Tampere University

TERO PENTTILÄ

Atrial Fibrillation

Risk stratification and use of medical therapies

Tampere University Dissertations 20

Tampere University Dissertations 20

TERO PENTTILÄ

Atrial Fibrillation

Risk stratification and use of medical therapies

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty Council of Medicine and Life Sciences
of the University of Tampere,
for public discussion in the Jarmo Visakorpi auditorium
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 8 March 2019, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland

Supervisors	Docent Pekka Raatikainen University of Oulu Finland	Docent Heikki Mäkynen Tampere University Finland
Pre-examiners	Professor Jari Laukkanen University of Jyväskylä Finland	Docent Tuomas Kiviniemi University of Turku Finland
Opponent	Professor Juhani Airaksinen University of Turku Finland	
Custos	Professor Kjell Nikus Tampere University Finland	

Cover design: Roihu Inc.

ISBN 978-952-03-0940-4 (print)
ISBN 978-952-03-0941-1 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-0941-1

PunaMusta Oy – Yliopistopaino
Tampere 2019

To my family,

ABSTRACT

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults. It is associated with an increased risk of stroke and other thromboembolic complications, myocardial infarction, heart failure, and a reduced quality of life in symptomatic patients; it also increases mortality. The treatment of AF and its complications, along with numerous visits to emergency departments (ED) by the patients, lead to elevated health care costs.

Identifying the risk factors of AF is crucial in fighting against the worldwide AF epidemic. Early recognition of individuals at risk helps in the adaptation of preventive therapies. Like in coronary artery disease, the way of thinking should be switched towards primary instead of secondary prevention.

Assessing the stroke risk and prevention of thromboembolic complications is a main target when treating patients with AF. According to the clinical practice guidelines of the European Society of Cardiology (ESC), patients at a high risk for thromboembolic complications according to the CHA2DS2-VASc score should be offered oral anticoagulation (OAC) therapy. Proper OAC for high-risk patients reduces strokes and mortality. Antiarrhythmic drug (AAD) therapy is recommended to reduce the ventricular rate in AF (rate control) and for symptomatic AF patients when aiming to maintain sinus rhythm (rhythm control). Thus, AAD therapy aims to prevent AF recurrences and to alleviate symptoms associated with AF.

The aim of this thesis was to improve the risk stratification and the treatment of patients with atrial fibrillation. We studied two different Finnish AF patient cohorts. The FinFib2 population consisted of 1013 patients admitted to 35 EDs due to symptomatic AF. The FinWAF population was formed by linking data from multiple Finnish registries; it included 54 568 AF patients taking warfarin.

Hypertension was found to be the most common cardiovascular risk factor for AF in addition to age. Its role was highlighted in symptomatic patients admitted to the

ED. Overall, the risk factors of AF were similar to those reported in other Western countries.

We evaluated the CHA2DS2-VASc score as a predictor of myocardial infarction (MI) and cardiovascular mortality in anticoagulated AF patients. The CHA2DS2-VASc score has previously been validated to assess the stroke risk in AF patients without anticoagulation. A number of the components in the CHA2DS2-VASc score are also known to be related to the risk of MI and cardiovascular mortality. In our study, a high CHA2DS2-VASc score had a direct linear association with the risk of MI and cardiovascular mortality.

The female sex has been suggested to be a risk factor for stroke and, therefore, has been included into the CHA2DS2-VASc score. In recent studies, the role of the female sex as a risk factor has been questioned. Sex differences in several endpoints, including stroke, bleeding events, cardiovascular and all-cause mortality, were analyzed in the FinWAF registry. When adjusted for baseline characteristics, there were no sex-related differences in the risk of stroke. Bleeding events, cardiovascular and all-cause mortality were lower in females than in males.

In warfarin therapy, good-quality treatment is crucial. In our study, the quality was assessed continuously by calculating the time in therapeutic range within a 60-day period before the index event (TTR60). Well-managed warfarin therapy (TTR60 > 80%), was associated with a lower risk for MI, bleeding events, and cardiovascular and all-cause mortality. We also found that among patients with TTR60 > 50%, there were no sex differences in the risk of stroke, cardiovascular or all-cause mortality, whereas the risk of bleeding events was lower for females. The better the TTR, the better the outcome in all endpoints.

