anticoagulation therapy were poorly reported, particularly for women. Secondly, controversial anticoagulation was frequently used in younger men with a low or moderate stroke risk. Data regarding antithrombotic drug therapy in elderly patients with atrial fibrillation undergoing percutaneous coronary intervention is limited. This dissertation showed that octogenarians are at risk for major adverse cardiac and cerebrovascular events at 12-month follow-up after PCI with no significant difference in bleeding complications between octogenarians and non-octogenarians and/or women and men.

In conclusion elderly atrial fibrillation patients, especially elderly women, are suboptimally treated despite a higher risk for stroke and adverse events after routine cardiac procedures related to atrial fibrillation. This patient population is increasing worldwide with important economic and public health implications. Guidelines recommend effective treatment, but more research is needed to assess the efficacy and safety in special patient subgroups so that appropriate therapies can be globally, safely, and equally implemented for all atrial fibrillation patients irrespective of sex and age.

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ORIGINAL PUBLICATIONS (I – III)

I

Sex, age and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation. The FinCV Study.

Bah A, Nuotio I, Grönberg T, Ylitalo A, Airaksinen K.E.J, Hartikainen J.E.K.

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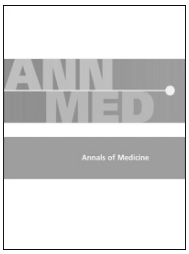

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Sex, age, and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation from the FinCV study

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ORIGINAL ARTICLE

Sex, age, and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation from the FinCV study

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ABSTRACT

Background: Female sex, old age, and time to cardioversion increase the risk of thromboembolic complications (TEC) after cardioversion of atrial fibrillation (AF) <48 h. The interaction of these variables is not known. We investigated the interaction of sex, age, and time to electrical cardioversion (ECV) on TEC in anticoagulant-naive patients with acute AF.

Methods and results: The primary outcome was a TEC within 30 days following ECV. Patients were divided into three age groups and time to cardioversion into <12 h and ≥ 12 h in 4715 ECVs. TEC occurred in 40 (0.8%) patients. In multivariate analysis, female sex, time to ECV, and vascular disease were independent predictors of TEC. For patients ≤ 75 cardioverted within 12 h, the incidence of TEC was low. In patients >75 TEC increased in both sexes and particularly in women (1.4% vs. 0.9%, $p = 0.03$). When ECVs exceeded 12 h, the risk of TEC was two- to four-fold higher in women in all age groups.

Conclusions: The risk of TEC increases substantially in patients >75 and ECVs ≥ 12 h, particularly in women. Time to cardioversion should be added to risk-stratification of ECVs of acute AF.

KEY MESSAGES

- The ideal timing of cardioversion is still unknown and not based on solid evidence. Delay to cardioversion ≥ 12 h should be added to the risk stratification of atrial fibrillation cardioversion.
- Female sex increases the risk of complications and failure of cardioversion after electrical cardioversion of atrial fibrillation <48 h, especially with age >75 years and time to cardioversion exceeding 12 h.

Abbreviations: AF: atrial fibrillation; ECV: electrical cardioversion; TEC: thromboembolic complications

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KEYWORDS
Age; atrial fibrillation; electrical cardioversion; female sex; time to cardioversion

Introduction

Female sex is associated with an increased risk of thromboembolic complications (TEC) in patients with paroxysmal and chronic atrial fibrillation (AF) (1–7) as well as after cardioversion of acute (duration <48 h) AF (8). In addition, the risk of TEC increases substantially with aging and with time from the onset of AF to cardioversion (9). However, previous studies have addressed these variables separately and the interaction between sex, age, and time to electrical cardioversion (ECV) is not known.

In this FinCV substudy, we evaluated the interaction of sex, age, and time on the risk of TEC after ECV in patients admitted to the hospital due to acute AF without periprocedural anticoagulation.

Materials and methods

FinCV is a multicenter study, which is part of the ongoing study program assessing thrombotic and bleeding complications related to cardiac procedures in Finland (8,9).

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Study population

Patients admitted to the emergency clinics of two university hospitals from 2003 through 2010 and one central hospital during year 2010 with a diagnosis of AF (ICD-10 code I48) and undergoing cardioversion (NOMESCO Classification of Surgical Procedures code TFP20) were identified from the hospital discharge registries. Each hospital is the only referral hospital responsible for the acute care of patients with cardiac and TEC in their catchment area. For this substudy, we included only patients $\geq$18 years undergoing ECV within the first 48 h of AF without peri- or postprocedural anticoagulation and residing in the hospital catchment area.

The study population consisted of 4715 ECVs in 2313 patients. Patients' clinical characteristics, medical history, medication and laboratory values during admission, details about the care of the index AF as well as outcome during 30-day follow-up were retrospectively collected from the individual medical reports.

ECV was performed according to the contemporary guidelines under general anesthesia. During and after the procedure ECG, blood pressure and oxygen saturation were monitored. Paddles or pads were positioned in antero-posterior or antero-lateral configuration. The energy was set from 70 to 150 J with biphasic defibrillator devices and from 70 to 360 J with monophasic devices. A 12-lead ECG was controlled before and after ECV.

The protocol was approved by the ethics committees of the Hospital District of Southwest Finland and the National Institute for Health and Welfare with a waiver of informed consent.

Outcomes

The primary purpose was to evaluate the interaction of sex, age, and time to cardioversion on TEC within 30 days after ECV. In addition, we compared women and men with respect to cardiovascular comorbidities, clinical presentation, success of ECV, and recurrence of AF during 30-day follow-up.

Cardioversion was successful if the patient was discharged from the emergency unit in sinus rhythm. AF recurrence was defined as ECG documented recurrence of AF after ECV. TEC in this study was defined as (1) a stroke, documented clinically by a neurologist and confirmed to be caused by cerebral infarction or a systemic embolism ascertained by imaging (computerized tomography or magnetic resonance imaging), surgery, or autopsy or (2) a transient ischemic attack diagnosed clinically by a neurologist. All potential TEC were double-checked and confirmed by two senior investigators.

Statistical analysis

To assess the role of age on TEC, the patients were divided into three age groups according to the $CHA_2DS_2VAS_c$ scoring: $<$65 years, 65–75 years and $>$75 years. Time to cardioversion was classified into $<$12 h and $\geq$12 h (12–48 h). Comparisons between the groups were performed with the Chi-square or Fisher's exact test for categorical variables and student's *t*-test and Mann–Whitney *U*-test for analysis of continuous data. A univariate regression analysis was performed to identify predictors of TEC. Variables with significant p value ($<$0.05) (age, aspirin or clopidogrel use, heart failure, diabetes, sex, time to cardioversion, vascular disease) were used in the multivariate logistic regression analysis with repeated measures option to assess the predictors of TEC. This study focuses on the interaction of sex, age, and time which is why these variables were chosen instead of other clinical variables included in the CHADS-VASc-score. Because the primary study outcome was binary and repeated cardioversions of same individuals were included in the analyses, the GENMOD procedure with repeated measures option was used in univariate and multivariate analyses. Two-sided differences at $p < 0.05$ were considered statistically significant. Statistical analyses were performed using version 9.2 of the SAS software (SAS Institute Inc., Cary, NC).

Institutional review board

The study protocol was approved by Hospital District of Southwest Finland (K23/11) and the National Institute for Health and Welfare (THL/393/5.05.00/2011) and complies with the Helsinki Declaration (2008). Informed consent was not required because of the register-based nature of the study and patient data were analysed anonymously.

Results

Sex and clinical characteristics of the patients

Women were older and had more comorbidities such as hypertension, heart failure, and a higher $CHA_2DS_2VAS_c$-score (Table 1). In comparison with men, women used beta-blockers more often (75.4% vs. 71.2%, $p = 0.003$) and antiarrhythmic drugs (14.3% vs. 20.6%, $p < 0.001$) less frequently. Time to ECV was shorter for women than for men (50.9% vs. 45.1%

Table 1. Clinical characteristics of the patients during admission.