The use of medical therapies and the quality of the treatment in patients with AF is not well-known. In the FinFib2 population, OAC therapy (mostly warfarin) was used by 76% of the patients with previously diagnosed AF and the CHA2DS2-VASc score of at least 2. At discharge, 86% of the high-risk patients with previous AF diagnosis were anticoagulated. OAC was started in 80% of the patients with newly diagnosed AF. Although most patients were prescribed OAC, it was shown that only

in 59% of the patients, the international normalized ratio (INR) was at the therapeutic level, indicating that the quality of OAC therapy was not good.

The use of AAD therapies in patients with symptomatic AF was also analyzed. In the FinFib2 population, the most frequently used AAD among patients with previously diagnosed AF was a beta blocker (81%) and was initiated for 71% of patients with newly diagnosed AF. Prior use of class I (11%) and class III (9%) AADs, as well as starting or adjusting their dosage (7%), were uncommon.

In conclusion, hypertension was the most common cardiovascular risk factor for AF. The role of hypertension was highlighted among patients with symptoms in ED. This underlines the importance of treatment of hypertension not only in the primary prevention of AF, but also to avoid symptomatic episodes of AF. We validated the CHA2DS2-VASc score in the risk assessment of MI in anticoagulated AF patients, and it can be used to identify patients who would benefit from strict management of cardiovascular risk factors. AF patients at a high risk of thromboembolic events were well-recognized in EDs, but the quality of anticoagulation therapy should be improved. Higher TTR levels of up to > 80% should be targeted when using warfarin to minimize the risk of adverse events. Good-quality OAC therapy is critical not only to prevent stroke, but also with regard to cardiovascular outcome. According to our data, anticoagulated female AF patients do not have increased residual risk of adverse events compared to males. The use of AAD therapies in Finland was rare. Hence, more education for physicians working in EDs is needed to alleviate AF burden and to improve patients quality of life.

TIIVISTELMÄ

Eteisvärinä on yleisin aikuisilla esiintyvä rytmihäiriö. Siihen liittyy lisääntynyt aivoinfarktin ja hyytymäkomplikaation riski. Se myös lisää sydäninfarktin ja sydämen vajaatoiminnan riskiä sekä kuolleisuutta. Eteisvärinän ja siihen liittyvien komplikaatioiden hoito kuormittaa terveydenhuoltoa ja aiheuttaa kustannuksia.

Eteisvärinän esiintyvyys kasvaa maailmanlaajuisesti. Sen estämiseksi on tärkeää tunnistaa eteisvärinän riskitekijät väestössä ja hoitaa ne yksilötasolla mahdollisimman varhaisessa vaiheessa. Kuten sepelvaltimotaudissa, eteisvärinässä tulisi pyrkiä löytämään ennaltaehkäiseviä keinoja ja toteuttaa niitä sekä väestö- että yksilötasolla.

Eteisvärinäpotilaan hoidossa aivoinfarktin ja muiden hyytymäkomplikaatioden esto on tärkeää. Euroopan kardiologisen seuran (ESC) eteisvärinän hoitosuosituksen mukaan korkean aivoinfarktiriskin potilailla tulisi käyttää verenohennuslääkitystä. Riskiarvion tulisi perustua CHA2DS2-VASc-pisteytykseen. Laadukas verenohennuslääkitys vähentää eteisvärinään liittyvää aivoinfarktiriskiä ja kuolleisuutta. Eteisvärinän estolääkitystä suositellaan käytettäväksi hidastamaan rytmihäiriön aikaista nopeaa syketasoa (sykekontrolli) ja vaikeaoireisilla potilailla estämään eteisvärinän uusiutumista (rytmikontrolli).

Tämän tutkimuksen tavoitteena oli parantaa eteisvärinäpotilaiden riskinarviota ja hoitoa. Käytimme kahta erilaista suomalaista potilasaineistoa. FinFib2-aineisto koostui 1013 potilaasta, jotka hakeutuivat ensiapuun oireisen eteisvärinän vuoksi. FinWAF-aineisto muodostettiin yhdistämällä tieto useasta suomalaisesta kansallisesta rekisteristä ja laboratoriotietokannasta. Se sisälsi 54 568 eteisvärinäpotilasta, jotka käyttivät varfariinia verenohennuslääkkeenä.

Kohonnut verenpaine oli iän lisäksi yleisin eteisvärinän riskitekijä. Sen vaikutus korostui FibFib2-aineistossa, missä potilaat hakeutuivat ensiapuun oireisen eteisvärinän vuoksi. Eteisvärinän riskitekijät olivat tutkimuksessamme yhtenevät aiemmin länsimaissa julkaistujen tulosten kanssa.

Tutkimme CHA2DS2-VASc-pisteytyksen soveltuvuutta verenohennuslääkitystä käyttävien eteisvärinäpotilaiden sydäninfarktiriskin ennustamiseen. CHA2DS2-VASc-pisteytys on aiemmin validoitu arvioimaan aivoinfarktiriskiä eteisvärinäpotilailla, joilla ei ole verenohennuslääkitystä käytössä. Osan pisteytyksen tekijöistä tiedetään lisäävän sydäninfarktiriskiä ja -kuolleisuutta. Tutkimuksemme osoitti, että CHA2DS2-VASc-pisteytys ennustaa hyvin sydäninfarktiriskiä ja -kuolleisuutta tässä potilasryhmässä.

Naissukupuolen on epäilty lisäävän eteisvärinäpotilaiden aivoinfarktiriskiä, minkä vuoksi se on osa CHA2DS2-VASc-pisteytystä. Tuoreiden tutkimusten perusteella naissukupuolen osuus aivoinfarktiriskissä vaikuttaa vähäiseltä. Analysoimme FinWAF-aineistossa naissukupuolen vaikutusta aivoinfarkti-, verenvuoto- ja kuolleisuusriskiin. Kun ikä ja taustasairaudet otettiin huomioon, sukupuolieroa aivoinfarktiriskissä ei todettu. Naisilla verenvuotoriski ja kuolleisuus olivat miehiä matalammat.

Varfariinia käyttävillä potilailla hoidon laadun seuranta on tärkeä osa hoitoa. Laatua voidaan arvioida käyttämällä TTR-arvoa (the time in therapeutic range). Arvioimme tutkimuksessamme varfariinihoidon laatua 60 vuorokautta ennen jokaista päätetapahtumaa (TTR60). TTR60 korreloi lineaarisesti sydäninfarkti- ja verenvuotoriskin sekä kuolleisuuden kanssa. Sukupuolieroa aivoinfarktiriskissä ei todettu, kun TTR60 oli yli 50%.

Tietoa eteisvärinäpotilaiden lääkehoitojen käytöstä on vähän. FinFib2-aineistossa verenohennuslääkitys (useimmiten varfariini) oli käytössä 76%:lla niistä potilaista, joilla oli ensiapuun tullessa aiempi eteisvärinädiagnoosi ja CHA2DS2-VASc-pisteytys vähintään kaksi. Kotiutusvaiheessa näistä potilaista 86%:lle määrättiin verenohennuslääkitys. Ensimmäistä kertaa eteisvärinädiagnoosin saaneista potilaista 80%:lle aloitettiin verenohennuslääkitys. Vaikka korkean aivoinfarktiriskin potilaat tunnistettiin hyvin ja verenohennuslääkitys aloitettiin useimmille, hoidon laadussa todettiin puutteita. Vain 59%:lla potilaista INR oli hoitotavoitteessa ensiapuun tullessa.