Total n	Women (n = 1455)	Men (n = 3260)	p Value	<12 h (n = 2211)	>12h (n = 2504)	p Value
Age	66.7 ± 10.8	59.1 ± 12.3	<0.001	61.6 ± 12.2	61.4 ± 12.5	0.34
Women				741 (33.5)	714 (28.5)	<0.001
Hypertension	785 (53.0)	1377 (42.2)	<0.001	1019 (46.1)	1143 (45.7)	0.76
Heart failure	66 (4.5)	119 (3.6)	0.15	73 (3.3)	112 (4.5)	0.04
Diabetes	127 (8.7)	261 (8.0)	0.40	194 (8.8)	194 (7.8)	0.20
Vascular disease	369 (25.4)	740 (23.0)	0.05	533 (24.1)	578 (23.1)	0.41
$CHA_2DS_2VAS_c$ score	2.9	1.3	<0.001	1.8	1.7	0.09
Kidney disease	16 (1.1)	65 (2.0)	0.03	45 (2.0)	36 (1.4)	0.12
Permanent pacemaker	50 (3.5)	106 (3.3)	0.80	68 (3.1)	88 (3.5)	0.39
Alcohol overuse	9 (0.6)	129 (4.0)	<0.001	65 (2.9)	73 (2.9)	0.96
Beta blocker on admission	1097 (75.4)	2320 (71.2)	0.003	1558 (70.5)	1859 (74.2)	0.004
AAD on admission	208 (14.3)	671 (20.6)	<0.001	371 (16.8)	508 (20.3)	0.002
First-ever AF episode	445 (30.6)	773 (23.7)	<0.001	540 (24.4)	723 (28.9)	<0.001
AF within 30 days before	158 (10.9)	361 (11.1)	0.80	240 (10.9)	279 (11.2)	0.75
Time to cardioversion <12h	741 (51.0)	1470 (45.1)	<0.001			
Heart rate during AF	117 ± 23	108 ± 25	<0.001	114.0 ± 25.1	107.7 ± 24.6	<0.001

AF: atrial fibrillation; AAD: antiarrhythmic drugs. The values denote mean ± SD or n (%).

Table 2. Multivariate predictors of thromboembolic complications after ECV of acute AF.

	OR	95% CI	p Value
Age	1.04	1.01–1.07	0.003
Vascular disease	2.04	1.06–3.91	0.03
Female sex	2.10	1.09–4.11	0.03
Time to cardioversion	3.70	1.69–8.20	0.001
Heart failure	2.50	0.88–7.15	0.09
Diabetes	2.33	0.92–5.41	0.08
Aspirin or clopidogrel	1.13	0.51–2.53	0.77

The values denote odds ratio (OR) and 95% confidence interval (CI).

<12 h, $p < 0.001$) (Table 1). Heart rate on admission was higher (117 bpm vs. 108 bpm, $p < 0.001$) and the index AF was the first-ever more often in women (30.6% vs. 23.7%, $p < 0.001$).

Outcomes

Cardioversion failed more often in women (6.7% vs. 4.0%, $p < 0.001$) and recurrence of AF within 30 days in patients with successful cardioversion tended to be higher in women (13.7% vs. 11.7%, $p = 0.055$). During 30-day follow-up, TEC was diagnosed in 40 patients (0.8%). Of these 30 were strokes, seven were systemic embolisms and four were TIAs. One patient had both stroke and systemic embolism. Three patients died of a fatal stroke. In multivariate analysis, female sex was an independent predictor of TEC (OR 2.12, CI 1.09–4.11, $p = 0.03$) (Table 2). The other significant predictors of TEC were old age (OR 1.04, CI 1.01–1.07, $p = 0.003$), time to cardioversion (OR 3.70, CI 1.69–8.20, $p = 0.001$), and history of vascular disease (OR 2.04, CI 1.06–3.91, $p = 0.03$).

TEC, sex, age, and time to cardioversion

In patients cardioverted within 12 h, the incidence of TEC in women and men aged <65 years (0.0% vs. 0.3%, respectively) and 65–75 years (0.4% vs. 0.3%, respectively) was low and did not differ between sexes ($p = 1.00$). However, in the age group >75 years the risk of TEC increased in both sexes and was significantly higher in women (1.4% vs. 0.9%, $p = 0.03$ respectively). More strikingly, in patients cardioverted after 12 h, the risk of TEC increased and was two- to four-fold in women as compared with men in all age groups (1.9% vs. 0.5%, $p = 0.034$, 3.5% vs. 1.2%, $p = 0.052$, and 2.7% vs. 1.4%, $p = 0.469$ in the youngest, middle, and oldest age groups respectively) (Figure 1).

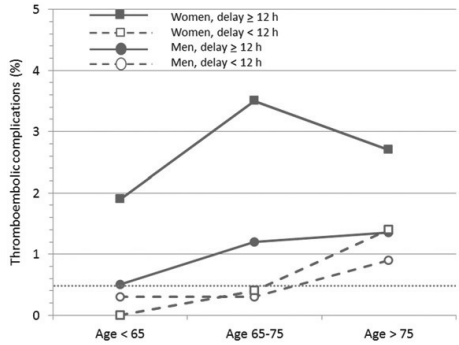

Figure 1. Thromboembolic complications according to sex, age, and time to cardioversion.

Discussion

We demonstrated that in patients <75 years undergoing ECV of acute AF (duration <48 h) within 12 h from the onset of AF symptoms the risk of TEC is very low (< 0.4%) and no significant difference between sexes exists. As time to cardioversion exceeds 12 h, the risk of TEC rises substantially, particularly in women in

whom the risk was ≥1.9%. In addition, cardioversion failed more often in women and recurrence of AF tended to occur more frequently among women than men during 30-day follow-up. Women were older and had more cardiovascular comorbidities.

Previously, it has been shown that female sex, high age, and time (delay) to cardioversion are associated with an increased risk of TEC in patients undergoing cardioversion of acute AF (8,9). Although the risk of TEC after cardioversion of acute AF in our study was low on the whole (0.8%), there are patients in whom the risk of TEC rises up to 10% (8). TEC has devastating consequences and results often in permanent disability. Thus, there is an unmet need to identify patients who are at high risk of this serious complication. On the other hand, in order to run the emergency clinics efficiently, it is also important to identify patients who are at low risk of TEC and in whom cardioversion can be performed safely without delay. Based on our study, patients ≤75 years can be cardioverted with a risk that is equivalent (i.e. ≤0.6%) to the risk of TEC in elective cardioversion performed under recommended warfarin or novel anticoagulants (10–12) provided that ECV is performed early enough, i.e. within 12 h from the onset of AF.

As to the clinical implications of our study, the 2016 ESC AF guidelines recommend that for patients with an AF episode definitely <48 h of duration and no thromboembolic risk factors ($CHA_2DS_2VAS_c = 0$) cardioversion be performed without peri- or post-cardioversion anticoagulation (13). On the other hand, cardioversion in patients with risk factors must be performed under the cover of heparin followed by long-term anticoagulation. However, the time-limit of <48 h from onset of AF to cardioversion is arbitrary and based rather on common sense and consensus than solid evidence. Our study challenges the 48-h time-limit. Namely, in our study, the risk of TEC in women <65 years and time to ECV >12 h (but <48 h) was 1.9%. This is far beyond acceptable. Our study suggests that in patients with recent onset AF the concept of time to cardioversion in risk stratification should be revised.

At the time from which this study material was collected (2003–2010), it was a common practice to cardiovert patient with AF with duration <48 h without pre-, peri- or postprocedural anticoagulation. Also, the benefits of long-term anticoagulation in patients with paroxysmal or persistent AF were not well-known. Indeed, in the FinCV study, 71% of patients were not on anticoagulation at the time of hospital admission (8). Ongoing, permanent anticoagulation is known to protect from TEC after cardioversion of AF. However, it is not known whether periprocedural anticoagulation followed by initiation of long-term anticoagulation can prevent TEC which typically occurs two to three days after cardioversion. Warfarin therapy does not reach therapeutic level with the first days after initiation and is associated with a significant increase of stroke in the first month of use (14).

In line with Linhart et al. (15), we suggest that if rhythm control is the selected treatment strategy, cardioversion of acute AF should be performed as soon as possible, especially in patients with stroke risk factors. Remodeling of the heart due to the arrhythmia is minimal within a short time (24 h) (15). This is also in line with the study of Sohara et al. (16) who reported activation of platelets and coagulation factors already after 12 h of paroxysmal AF.

In our study, women sought medical attention earlier than men and were cardioverted with shorter delay after the onset of arrhythmic symptoms. Women also had a higher heart rate on admission. These findings indirectly suggest that women experienced more severe arrhythmia-induced symptoms. This is in line with earlier reports on patients with paroxysmal and persistent AF (13,17). Considering the shorter time from onset of AF to cardioversion among women, it is somewhat surprising that cardioversion failed more often in women as compared with men (18).

The risk of TEC in patients cardioverted within 12 h and age ≤75 years was very low (< 0.4%) and with no significant difference between sexes. In patients >75 years and as time to cardioversion exceeded 12 h, the risk of TEC increased substantially in both sexes. Most importantly, women were at an undeniably increased risk of TEC. Time to cardioversion ≥12 h should be added to the risk stratification in patients undergoing cardioversion of acute AF.

Limitations

Some limitations need to be addressed. The retrospective design of the FinCV study carries always some limitations with the accuracy of data collection. Particularly, we were dependent on the data recorded by the physicians responsible for the cardioversion. On the other hand, we only selected patients living in the catchment area of the hospitals participating in the study. Thus, we are very confident about the coverage and reliability of the outcome data.

The potential impact on the validity of the collected information needs to be discussed. Accuracy of the data collection in this setting is of utmost importance. This is particularly important when the data collection was performed by several reviewers (medical students,

residents-in-training, and experienced study nurses). Thus, the reviewers underwent a dedicated training program and they were given written structured instructions about interpretation of the clinical data similarly to multicenter prospective clinical trials.