Rytmihäiriölääkkeiden käyttöä arvioitiin FinFib2-aineistossa. Yleisimmin käytetyt rytmihäiriölääkkeet olivat beetasalpaajaryhmän lääkkeet (81%). Ryhmän I (11%) ja

III (9%) rytmihäiriölääkkeiden käyttö oli vähäistä potilailla, joilla oli aiempi eteisvärinädiagnoosi. Myös näiden lääkkeiden annosmuutokset olivat ensiapukäynnin yhteydessä harvinaisia (7%).

Yhteenveto:

Kohonnut verenpaine oli tutkimuksessamme yleisin sydän- ja verisuonitautien riskitekijä suomalaisilla eteisvärinäpotilailla. Se vaikuttaa lisäävän eteisvärinään liittyvää oireisuutta ja sen rooli korostuu ensiapuun hakeutuvien oireisten potilaiden kohdalla. Kohonneen verenpaineen hoito onkin tärkeää paitsi eteisvärinän ehkäisemisessä, myös siihen liittyvien oireiden vähentämisessä. Osoitimme CHA2DS2-VASc-pisteytyksen ennustavan hyvin verenohennuslääkitystä käyttävien eteisvärinäpotilaiden sydäninfarktiriskiä ja totesimme sen soveltuvan sydäninfarktiriskin arviointiin näillä potilailla. Korkean aivoinfarktiriskin potilaat tunnistettiin ensiavuissa hyvin, mutta verenohennuslääkityksen laadussa oli puutteita. Varfariinihoidon laatu vaikuttaa tutkittujen päätetapahtumien ilmaantumiseen ja siinä tulisi pyrkiä korkeaan TTR-arvoon (TTR yli 80%) päätetapahtumien minimoimiseksi. Sukupuolten välillä ei todettu eroa aivoinfarktiriskissä. Rytmihäiriölääkkeitä käytetään eteisvärinän sykekontrollissa hyvin, mutta estolääkitysten (luokka I ja III) käyttö on vähäistä. Lääkäreiden koulutusta rytmihäiriölääkkeiden käytöstä tulisi lisätä, jotta voitaisiin vähentää eteisvärinään liittyviä sairaalahoitoja ja potilaiden oireita.

CONTENTS

1 Introduction 17

2 Review of the literature 19

2.1 Atrial fibrillation 19

2.1.1 Mechanisms 19

2.1.2 Epidemiology 20

2.1.3 Risk factors 21

2.2 Risk of thromboembolic complications in atrial fibrillation 22

2.2.1 Risk of stroke and transient ischemic attack 22

2.2.2 Risk stratification for stroke and transient ischemic attack – the CHA2DS2-VASc score 22

2.2.3 Risk stratification for bleeding – the HAS-BLED score 24

2.2.4 Indications for oral anticoagulation therapy 24

2.3 Mortality and cardiovascular morbidity in patients with atrial fibrillation 25

2.3.1 Cardiovascular and all-cause mortality 25

2.3.2 Myocardial infarction 26

2.3.3 Heart failure 27

2.4 Oral anticoagulation therapy 28

2.4.1 Mechanism of action 28

2.4.1.1 Warfarin 28

2.4.1.2 Direct oral anticoagulants 28

2.4.2 INR and the time in therapeutic range (TTR) 29

2.4.3 Effect of oral anticoagulation on the risk of thromboembolic complications 30

2.4.4 Effect of oral anticoagulation on mortality and cardiovascular morbidity 31

2.4.4.1 Mortality 31

2.4.4.2 Bleeding events 32

2.4.4.3 Myocardial infarction 32

2.5 Antiarrhythmic medication in patients with atrial fibrillation 33

2.5.1 Classification of antiarrhythmic drugs according to Vaughan-Williams 33

2.5.2 Mechanisms of action 34

2.5.3 Indications and efficacy of antiarrhythmic drugs in AF 37

2.5.3.1 Rate control 37

2.5.3.2 Rhythm control 38

2.6 Use of medical therapy in prior studies 39

2.6.1 Oral anticoagulation therapy 39
2.6.2 Antiarrhythmic drug therapy 40
2.7 Efficacy and safety of medical therapy compared with invasive procedures 41
2.7.1 Anticoagulation vs. left atrial appendage closure 41
2.7.2 Antiarrhythmic drug therapy vs. catheter ablation 42