When the whole data had been gathered, the medical records of all patients with a suspicion of primary end-points (TEC) were checked and the outcome events verified by at least two members of the study group (senior investigators).

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Disclosure statement

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II

Inadequate oral anticoagulation with warfarin in women with cerebrovascular event and history of atrial fibrillation. The FibStroke Study.

Bah A, Nuotio I, Palomäki A, Mustonen P, Kiviniemi T, Ylitalo A, Hartikainen P, Airaksinen K.E.J, Hartikainen J.E.K.

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ORIGINAL ARTICLE

Inadequate oral anticoagulation with warfarin in women with cerebrovascular event and history of atrial fibrillation: the FibStroke study

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ABSTRACT

Background: Women with atrial fibrillation (AF) may be treated less actively with oral anticoagulation (OAC) than men.

Patients and methods: We assessed sex differences in the implementation of stroke risk stratification with $CHADS_2$ and CHA_2DS_2-VASc scores and reasons not to use OAC in 1747 AF patients suffering their first cerebrovascular event after the AF diagnosis.

Results: Women were older and had more often a high stroke risk ($CHADS_2/CHA_2DS_2$-VASc ≥ 2) than men ($p < .001$). On admission, 46.4% of women and 48.2% of men were on OAC with no sex difference ($p = .437$). However, of patients without OAC, 74.4% of women and 49.5% of men should have been on OAC based on $CHADS_2/CHA_2DS_2$-VASc ≥ 2 ($p < .001$). Conversely, 34.8% of men and 17.5% of women on OAC had a low or moderate risk ($CHADS_2/CHA_2DS_2$-VASc 0–1, $p < .001$). A valid reason to omit OAC was reported in 38.6% of patients and less often in women ($p < .001$).

Conclusions: OAC was underused in high-risk AF patients, particularly women, but prescribed often in men with low or moderate stroke risk. Reasons for omitting OAC treatment were poorly reported, particularly for women.

KEY MESSAGE

- Women were at higher stroke risk, but were less often treated with oral anticoagulation (OAC).
- Men were more often on OAC at low or moderate stroke risk.
- Reasons for omitting guideline based OAC were poorly reported, particularly for women.

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Atrial fibrillation (AF); oral anticoagulation (OAC); $CHADS_2$; CHA_2DS_2-VASc; sex

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and its prevalence increases with age [1,2]. A 2.5-fold increase in AF prevalence has been estimated in the United States by 2050 [3] as well as an 18% global rise in disability-adjusted life-years [4]. AF is more common in men in general, but in the elderly the proportion of women increases due to their longer survival [5] and women have more comorbidities and a higher thromboembolic risk than men [1,2].

Oral anticoagulation (OAC) therapy reduces the risk of thromboembolic complications by two-thirds [6]. In addition, strokes that occur during proper anticoagulation are not as severe as those without adequate therapy [7]. Guidelines recommend OAC for AF patients with risk factors for stroke unless contraindicated [1,2]. Despite solid evidence, guidelines and effective treatment available, there is substantial heterogeneity and inappropriateness in the use of OAC worldwide [8]. OAC is often underused in community practice [8,9] and discontinuation of OAC after the first years is a major problem [10]. Particularly, there are reports suggesting that women with AF are treated less actively than men both with anticoagulation [11,12] as well as with rhythm control therapy [13].

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This study aims to investigate whether there are gender differences in the implementation of risk stratification and the use of OAC in patients with a history of AF and subsequently suffering a cerebrovascular event (stroke or intracranial haemorrhage). Particularly, we evaluated the time-period between the diagnosis of AF and the cerebrovascular event. We also assessed the reasons for omitting OAC in AF patients with a high thromboembolic risk.

Materials and methods

The FibStroke study is a multicentre study, which is part of an ongoing study program assessing cerebrovascular thrombotic and bleeding complications related to AF in Finland (ClinicalTrials.gov Identifier: NCT02146040) [9,14,15].

Study population

The study population consists of all patients admitted to two university hospitals and two central hospitals from 2003 through 2012 with a diagnosis of AF (ICD-10 code I48) and stroke, transient ischaemic attack or intracranial haemorrhage [16]. The appropriate ICD-10 codes were identified from the hospital discharge registries. This prespecified substudy included 1747 patients (1) $\geq$18 years of age with (2) previously known history of AF (paroxysmal, persistent or permanent) and either (3) intracranial haemorrhage or (4) first-ever ischaemic stroke or TIA occurring after the diagnosis of AF. Each hospital is the only referral hospital responsible for the acute care of patients with cardiac and neurologic events in their catchment area and thus, ensures that the patient had an established diagnosis of AF and that the index event was indeed the patient's first cerebrovascular event.

Patients' clinical characteristics, date of AF diagnosis, medical history and laboratory values during admission as well as medication prior to and at the time of admission were collected by reviewing the individual secondary care medical records. Reasons for not being on OAC were identified from patient records and divided into (1) valid reasons ($CHADS_2$ or CHA_2DS_2-VASc score 0–1, prior intracerebral haemorrhage), (2) relative reasons (dementia, prior gastrointestinal bleed, excessive alcohol consumption and history of frequent falls), (3) non-valid reasons (anaemia, patient refusal, small stroke risk, paroxysmal AF and restored sinus rhythm after electrical cardioversion) or (4) undocumented reasons.

At the time of our study, $CHADS_2$ score was used to assess thromboembolic risk until 31 December 2009 and CHA_2DS_2-VASc score from 1 January 2010 onwards [1,2]. The index cerebrovascular event was not included in the calculation of $CHADS_2$/CHA_2DS_2-VASc scores. A high stroke risk score was defined as $CHADS_2$ or CHA_2DS_2-VASc score $\geq$2. INR data were available only from the last 30 days prior to the cerebrovascular event. Thus, a modified HAS-BLED score omitting labile INR was used to assess bleeding risk. Direct oral anticoagulants (DOACs) were used in less than 0.5% of patients. Thus, they were excluded from the analyses.

Stroke and intracranial haemorrhage

All patients underwent computed tomography or magnetic resonance imaging during the index hospitalization. Thrombotic events were defined as (1) a stroke documented clinically and considered definite by a neurologist and confirmed by imaging (computed tomography or magnetic resonance imaging) or (2) a transient ischaemic attack defined according to Albers et al. [17] and diagnosed clinically by a neurologist. Intracranial haemorrhage events including intracerebral haemorrhage, subdural haematoma and subarachnoid bleeding were diagnosed by the neurologist and confirmed by imaging.

Statistical analysis

Comparisons between groups were performed with the Chi-square or Fisher's exact test for categorical variables and Student's *t*-test and Mann–Whitney's *U*-test for analysis of continuous data as appropriate. Time-specific calculations were made with the Mann–Whitney *U*-test and reported as the median and interquartile ranges. In addition, we evaluated the use of OAC in women and men by calculating odds ratios (ORs) between women and men in respect with (1) the use of OAC in patients with high risk score as well as (2) the prevalence of patients with high risk score among those on and not on OAC. Two-sided differences at $p < .05$ were considered statistically significant. Statistical analyses were performed using version Statistics 22 of IBM SPSS (IBM Corporation and Others 1989, 2013, Armonk, NY).

Institutional review board

This study conforms to the Declaration of Helsinki as revised in 2013 and the protocol was approved by the Ethics Committees of the Hospital District of

Southwest Finland and the National Institute for Health and Welfare. Informed consent was not required because of the register-based nature of the study and all patient data were anonymized.

Results

Clinical characteristics of patients

Women were approximately seven years older than men and approximately three quarters of women and half of men were at least 75 years old (Table 1). Women had more comorbidities such as hypertension, congestive heart failure, a cardiac pacemaker and renal dysfunction. Men had more frequently a history of myocardial infarction, alcohol overuse and liver disease than women. The index cerebrovascular event was stroke more often for women whereas intracranial bleeds were more frequent among men.

Risk stratification

At the time of the index cerebrovascular event, both $CHADS_2$ score (until end 2009) and CHA_2DS_2-VASc score (from 2010 onwards) were higher in women (Table 1). Correspondingly, a high thromboembolic risk ($CHADS_2/CHA_2DS_2$-VASc score ≥ 2) was found more often in women (78.5%) compared to men (57.9%). $CHADS_2$ score ≥ 2 was present in 64.7% of women and in 43.1% of men. The difference was even more pronounced for the CHA_2DS_2-VASc score: CHA_2DS_2-VASc score ≥ 2 was present practically in all (98.2%) women in comparison with 78.7% of men. Women had also slightly higher HAS-BLED scores (Table 1).

Oral anticoagulation

At the time of the cerebrovascular event approximately half of the patients were on OAC therapy (warfarin) with no sex difference (Table 1). Nor was there any significant sex-related difference in INR levels during admission: about half of the patients had INR within the therapeutic range (2.0–3.0) (Table 1).

However, when risk stratification was taken into account, women with a high-risk score ($CHADS_2/CHA_2DS_2$-VASc ≥ 2) were significantly less often on

Table 1. Clinical characteristics of the patient population at the time of cerebrovascular event.

	Women	Men	All	*p* Value
	(*n* = 960)	(*n* = 787)	(*n* = 1747)	
Age	79.8 ± 8.5	73.5 ± 10.6	77.0 ± 10.0	<.001
Age 65–75 years	190 (19.8)	240 (30.5)	430 (24.6)	<.001
Age ≥ 75 years	716 (74.6)	381 (48.3)	1096 (62.7)	<.001
Hypertension	674 (70.3)	492 (62.5)	1166 (66.8)	.001
Heart failure	220 (22.9)	136 (17.3)	356 (20.4)	.004
Severe renal impairment*	43 (4.6)	18 (2.3)	61 (3.5)	.012
Anaemia (haemoglobin <10 g/dL)	34 (3.6)	14 (1.8)	48 (2.8)	.024
Chronic liver disease	2 (0.2)	16 (2.0)	18 (1.0)	<.001
Alcohol overuse	17 (1.8)	103 (13.1)	120 (6.9)	<.001
Prior myocardial infarction	134 (14.0)	163 (20.7)	297 (17.0)	<.001
Prior bleeding	70 (7.3)	47 (6.3)	117 (6.7)	.270
Permanent pacemaker	95 (9.9)	55 (7.0)	150 (8.6)	.032
Biological valve prosthesis	11 (1.1)	11 (1.4)	22 (1.5)	.068
Paroxysmal AF	448 (46.7)	324 (41.2)	772 (44.2)	.021
Permanent or persistent AF	411 (42.8)	359 (45.6)	770 (44.1)	.240
Stroke	653 (68.0)	461 (58.6)	1114 (63.8)	<.001
TIA	162 (16.9)	160 (20.4)	322 (18.4)	.062
Intracranial haemorrhage	147 (15.3)	169 (21.5)	316 (18.1)	.004
Warfarin	445 (46.4)	379 (48.2)	824 (47.2)	.437
Aspirin	328 (34.4)	295 (37.5)	623 (35.8)	.173
INR (admission)	2.0 ± 1.1 1.9 [1.3–2.5]	2.1 ± 1.1 2.0 [1.4–2.6]	2.1 ± 1.1 1.9 [1.3–2.6]	.146
INR 2–3 (of those on OAC)	206 (45.0)	189 (48.6)	395 (46.6)	.446
$CHADS_2$ (until end 2009)	1.8 ± 1.0	1.4 ± 1.0	1.6 ± 1.0	<.001
$CHADS_2 \geq 2$	364 (64.7)	198 (43.1)	562 (55.0)	<.001
CHA_2DS_2-VASc (from 2010)	4.2 ± 1.3	2.7 ± 1.4	3.5 ± 1.5	<.001
CHA_2DS_2-VASc ≥2	390 (98.2)	258 (78.7)	648 (89.4)	<.001
$CHADS_2/CHA_2DS_2$-VASc ≥2	754 (78.5)	456 (57.9)	1210 (69.3)	<.001
HAS-BLED*	2.3 ± 0.9	2.1 ± 1.0	2.2 ± 0.9	.001

AF: atrial fibrillation; TIA: transient ischaemic attack; $CHADS_2$: congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years (two points), diabetes, prior stroke/transient ischaemic attack/systemic embolism (two points), associated Vascular disease, age 65–74 years and female sex category; HAS-BLED* (labile INR omitted): hypertension, abnormal liver or kidney function, prior stroke, bleeding history or predisposition, labile INR (omitted), elderly and concomitant drugs; severe renal dysfunction*: estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration)<30 ml/min/1.73 m^2.

The values denote mean (standard deviation), median [interquartile range] or *n* (%). *p* Value refers to women vs. men.

OAC than men: 49.2% of women and 56.7% of men were on OAC (OR 0.80, 95% CI 0.50–0.93, $p = .011$) (Figure 1). During the $CHADS_2$ era, 44.8% of women and 48.0% of men with a high stroke risk were on OAC with no difference between the sexes (OR 0.88, 95% CI 0.62–1.25, $p = .467$). However, during the CHA_2DS_2-VASc era 53.3% of women with high risk were on OAC compared with 63.4% of men (OR 0.66, 95% CI 0.48–0.91, $p = .011$).

In addition, among patients without OAC a high-risk score was present more often in women (74.4%) than in men (49.5) ($p < .001$) (Figure 2). During the $CHADS_2$ era, 61.5% of women and 38.1% of men not on OAC had a high risk score ($p < .001$) and during the CHA_2DS_2-VASc era a high risk score was present in 96.8% of women and 66.2% of men ($p < .001$).

The use of OAC treatment was inconsistent in patients with a low or moderate stroke risk as well ($CHADS_2/CHA_2DS_2$-VASc score 0–1): A total of 34.8% of men on OAC had low or moderate risk compared to 17.5% of women ($p < .001$) (Figure 3).

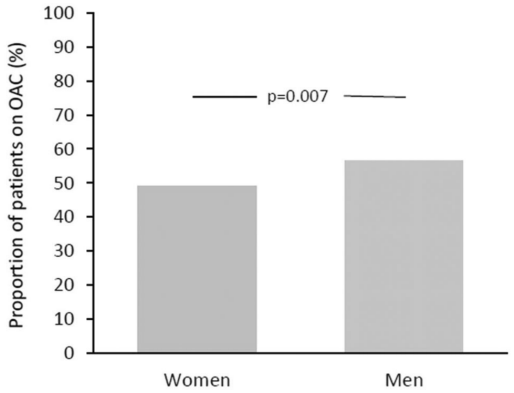

Figure 1. Oral anticoagulation in patients with high stroke risk ($CHADS_2/CHA_2DS_2$-VASc ≥ 2).

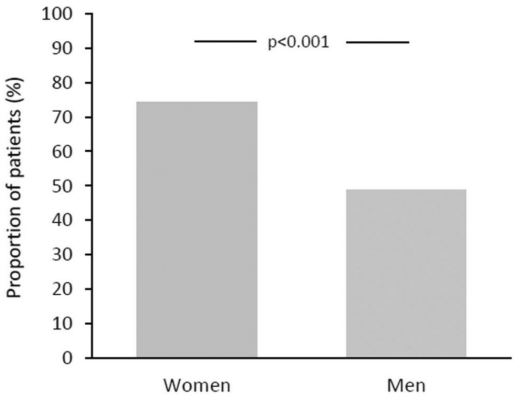

Figure 2. Proportion of high-risk patients ($CHADS_2/CHA_2DS_2$-VASc ≥ 2) among those not on oral anticoagulation.

Reasons for not being anticoagulated

A valid reason for omitting OAC was recorded in 38.6% of patients with a marked difference between sexes: approximately one quarter of women had a valid reason not to be prescribed OAC compared with half of men (Table 2). If only $CHADS_2/CHA_2DS_2$-VASc 0 and intracranial haemorrhage were accepted as valid reasons to withhold OAC, 8.9% of women and 19.6% of men presented with a valid reason.

When evaluating patients with high stroke risk ($CHADS_2/CHA_2DS_2$-VASc score ≥ 2) and not on OAC, women not on OAC were older than men ($p = .008$), had more often a high HAS-BLED score ($p = .041$) and were more often on aspirin ($p = .002$) (Table 3). A majority of patients not on OAC had a history of paroxysmal AF and about half of them were >75 years old with no difference between the sexes.

Discussion

The main finding of our study was that stroke risk evaluation in AF patients was performed poorly resulting in underuse of OAC particularly in women. Three quarters of women and half of men were not using OAC at the time of the cerebrovascular event in spite of guideline-based indication ($CHADS_2/CHA_2DS_2$-VASc ≥ 2) for OAC. Second, futile use of OAC was frequent in younger men with only low or moderate stroke risk.

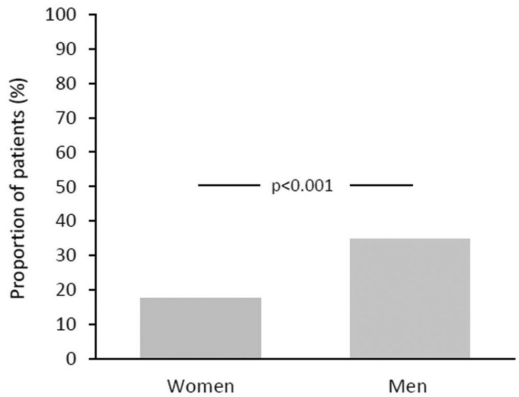

Figure 3. Proportion of low and moderate risk patients ($CHADS_2/CHA_2DS_2$-VASc 0–1) among those on oral anticoagulation.

Table 2. Reasons for not being anticoagulated in patients with AF diagnosed before cerebrovascular event.