3 Aims of the study 45

4 Materials and methods 46
4.1 The FinFib2 population 46
4.2 The FinWAF population 49

5 Results 55
5.1 Characteristics of atrial fibrillation patients in Finland (I and IV) 55
5.2 Risk stratification of stroke and other cardiovascular outcomes 56
5.2.1 The CHA2DS2-VASc score and a risk of myocardial infarction 56
5.2.2 The female sex as a risk factor for stroke, bleeding events, and mortality 58
5.3 The quality of warfarin therapy and clinical outcome 59
5.3.1 The overall quality of oral anticoagulation therapy 59
5.3.2 The Association between TTR and the risk of myocardial infarction and cardiovascular mortality 60
5.3.3 Impact of the female sex on the association between TTR and the risk of stroke, bleeding events, and mortality 62
5.4 Use of oral anticoagulation therapy 64
5.5 Use of antiarrhythmic medication 65

6 Discussion 67
6.1 Main findings of the study 67
6.2 Risk factors of atrial fibrillation 68
6.3 Risk stratification of stroke and other cardiovascular outcomes 70
6.3.1 The CHA2DS2-VASc score and myocardial infarction 70
6.3.2 Female sex as a risk factor for stroke, bleeding events, and mortality 71
6.4 Quality of warfarin therapy and clinical outcome 72
6.4.1 Association between TTR and the risk of myocardial infarction and cardiovascular mortality 72
6.4.2 Impact of the female sex on the association between TTR and the risk of stroke, bleeding events, and mortality 74
6.5 Use of medical therapies in patients with atrial fibrillation in the emergency department 75
6.5.1 Oral anticoagulation therapy 75

6.5.2 Antiarrhythmic drug therapy 76

7 Limitations 79

8 Summary and conclusions 81

9 Acknowledgements 83

10 References 85

11 Publications 101

ABBREVIATIONS

AAD	antiarrhythmic drug
ACS	acute coronary syndrome
AF	atrial fibrillation
APD	action potential duration
CED	cohort entry date
CHA2DS2-VASc	a risk score to estimate a stroke risk in patients with AF
DOAC	direct oral anticoagulant
EF	ejection fraction
ERP	effective refractory period
ESC	European Society of Cardiology
HAS-BLED	a risk score to estimate a bleeding risk in patients with AF
HF	heart failure
HR	hazard ratio
LAA	left atrial appendage
LMWH	low molecular weight heparin
LV	left ventricle
MACE	major adverse cardiac event
MI	myocardial infarction
NOAC	non-vitamin K oral anticoagulant
OAC	oral anticoagulation
OSA	obstructive sleep apnea
RCT	randomized controlled trial
RFA	radiofrequency catheter ablation
TMP	transmembrane potential
TTR	time in therapeutic range
VKA	vitamin-K antagonist

ORIGINAL PUBLICATIONS

This dissertation is based on the following four original articles, which are referred to in the text by their Roman numerals, I-IV.

I. Penttilä T, Mäkynen H, Hartikainen J, Lauri T, Lehto M, Lund J, Mäkijärvi M, Raatikainen P. Anticoagulation therapy among patients presenting to the emergency department with symptomatic atrial fibrillation – the FinFib2 study. Eur J Emerg Med. 2017;24:347-352. doi: 10.1097/MEJ.0000000000000402.

II. Penttilä T, Mäkynen H, Hartikainen J, Hyppölä H, Lauri T, Lehto M, Lund J, Raatikainen MJP. Antiarrhythmic drug therapy among patients presenting to emergency department with symptomatic atrial fibrillation – a prospective nationwide cohort. Scand J Trauma Resusc Emerg Med. 2017;15:81. doi: 10.1186/s13049-017-0424-7.