	Women	Men	All	*p* Value
	(*n* = 515)	(*n* = 408)	(*n* = 923)	
Valid reason	139 (27.0)	217 (53.2)	356 (38.6)	<.001
$CHADS_2$/CHA_2DS_2-VASc 0–1	132 (25.6)	210 (51.5)	342 (37.1)	<.001
$CHADS_2$ 0	33 (6.4)	57 (14.0)	90 (9.8)	<.001
$CHADS_2$ 1	93 (18.1)	104 (25.5)	197 (21.3)	.005
CHA_2DS_2-VASc 0	6 (1.2)	16 (3.9)	22 (2.4)	.004
CHA_2DS_2-VASc 1	0 (0.0)	33 (8.1)	33 (3.6)	<.001
Intracranial haemorrhage	7 (1.4)	7 (1.7)	14 (1.5)	.657
Relative reason	35 (6.8)	37 (9.1)	72 (7.8)	.197
Non-valid reason	82 (15.9)	57 (14.0)	139 (15.1)	.755
Undocumented reason	259 (50.3)	97 (23.8)	356 (38.6)	.898

Valid reason: $CHADS_2$/CHA_2DS_2-VASc < 2 or intracranial haemorrhage; relative reason: dementia, prior gastrointestinal bleed, excess alcohol intake, frequent falls; non-valid reason: anaemia, patient refusal, small stroke risk, paroxysmal AF and restoration of sinus rhythm after electrical cardioversion.

$CHADS_2$ and CHA_2DS_2-VASc, see Table 1. The values denote *n* (%). *p* Value refers to women vs. men.

Table 3. Clinical characteristic on patients with $CHADS_2$ and CHA_2DS_2-VASc ≥ 2 and not on OAC.

	Women	Men	All	*p* Value
Age	82.2 ± 8.2	78.6 ± 8.4	81.0 ± 8.4	.008
Age ≥ 75 years	335 (51.5)	150 (45.7)	485 (49.5)	.091
HAS-BLED ≥3	234 (73.1)	132 (64.7)	366 (69.8)	.041
Paroxysmal AF	215 (68.3)	108 (65.1)	323 (67.2)	.478
Aspirin use	219 (86.2)	139 (74.7)	358 (81.4)	.002

AF: atrial fibrillation.

$CHADS_2$ and CHA_2DS_2-VASc, see Table 1. The values denote mean ± SD (age) or *n* (%). *p* Value refers to women vs. men.

Reasons for omitting guideline based OAC were poorly reported, particularly for women.

The 2006 ESC guidelines were the first to recommend routine use of risk stratification scores to guide OAC initiation. At the time of our study, guidelines recommended OAC for AF patients with $CHADS_2$ ≥2 (until 2009) or CHA_2DS_2-VASc ≥2 (after 2010) for women and men [1,2]. In the current ESC 2020 guidelines, all women are given one risk point and OAC is recommended with CHA_2DS_2-VASc ≥3 for women and ≥2 for men. This was not applied in our study and the adherence to risk stratification was based on the ESC 2006 and 2010 guidelines, i.e. those valid at the time of the cerebrovascular event. In line with earlier reports on real-life use of OAC, the implementation of these recommendations was inadequate also in AF patients suffering a cerebrovascular event [8,11,18,19]. Also in accordance with earlier reports, only half of the patients in our study had an INR within the therapeutic target [8,19].

Our study shows that there were sex-related differences in the guideline-based use of OAC. Almost three quarters of women not using OAC at the time of the index cerebrovascular event had a high-risk score for stroke. The sex difference in OAC use became even more marked after 2010 when the CHA_2DS_2-VASc score was implemented and women aged 65–75 years are reclassified from low to high risk category (from 0 to 2) [2]. It seems that this change did not penetrate clinical practice [7,19,20]. During the CHA_2DS_2-VASc era 98% of women belonged to the high stroke risk category (score ≥2) but only 53% were on OAC.

The effect of age on the risk evaluation is more pronounced in the CHA_2DS_2-VASc score. In the $CHADS_2$ era, age ≥75 years merited one risk point, whereas in the CHA_2DS_2-VASc era, age 65–74 years scores one point and age ≥75 years two points. In our study, women were older than men increasing the stroke risk in women, but this was not reflected in the more frequent use of OAC in older women. Earlier studies have reported that not only OAC but also rhythm control strategy are less often used in women than in men with AF [13,21,22].

Valid reasons for not prescribing OAC (intracranial haemorrhage and $CHADS_2$/CHA_2DS_2-VASc 0–1) were identified in half of men but only in a quarter of women. The risk of stroke in patients with $CHADS_2$/CHA_2DS_2-VASc 0 is very low and these patients do not need OAC. Patients with $CHADS_2$/CHA_2DS_2-VASc score 1 are at moderate risk and the current ESC guidelines (2020) recommend considering OAC in these patients [23]. If intracranial haemorrhage and $CHADS_2$/CHA_2DS_2-VASc 0 are used as justifiable reasons to omit OAC, only 14% of patients presented with such a valid reason to omit OAC. These findings are in line with Xian et al. who reported that the reason for not using OAC therapy was documented only in one-third of high-risk AF patients [19].

In the present study, the most common non-valid reason to omit OAC was paroxysmal AF with successful cardioversion to sinus rhythm. Two-thirds, both women and men, not on OAC had a history of paroxysmal AF. Paroxysmal AF is, however, associated with an increased stroke risk and the risk is considered to be similar to permanent or persistent AF [24]. One possible explanation for omitting OAC is older age and frailty [25]. In our study, OAC was deferred particularly in elderly women. Although old age increases the risk of bleeding, it is also a strong predictor of stroke [26]. Therefore, the benefits of stroke prevention usually overweigh the risk of bleeding also in older patients [27].

Stroke risk and bleeding risks often overlap and almost three quarters of women not being on OAC had HAS-BLED score ≥3 [28]. High bleeding risk should not automatically result in withholding OAC, but in the elimination of modifiable bleeding risk

factors such as hypertension, non-steroidal anti-inflammatory drugs and alcohol use [23].

Potential reasons leading the patient to discontinue OAC are warfarin side effects, poor INR control and minor bleedings, which may not be recorded in the patient files. In the Re-LY trial, the incidence of minor bleedings in the warfarin group was 16.2% per year and 10.2% of patients discontinued warfarin therapy at 1-year follow-up [29].

Withholding OAC seems often to result in the prescription of aspirin. A majority of patients not on OAC were using aspirin in spite of the fact that the bleeding risk is similar to OAC particularly in the elderly with minimal effect on thromboembolic risk [30].

One important finding of our study was the frequent use of OAC in low and moderate risk patients, particularly in men, which is in line with previous reports [31,32]. One-third of men using OAC were at low or moderate risk ($CHADS_2$ or CHA_2DS_2-VASc 0–1). Unfortunately, data regarding reasons for initiation of OAC in low and moderate risk patients were not collected in our study.

Limitations

The retrospective nature is a limitation of the current study. The data were derived from hospital (secondary care) medical records. Thus, we do not have data from primary care for example on discontinuation of OAC and reasons leading to discontinuation. Prescription of OAC was always at the treating physician's discretion and may have been affected by factors not written in the patient records. This, however, is one of the main results of the report and indicates the need for assessing valid reasons for initiation/withdrawing OAC in clinical practice. The strengths of the study include the identification of all consecutive stroke and TIA patients with a diagnosis of AF from reliable hospital discharge records and the thorough individual case by case review of patient records. We also included only patients living in the catchment area of the participating hospitals. Thus, medical history was well captured in our registry. INR data were collected only from the last 30 days prior to the cerebrovascular event.

Warfarin was the most commonly used OAC during the study period while DOACs are currently the dominant OAC therapy. However, the fundamental question, when to start OAC, remains also in the DOAC era. At present, there is no evidence to suggest that DOACs or new guidelines have changed the sex-gap between women and men in the treatment of AF. A recent EHRA position paper summarizes: "Sex-specific barriers to the implementation of contemporary AF guidelines and the use of guideline-recommended OAC therapy need to be identified and addressed" [21].

Conclusions

Our results suggest that OAC is underused in high-risk AF patients, particularly women, and often prescribed in men with low or moderate stroke risk. In addition, the decision to omit OAC was rarely based on risk stratification scores and contemporary guidelines. Reasons for not being anticoagulated were poorly justified, particularly in women. These findings underline the need for improving the use of risk scores and OAC, especially in women with AF.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Access to data is regulated by Finnish law. Data are available from the Turku University Hospital for researchers who meet the criteria as required by the Finnish law for access to confidential data. Contact person who will distribute data upon request to qualified researchers: Tuija Vasankari, Heart Centre, Turku University Hospital, PO BOX 52, FIN-20521 Turku, Finland; tuija.vasankari@tyks.fi.

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III

Outcome of octogenarians with atrial fibrillation undergoing percutaneous coronary intervention: insights from AFCAS registry.

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CLINICAL INVESTIGATIONS

Outcome of octogenarians with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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Background: More evidence is needed on the optimal antithrombotic regimen in elderly patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI).

Hypothesis: Octogenarian patients (aged ≥80 years) with AF who underwent PCI have worse 12-month clinical outcome, compared with younger patients.

Methods: We performed a post-hoc analysis of data from the prospective, multicenter AFCAS registry, which enrolled consecutive patients with AF who underwent PCI and stenting. Outcome measures included major adverse cardiac/cerebrovascular events (MACCE; all-cause death, myocardial infarction, repeat revascularization, stent thrombosis, or stroke/transient ischemic attack) and bleeding events at 12-month follow-up.

Results: Out of 925 AF patients enrolled in AFCAS registry, 195 (21.1%) were ≥80 years. Mean age was 82.9 ± 2.6 years; 41.5% were women; 32.3% had diabetes mellitus. Compared with patients aged <80 years, there were more females among the octogenarians ($P < 0.001$). Compared with younger patients, octogenarians smoked and had dyslipidemia less often, and presented more frequently with acute coronary syndrome. The frequency and duration of antithrombotic regimens prescribed at discharge were comparable. At 12-month follow-up, overall MACCE rate was higher in octogenarians compared with younger patients (27.7% vs 20.1%, $P = 0.02$). The rate of acute myocardial infarction was higher in octogenarians (9.2% vs 4.9%, $P = 0.02$), but the rates of all bleeds and BARC >2 bleeds were similar ($P = 0.13$, $P = 0.29$, respectively).

Conclusions: In real-world patients with AF undergoing PCI, patients aged ≥80 years had higher incidence of MACCE at 12-month follow-up compared with younger patients, although they received comparable antithrombotic treatment. The rates of bleeding events were similar.

KEYWORDS

Atrial Fibrillation, Octogenarians, Oral Anticoagulation, Percutaneous Coronary Intervention

1 | INTRODUCTION

Life expectancy has increased in the Western world, and more octogenarian patients (aged ≥80 years) now undergo percutaneous coronary intervention (PCI) with stent implantation. Octogenarians have a high-risk clinical profile and more complex coronary disease compared with younger patients.[1] Expectedly, older age is associated with worse short-term and long-term clinical outcomes following PCI.[2,3] Yet limited evidence is available on the efficacy and safety of PCI in both elderly and female patients, because they are underrepresented in clinical trials.[4]

Prevalence of atrial fibrillation (AF) increases with age.[5] Nearly 5% of patients undergoing PCI and stenting have an indication for

long-term oral anticoagulation (OAC) due to AF.[6] The current management guidelines recommend triple therapy (dual antiplatelet therapy [DAPT] on top of OAC), at least for a short period after PCI.[7] However, the optimal antithrombotic regimen in this particularly high-risk group of older patients remains unclear, and there is a need for more data on antithrombotic treatment and outcomes of octogenarian patients with AF undergoing PCI.

We performed a post-hoc analysis of data from the prospective Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) Registry to explore the 12-month clinical outcome of patients aged ≥80 years undergoing PCI in comparison with younger patients, with gender-based analysis of outcome.

2 | METHODS

2.1 | Patient selection and study design

The AFCAS Registry is a prospective, multicenter, observational study that enrolled consecutive patients with AF undergoing PCI and stenting.[8] The inclusion criterion was ongoing AF or a history of AF (paroxysmal, persistent, or permanent). The only exclusion criterion was unwillingness or inability to participate in the study or to give informed consent. In each participating center, PCI was performed according to local practice, and follow-up time was 12 months. Periprocedural and postprocedural antithrombotic regimens were at the operators' discretion. Follow-up was performed by phone calls or clinical controls at 1, 3, 6, and 12 months after PCI. Patients were asked about clinical outcome endpoints (described below), hospitalization, and medications. CHA_2DS_2-VASc and HAS-BLED scores were calculated before PCI to evaluate the individual risks for stroke and bleeding events, respectively.

This investigator-driven study was conducted according to the guidelines of the 1964 Declaration of Helsinki as revised in 2013. The study protocol was approved by the ethics committees of the participating centers. Informed written consent was obtained from every patient after full explanation of the study protocol. The AFCAS Registry is registered under http://www.ClinicalTrials.gov at NCT00596570.

2.2 | Study definitions and endpoints

The primary outcome measures were (1) major adverse cardiac/cerebrovascular events (MACCE) and (2) bleeding events. The composite endpoint of MACCE was defined as the first occurrence of all-cause death, myocardial infarction (MI), repeat revascularization, stent thrombosis (ST), or stroke/transient ischemic attack. MI was defined according to the Third Universal Definition.[9] Repeat revascularization was defined as PCI or coronary bypass surgery to treat significant stenosis (>50%) in the previously treated vessel. ST was adjudicated according to the criteria of definite or probable ST described by the Academic Research Consortium (ARC).[10] TIA was defined as a transient (<24 hours) focal neurological deficit adjudicated by a neurologist, whereas stroke was defined as a permanent focal neurological deficit confirmed by computed tomography or magnetic resonance imaging and adjudicated by a neurologist. Bleeding events were defined according to the BARC criteria and included events adjudicated as minor (BARC 2) and major (BARC 3a, 3b, 3c, and 5).[11]

2.3 | Statistical analysis

Continuous variables were reported as the mean ± SD or median (interquartile range [IQR]). Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons were performed using the unpaired 2-tailed *t* test for continuous variables and the Pearson χ^2 test or Fisher exact test for categorical variables, as appropriate. Kaplan–Meier estimates of MACCE and all bleeding events were used to construct time-to-event curves. These estimates were based on all the available data for MACCE and all bleeding events, with follow-up data censored at the time of first event or latest known follow-up. All tests were 2-sided, and statistical significance was set at 5%. Statistical analysis was performed using SPSS software, version 20 (IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Baseline clinical and procedural data

Out of 925 AF patients enrolled in the AFCAS registry, a total of 195 (21.1%) patients were ≥80 years: 189 (96.9%) were octogenarians and 6 (3.1%) nonagenarians (aged ≥90 years). Their mean age was 82.9 ± 2.6 years (median, 82; range, 80–92 years). Eighty-one patients (41.5%) were females, and 63 (32.3%) had diabetes mellitus. Mean CHA_2DS_2-VASC score was 5.1 ± 1.2 (median [IQR] 5 [2]) and mean HAS-BLED score was 3.1 ± 0.7 (median [IQR] 3 [0]).

The octogenarians were more often females. They smoked and had dyslipidemia less often in comparison with younger patients, and their body mass index and glomerular filtration rate were lower ($P < 0.01$ for all). Patients aged ≥80 years had a higher risk of thromboembolism and bleeding ($P < 0.001$ both). The 2 groups were comparable regarding prior coronary and cerebrovascular events, prior bleeding events, as well as prior heart failure and mean left ventricular ejection fraction ($P > 0.05$ for all). These findings were almost consistent in both gender subgroups (Table 1).

Compared with younger patients, the patients aged ≥80 years presented more often with acute coronary syndrome (ACS). This was consistent in males ($P < 0.001$), but not in females ($P = 0.23$). There was no significant difference in the use of drug-eluting stents or other periprocedural data between the 2 groups (Table 2).

3.2 | Antithrombotic regimens

Among patients aged ≥80 years, triple therapy (OAC + clopidogrel + aspirin) was the most common antithrombotic regimen prescribed at discharge (70.3%), followed by DAPT (clopidogrel + aspirin; 19.5%). The mean duration of clopidogrel use was 5.7 ± 4.8 months. The frequency of antithrombotic regimens prescribed at discharge was comparable between octogenarians and younger patients (Table 3). The proportions of patients on clopidogrel were comparable between patients aged ≥80 years and younger patients at 3, 6, 9, and