III. Raatikainen MJP, Penttilä T, Korhonen P, Mehtälä J, Lassila R, Lehto M. The quality of warfarin therapy and CHA2DS2-VASc score associate with the incidence of myocardial infarction and cardiovascular outcome in patients with atrial fibrillation. Data from the nationwide FinWAF registry. Eur Heart J Cardiovasc Pharmacother. 2018 Mar 5. doi: 10.1093/ehjcvp/pvy009.

IV. Penttilä T, Lehto M, Niiranen J, Mehtälä J, Khanfir H, Lassila R, Raatikainen P. Differences in the risk of stroke, bleeding events, and mortality between female and male patients with atrial fibrillation during warfarin therapy. Eur Heart J Cardiovasc Pharmacother. 2018 Jul 21. doi: 10.1093/ehjcvp/pvy026.

1 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults (Kannel et al. 1982). Furthermore, the incidence of AF has been increased rapidly during the last few decades (McDonald et al. 2008, Chugh et al. 2014). It has been estimated that there will be 14-17 million patients with AF in Europe in 2030. AF is associated with significant morbidity and mortality, which has led to high AF-related health care costs. Hence, AF has major public health implications (Magnani et al. 2011, Zoni-Berisso et al. 2014).

To fight against the worldwide AF epidemic, the risk factors and complications of AF should be recognized and treated early. The rising prevalence and incidence of AF is mainly due to population aging, lifestyle changes, improved detection of the disease, and longer survival following the onset of AF (Schnabel et al. 2015). The treatment of AF patients consists of identifying and treating concomitant diseases, prescribing OAC for patients at a high thromboembolic risk, and opting for rhythm or rate control strategy individually (Kirchhof et al. 2016).

Physicians in emergency departments (ED) have an important role in diagnosing AF, identifying risk factors, and optimizing therapies for AF, as the AF burden in EDs is increasing. The first two studies in this thesis were focused on evaluating AF patient risk factors and treatment in an ED setting; firstly recognizing high thromboembolic risk patients and the use of OAC therapies and, secondly, the use of antiarrhythmic medications (AAD). The results were analyzed in light of

contemporary clinical practice guidelines (Camm et al. 2012) and compared to similar types of studies in other countries.

In two other studies of this thesis, the focus was on the evaluation of the quality of OAC and its association with myocardial infarction (MI) and sex-related differences in the risk of stroke, bleeding events, and mortality. The CHA2DS2-VASc score was also validated to assess the risk of MI in patients with AF using OAC.

It is important to investigate the risk factors of AF in order to establish the primary preventive strategies and to improve individualized patient care. It is also crucial to evaluate the adherence of clinical practice guidelines and to optimize fluent patient care in the health care system. This information can be used to assess the need for health care professional education.

2 REVIEW OF THE LITERATURE

2.1 Atrial fibrillation

2.1.1 Mechanisms

AF is a complex arrhythmia, characterized by extremely rapid atrial rate (350-600 bpm) and irregular ventricular rhythm. It is classified as paroxysmal (<7 days), persistent (>7 days), long-standing persistent (>1 year and rhythm control strategy), or permanent by its duration (Kirchhof 2016). Sustained AF requires a trigger and a substrate. The trigger for an initiation of paroxysmal arrhythmia is most often a focal atrial ectopy, caused by enhanced electrical activity in the cardiomyocyte sleeves of pulmonary veins (Haissaguerre et al. 1998). Non-pulmonary vein triggers are more common in patients with persistent AF. Rapid focal activity or atrial re-entry are the primary driver mechanisms in AF. The role of re-entry is important as a substrate for AF, especially in a structurally modified atria. (Ferrari et al. 2014, Lau et al. 2017)

Sustained AF leads to electrophysiological remodeling. Changes in K+ and Ca2+ currents in the atrial cardiomyocyte cell membrane causes a shortening of the action potential duration (APD) and effective refractory period (ERP) (Nattel et al. 2008). Electrophysiological remodeling is associated with a higher incidence of delayed afterdepolarizations and triggered activity (Voigt et al. 2014).

Structural remodeling of the atria, mainly fibrosis and hypertrophy, act as a substrate for persistent AF (Mahnkopf et al. 2010). Its development takes longer than

electrophysiological remodeling. Age, hypertension, cardiac comorbidities, and other external stressors induce a slow but progressive structural remodeling in the atria (Nattel et al. 2014). This includes the activation of fibroblasts, enhanced connective tissue deposition, and fibrosis (Chimenti et al. 2010).

2.1.2 Epidemiology

The prevalence and incidence of AF are rising worldwide (Chugh et al. 2014). In older studies, the estimated prevalence of AF ranged between 0.5-1% in developed countries (Go et al. 2001, Murphy et al. 2007). More recent studies indicate that the prevalence of AF has doubled (1.9-2.9%) in European countries during the last decade (Zoni-Berisso et al. 2014). There is a significant local variation in the prevalence between continents and countries; the highest prevalence rates have been reported in North America and the lowest in the Asia Pacific region (Chugh et al. 2014). The prevalence of AF also varies markedly with age. AF is a rare arrhythmia among subjects under 60 years of age, but in those over 75 years of age, the prevalence is increased up to 10%. The increasing prevalence of AF worldwide may be explained by the aging of the population, improved detection of disease, longer survival following the onset of AF, and changes in lifestyle variables. (Schnabel et al. 2015)

Less data is available on the incidence of AF, and more variability in populations and methods to define AF. In Europe, the incidence of AF has been reported to be 0.23-0.9 per 1000 person/years in general populations, but markedly higher among elderly people over 85 years old (6.2-33.5 per 1000 person/years) (Zoni-Berisso et al. 2014).

The prevalence and incidence of AF in Finland are not well-known, but it has been estimated that in 2011, there were about 100 000 patients with AF (Lehto et al. 2011).

2.1.3 Risk factors

Clinical risk factors associated with the risk of AF can be divided into two categories: cardiovascular and modifiable lifestyle risk factors. Several cardiovascular risk factors are known to be independent predictors of AF development (Lau et al. 2017). The Framingham Heart Study identified advanced age, hypertension, congestive heart failure, coronary artery disease, valvular heart disease, and diabetes as independent cardiovascular risk factors for AF (Benjamin et al. 1994). Obesity and excessive weight is a growing risk factor worldwide, and along with aging, it is a major factor in the AF epidemic (Du et al. 2017). Obstructive sleep apnea (OSA) has also been identified to be an important risk factor for AF (Gami et al. 2004). Recently, the ARIC investigation demonstrated that suboptimal cardiovascular risk factor control could account for over 50% of AF cases seen in the middle-aged population (Huxley et al. 2011).

Several modifiable lifestyle risk factors for AF have also been identified. According to two large meta-analyses, excessive alcohol consumption has a direct linear correlation with the risk of AF (Kodama et al. 2011, Larsson et al. 2014). Further, physical activity and cardiovascular fitness are closely associated with the risk of AF. In light of large scale of studies, the correlation seems to be U-shaped; moderate physical activity decreases the risk of AF, whereas both very intensive endurance training and physical inactivity increases the risk. Some studies have also indicated that emotions (anger, tension, stress) are associated with an increased AF risk (Boriani et al. 2017).

2.2 Risk of thromboembolic complications in atrial fibrillation

2.2.1 Risk of stroke and transient ischemic attack

AF is an independent risk factor for stroke and thromboembolisms (Benjamin et al. 1998). In AF, atria lose their normal contractility, which slows blood flow and predisposes to thrombus formation and systemic embolization to the brain. The typical primary localization for thrombus formation is the left atrial appendage (LAA) (Blackshear et al. 1996); additionally, vessel wall endothelial injury and hypercoagulability have also been demonstrated in AF (Brown et al. 2017). AF increases the risk of stroke or TIA by five-fold (Wolf et al. 1987). The findings from recent studies and registries have shown that at least 25-35% of patients with ischemic stroke, and over 80% of those with cardioembolic ischemic stroke, had AF. In over 25% of the cases, stroke was the first manifestation of previously unknown AF (Freedman et al. 2016). Patients with AF-related thromboembolic stroke have a higher mortality, morbidity, and longer hospital stays than patients with other stroke subtypes (Kannel et al. 1998).