TABLE 1 Baseline characteristics

	Whole Cohort, N = 925			Males, n = 650			Females, n = 275		
Variable	OG, n = 195	Younger, n = 730	*P* Value	OG, n = 114	Younger, n = 536	*P* Value	OG, n = 81	Younger, n = 194	*P* Value
Age, y, mean ± SD	82.9 ± 2.6	70.4 ± 6.7	<0.001	83.0 ± 2.8	69.7 ± 7.1	<0.001	82.9 ± 2.4	72.3 ± 5.3	<0.001
Age, y, median (IQR)	82 (3)	72 (8)		82 (4)	71 (9)		83 (3)	74 (6)	
Female sex	81 (41.5)	194 (26.6)	<0.001						
BMI	26.2 ± 3.5	28.8 ± 4.7	<0.001	26.2 ± 23.2	28.7 ± 4.5	<0.001	26.2 ± 3.9	29.1 ± 5.1	<0.001
Preprocedural GFR (ml/min/1.73m^2)	53 ± 19	80 ± 35	<0.001	55.3 ± 19.4	84.1 ± 35.9	<0.001	49.5 ± 18.5	69.3 ± 28.0	<0.001
LVEF, %	49 ± 14	50 ± 14	0.41	48.4 ± 14.8	48.5 ± 14.0	0.95	49.2 ± 11.9	53.3 ± 13.6	0.041
DM	63 (32.3)	274 (37.5)	0.18	36 (31.6)	189 (35.3)	0.45	27 (33.3)	85 (43.8)	0.11
HTN	160 (82.1)	616 (84.4)	0.43	88 (77.2)	447 (83.4)	0.12	72 (88.9)	169 (87.1)	0.68
Dyslipidemia	114 (58.5)	502 (68.8)	0.007	62 (54.4)	361 (67.4)	0.008	52 (64.2)	141 (72.7)	0.16
Smoking	9 (4.6)	83 (11.4)%	0.005	7 (6.1)	73 (13.6)	0.027	2 (2.5)	10 (5.2)	0.32
Prior MI	57 (29.2)	179 (24.5)	0.18	35 (30.7)	140 (26.1)	0.32	22 (27.2)	39 (20.1)	0.20
Prior PCI	25 (12.8)	135 (18.5)	0.063	16 (14.0)	99 (18.5)	0.26	9 (11.1)	36 (18.6)	0.13
Prior CABG	21 (10.8)	113 (15.5)	0.097	19 (16.7)	97 (18.1)	0.72	2 (2.5)	16 (8.2)	0.08
Prior HF	43 (22.1)	142 (19.5)	0.42	29 (25.4)	110 (20.5)	0.25	14 (17.3)	32 (16.5)	0.87
Prior stroke	26 (13.3)	85 (11.6)	0.52	16 (14.0)	64 (11.9)	0.54	10 (12.3)	21 (10.9)	0.72
Prior TIA	9 (4.6)	37 (5.1)	0.80	4 (3.5)	30 (5.6)	0.36	5 (6.2)	7 (3.6)	0.34
Prior hemorrhage	9 (4.6)	29 (4.0)	0.70	6 (5.3)	22 (4.1)	0.59	3 (3.7)	7 (3.6)	0.98
CHA_2DS_2-VASc score	5.1 ± 1.2	4.2 ± 1.5	<0.001	4.7 ± 1.1	3.8 ± 1.4	<0.001	5.8 ± 1.1	5.1 ± 1.3	<0.001
CHA_2DS_2-VASc ≥2	195 (100)	716 (98.1)	<0.001	114 (100)	522 (97.4)	0.081	81 (100)	194 (100)	1.0
HAS-BLED score	3.1 ± 0.7	2.9 ± 0.7	<0.001	3.1 ± 0.8	2.9 ± 0.8	0.007	3.2 ± 0.6	3.0 ± 0.7	0.030
HAS-BLED ≥3	167 (85.6)	540 (74.0)	0.001	92 (80.7)	384 (71.6)	0.047	75 (92.6)	156 (80.4)	0.012

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHA_2DS_2-VASc, congestive HF, HTN, age > 75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (female); DM, diabetes mellitus; GFR, glomerular filtration rate; HAS-BLED, HTN, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly age > 65 years; HF, heart failure; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OG, octogenarians; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack. Categorical variables are presented as n (%) and continuous variables as mean ± SD or median (IQR).

TABLE 2 Procedural data

Variable	Whole Cohort, N = 925			Males, n = 650			Females, n = 275		
	OG, n = 195	Younger, n = 730	*P* Value	OG, n = 114	Younger, n = 536	*P* Value	OG, n = 81	Younger, n = 194	*P* Value
Presentation by ACS	135 (69.6)	392 (53.7)	<0.001	81 (71.1)	276 (51.5)	<0.001	54 (67.5)	116 (59.8)	0.23
STEMI	32 (16.5)	93 (12.7)	0.18	17 (14.9)	68 (12.7)	0.52	15 (18.5)	25 (12.9)	0.23
Lesions per patient	1.2 ± 0.4	1.2 ± 0.4	0.64	1.2 ± 0.5	1.2 ± 0.4	0.15	1.1 ± 0.3	1.2 ± 0.4	0.30
DES	38 (20.3)	181 (25.8)	0.12	20 (17.9)	138 (26.3)	0.061	18 (22.8)	44 (23.0)	0.96
Total stent length (mm)	24.6 ± 16.8	25.0 ± 16.3	0.75	26.4 ± 19.1	25.1 ± 16.9	0.47	22.2 ± 12.7	25.0 ± 14.3	0.13
Procedural success	190 (97.4)	707 (96.8)	0.67	110 (96.5)	515 (96.1)	0.84	80 (98.8)	192 (99.0)	0.88
Radial access	57 (29.2)	201 (27.5)	0.64	39 (34.2)	149 (27.8)	0.17	18 (22.2)	52 (26.8)	0.43
Hospital stay (days)									
Mean ± SD	5.9 ± 7.8	4.8 ± 7.5	0.050	5.4 ± 6.9	5.0 ± 8.2	0.61	6.7 ± 8.9	4.0 ± 4.6	0.001
Median (IQR)	4 (5)	2 (5)		3 (5)	2 (5)		4 (6)	2 (5)	
TTR (%)	68 ± 34	68 ± 34	0.87	71 ± 33	68 ± 32	0.38	64 ± 34	68 ± 33	0.46

Abbreviations: ACS, acute coronary syndrome; DES, drug-eluting stents; IQR, interquartile range; OG, octogenarians; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TTR, time in therapeutic range. Categorical variables are presented as n (%) and continuous variables as mean ± SD or median (IQR).

12 months (61.8% vs 64.9%, 45.3% vs 44.7%, 35.3% vs 33.7%, and 33.5% vs 30.4%, respectively); similarly, the proportions of patients on aspirin were comparable (75.4% vs 77.3%, 67.7% vs 70.1%, 64.1% vs 64.9%, and 60.0% vs 61.4%, respectively).

3.3 | Short-term and long-term outcome

Adverse outcome events are summarized in Table 4. The cumulative incidence of MACCE in patients aged ≥80 years was comparable during hospital stay and at 30 days, but significantly higher at 12 months ($P = 0.02$), in comparison with younger patients. There was a similar trend in both gender subgroups ($P = 0.09$ both). This was mainly driven by a higher incidence of MI shortly after index PCI and at 12 months. A trend to higher all-cause mortality rate was evident at 12-month follow-up only. Despite a higher incidence of MI, the rate of repeat revascularization was not different between octogenarians and younger patients. The cumulative rates of BARC >2 bleeds were 12.3% vs 9.7% ($P = 0.29$) in patients ≥80 years compared with younger patients, respectively, and this was consistent in both gender subgroups.

4 | DISCUSSION

The AFCAS Registry shows that octogenarians have a higher incidence of MACCE at 12 months despite comparable antithrombotic regimens, mainly driven by higher incidence of MI. On the other hand, the bleeding rates were not significantly different between octogenarians and younger patients.

Few data exist on the optimal antithrombotic regimen in older patients with AF who need lifelong OAC and undergo PCI. In the randomized trials What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST), A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI), and Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting (REDUAL-PCI), the proportion of patients aged ≥80 years was not separately reported.[12–14] In the WOEST and PIONEER AF-PCI trials, a regimen of dual therapy with OAC (vitamin K antagonist and rivaroxaban, respectively) plus a P2Y12 inhibitor was associated with lower rates of clinically significant bleeding compared with triple therapy (OAC + P2Y12 inhibitor + aspirin).[12,13] In the recently reported REDUAL-PCI trial, dual therapy with OAC (dabigatran 110 mg twice daily) plus P2Y12 inhibitor was associated with lower rates of clinically relevant bleeding compared with warfarin triple therapy (warfarin + P2Y12 inhibitor + aspirin for 1–3 months).[14] In all 3 trials, the rates of thromboembolic events were not significantly different between the 2 comparison groups; however, the 3 trials were underpowered to examine thromboembolic events (composite efficacy endpoint).[12–14] Moreover, in the WOEST trial (69% of patients had AF), reduction of bleeding was driven by reduction of minor, rather than major, bleeding events[12]; the PIONEER AF-PCI trial excluded patients with prior stroke or transient ischemic attack and those with new-onset AF[13]; and REDUAL-PCI trial excluded those with severe

TABLE 3 Antithrombotic and cardiac medications

Variable	Whole Cohort, N = 925			Males, n = 650			Females, n = 275		
	OG, n = 195	Younger, n = 730	*P* Value	OG, n = 114	Younger, n = 536	*P* Value	OG, n = 81	Younger, n = 194	*P* Value
Periprocedural INR	1.9 ± 0.6	1.9 ± 0.7	0.98						
GPI	41 (21.0)	139 (19.0)	0.53	25 (21.9)	107 (20.0)	0.64	16 (19.8)	32 (16.5)	0.52
VKA + Clop + ASA	137 (70.3)	541 (74.1)	0.28	80 (70.2)	401 (74.8)	0.31	57 (70.4)	140 (72.2)	0.76
VKA + Clop/ASA	20 (10.3)	66 (9.0)	0.60	14 (12.3)	51 (9.5)	0.37	6 (7.4)	15 (7.7)	0.93
Clop + ASA	38 (19.5)	123 (16.8)	0.39	20 (17.5)	84 (15.7)	0.62	18 (22.2)	39 (20.1)	0.69
Clop duration (months)	5.7 ± 4.8	5.7 ± 4.7	1.0	5.7 ± 4.7	5.7 ± 4.7	1.0	5.8 ± 5.0	5.8 ± 4.7	0.96
Median (IQR) (months)	3 (11)	3 (11)		3 (11)	3 (11)		3 (11)	3 (11)	
β-Blockers	163 (83.6)	640 (87.7)	0.19	98 (86.0)	468 (87.3)	0.51	65 (80.2)	172 (88.7)	0.18
Lipid-lowering agents	154 (79.0)	637 (87.3)	0.013	89 (78.1)	465 (86.8)	0.059	65 (80.2)	172 (88.7)	0.18
ACEIs/ARBs	158 (84.9)	573 (80.5)	0.16	89 (81.7)	419 (80.1)	0.71	69 (89.6)	154 (81.5)	0.10

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid (aspirin); Clop, clopidogrel; GPI, glycoprotein IIb/IIIa inhibitors; INR, international normalized ratio; IQR, interquartile range; OG, octogenarians; SD, standard deviation; VKA, vitamin K antagonists. Categorical variables are presented as n (%) and continuous variables as mean ± SD or median (IQR).

renal impairment.[14] In the current registry, the prescribed antithrombotic regimens (medications, dosage, and duration) were widely heterogeneous because they were based on local practice and operators' discretion.

Unanswered questions include the duration of each antithrombotic medication and the change of antithrombotic regimen over time. Our findings provide important clinical data in this setting. In real-life practice, the duration of intensified antithrombotic therapy after PCI is often shortened in elderly patients because of a presumed higher bleeding risk. As expected, octogenarians in our cohort had a higher HAS-BLED score. The higher bleeding risk did not, however, lead to a less intensive antithrombotic treatment in octogenarians; and, surprisingly, both the total and clinically significant bleeding event rates did not differ between the age groups. The comparable 12-month bleeding rates, despite a higher bleeding risk in octogenarians, might by viewed in light of the similar periprocedural international normalized ratio, similar time in therapeutic range throughout the follow-up period, and similar duration of clopidogrel usage in the 2 age groups. Comparably, in an unselected cohort of patients with AF undergoing PCI, octogenarians (higher bleeding and thrombotic risk scores) experienced more MACCE (mainly driven by higher rates of all-cause death and embolism), higher major bleeding rates, and similar minor bleeding rates, compared with younger patients.[15] In that cohort, OAC prescribed at discharge for octogenarian patients was associated with lower rates of MACCE.[15] Notably, octogenarian women—often considered as "extra-frail" patients—had bleeding rates comparable with octogenarian men, and with younger women. Given the higher rates of thrombotic events and the comparable rates of bleeding events in octogenarians, and the largely comparable distribution of prescribed antithrombotic medications between the 2 age groups, our study supports the view that longer antithrombotic treatment might be considered in octogenarians, especially in those presenting with ACS. This assumption, however, needs to be confirmed in adequately powered randomized trials.

In accordance with a previous study,[16] octogenarians in the AFCAS registry presented more often with ACS compared with younger patients. In the same prior study, octogenarians (65.5% drug-eluting stents vs 80.1% in younger patients) had higher rates of mortality, ST, and clinically driven in-stent restenosis at 12-month follow-up, compared with younger patients.[16] This may partly explain the higher incidence of MI events, and consequently the higher incidence of MACCE, at 12-month follow-up in octogenarians in our cohort. In the AFCAS study, older patients were not treated more frequently with bare-metal stents, as is often recommended to enable shorter DAPT (Table 2). Octogenarians treated with PCI have more comorbidities compared with younger patients,[16,17] and this may affect noncardiac causes of mortality as well. Yet in a cohort of octogenarians who underwent PCI for ACS, cardiovascular death was responsible for 71% of all-cause mortality at 5-year follow-up.[18]

Increasing age is a well-known risk factor for mortality after PCI. Not surprisingly, the proportion of patients aged ≥80 years (21.1%) in the AFCAS registry was higher than recent reports from unselected patients (12%)[19] and from patients who underwent primary PCI for ST-segment elevation MI (10.3% and 11.6%).[20,21] This is comprehensible because the prevalence of AF increases progressively with age.

TABLE 4 Clinical outcome at 12-month follow-up

	Whole Cohort, N = 925			Males, n = 650			Females, n = 275		
Variable	OG, n = 195	Younger, n = 730	*P* Value	OG, n = 114	Younger, n = 536	*P* Value	OG, n = 81	Younger, n = 194	*P* Value
MACCE									
12 months	54 (27.7)	147 (20.1)	0.023	32 (28.1)	112 (20.9)	0.09	22 (27.2)	35 (18.0)	0.09
30 days	14 (7.2)	51 (7.0)	0.93	9 (7.9)	36 (6.7)	0.65	5 (6.2)	15 (7.7)	0.65
In-hospital	7 (3.6)	31 (4.3)	0.67	4 (3.5)	24 (4.5)	0.64	3 (3.7)	7 (3.7)	0.99
Death									
12 months	29 (14.9)	74 (10.1)	0.06	18 (15.8)	56 (10.4)	0.10	11 (13.6)	18 (9.3)	0.29
30 days	6 (3.1)	26 (3.6)	0.74	4 (3.5)	17 (3.2)	0.85	2 (2.5)	9 (4.6)	0.40
In-hospital	5 (2.6)	14 (1.9)	0.58	2 (1.8)	10 (1.9)	0.93	3 (3.7)	4 (2.1)	0.44
MI									
12 months	18 (9.2)	36 (4.9)	0.023	11 (9.6)	23 (4.3)	0.020	7 (8.6)	13 (6.7)	0.57
In-hospital	6 (3.4)	9 (1.3)	0.062	3 (2.9)	6 (1.2)	0.20	3 (4.0)	3 (1.6)	0.25
Re-revascularization	59 (8.1)	14 (7.2)	0.68	8 (7.0)	43 (8.0)	0.72	6 (7.4)	16 (8.2)	0.82
ST	5 (2.6)	10 (1.4)	0.24	3 (2.6)	7 (1.3)	0.30	2 (2.5)	3 (1.5)	0.60
Stroke/TIA	8 (4.1)	15 (2.1)	0.10	4 (3.5)	12 (2.2)	0.42	4 (4.9)	3 (1.5)	0.10
All TE	10 (5.1)	20 (2.7)	0.09	5 (4.4)	16 (3.0)	0.44	5 (6.2)	4 (2.1)	0.08
All bleeding									
12 months	51 (26.2)	154 (21.1)	0.13	31 (27.2)	102 (19.0)	0.050	20 (24.7)	52 (26.8)	0.72
In-hospital	26 (13.3)	77 (10.5)	0.27	14 (12.3)	55 (10.3)	0.53	12 (14.8)	22 (11.3)	0.43
BARC >2									
12 months	24 (12.3)	71 (9.7)	0.29	15 (13.2)	44 (8.2)	0.10	9 (11.1)	27 (13.9)	0.53
In-hospital	9 (4.6)	31 (4.2)	0.82	4 (3.5)	22 (4.1)	0.77	5 (6.2)	9 (4.6)	0.60

Abbreviations: BARC, Bleeding Academic Research Consortium; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; OG, octogenarians; ST, stent thrombosis; TE, thromboembolism; TIA, transient ischemic attack. Data are presented as n (%).

4.1 | Study limitations

The current study has all the inherent limitations of an observational study design, including unmeasured confounders and individual decision-making in treatment choice. Another limitation is the heterogeneity of cohort among the participating centers and some variations in periprocedural routines. The statistical power of our study is limited by the absolute low rates of ST and stroke and a relatively small sample size. Therefore, lack of significant difference between comparison groups might be due to type II statistical error. We could not provide data on adherence to OAC and antiplatelet medications in either group. The strength of the registry is enrollment of consecutive patients with the only exclusion criterion being unwillingness or inability to participate. In this sense, the registry cohort well represents real-world patients with AF referred for PCI.

5 | CONCLUSION

In a real-world cohort of patients with AF who underwent PCI, patients aged ≥80 years had a higher incidence of MACCE at 12-month follow-up in comparison with younger patients, although they received comparable antithrombotic treatment. The bleeding events did not differ between octogenarians and younger patients, despite higher bleeding risk assessed by HAS-BLED score.

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Conflicts of interest

The authors declare no potential conflicts of interest.

Author contributions

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Atrial fibrillation (AF) causes a five-fold increase in the risk of stroke and is responsible for 10 to 15% of ischemic strokes. Ageing, female sex and several comorbidities increase the risk of thromboembolic complications in AF. Oral anticoagulation reduces the thromboembolic risk by two thirds and is recommended for AF patients with risk factors for stroke. The aim of this dissertation was to evaluate sex- and age-related differences in anticoagulation treatment strategies and thromboembolic complications after cardiac procedures (electrical cardioversion, percutaneous coronary intervention) of AF patients.

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