2.2.2 Risk stratification for stroke and transient ischemic attack – the CHA2DS2-VASc score

The risk of thromboembolic complications is not homogenous and varies by the presence of other stroke risk factors. The Stroke in AF Working group identified the risk factors for stroke in a systematic review of studies using multivariate regression techniques. They found prior stroke or TIA (relative risk 2.5, 95% CI 1.8-3.5), increasing age (RR 1.5 per decade, 95% CI 1.3-1.7), hypertension (RR 2.0, 95% CI 1.6-2.5), and diabetes mellitus (RR 1.7, 95% CI 1.4-2.0) to be the strongest and most consisted risk factors for stroke in patients with AF. A left ventricular systolic

dysfunction was an independent predictor of thromboembolic complication in a multivariate analysis. (Stroke in AF Working group 2007) In another systematic review, previous stroke or TIA, an age of over 75 years, hypertension, structural heart disease, and previous myocardial infarctions were identified as strong risk factors for stroke. The evidence of diabetes mellitus as an independent predictor of stroke was not considered convincing, but it was still regarded as an important indicator for increased risk in the general AF population. (Hughes et al. 2008)

The results of some studies indicate that female patients with AF may are at an increased risk of stroke and peripheral embolism (Friberg et al. 2012, Lane et al. 2009, Piccini et al. 2016, Camm et al. 2017, Dagres et al. 2007), while others have found an association between the risk of stroke and sex only in a group of 75-year-olds and above (Mikkelsen et al. 2012, Wagstaff et al. 2014). A prospective Danish register study failed to show any increase in the risk of stroke in female AF patients without anticoagulation after the adjustment for lifestyle, antithrombotic therapy, and relevant comorbidities (Overvad et al. 2014). In many prior studies, female patients have been older and had more concomitant diseases compared with males (Overvad et al. 2014, Piccini et al. 2016, Gomberg-Maitland et al. 2006). In some studies of residual stroke risk in anticoagulated AF patients, INR control during warfarin therapy has been worse in women compared with men, or the assessment of a quality of OAC has been poor (Sullivan et al. 2012, Vinereanu et al. 2015). Recent studies indicate that after adjustment for baseline characteristics, there is no sex-related difference in the residual risk of stroke among patients with high-quality OAC therapy (Senoo et al. 2016, Renoux et al. 2017).

The European Society of Cardiology (ESC) clinical practice guidelines encourage the use of the CHA2DS2-VASc score to estimate the risk of stroke in patients with AF (Kirchhof et al. 2016). The score has been validated in AF patients without OAC therapy and widely used (Lip et al. 2010). It consists of AF risk factors based on

contemporary literature: congestive heart failure (1 point), hypertension (1 point), age 75 or older (2 points), diabetes mellitus (1 point), previous stroke, TIA or thromboembolism (2 points), vascular disease (1 point), age 65-74 years (1 point), and female sex (1 point). Compared to the previously used CHADS2 score, it better recognizes patients at a low risk of thromboembolic complications (Olesen et al. 2011).

2.2.3 Risk stratification for bleeding – the HAS-BLED score

Several factors have been identified to increase AF patient risk of major bleeding during OAC therapy. The assessment of bleeding risk using the HAS-BLED score should focus attention on reversible bleeding risk factors (Freedman et al. 2016). The HAS-BLED score consists of hypertension (1 point), renal or liver dysfunction (1 point each), stroke history (1 point), prior major bleeding or predisposition to bleeding (1 point), labile INR or TTR <60% (1 point), elderly age (1 point), excessive alcohol/drug history or medication usage predisposing to bleeding (1 point), all of which have been defined as risk factors for major bleeding. The HAS-BLED score has been validated in 2010 with data from the Euro Heart Survey. (Pisters et al. 2010)

2.2.4 Indications for oral anticoagulation therapy

OAC therapy in AF reduces strokes, thromboembolic complications, and mortality in high- and moderate-risk patients (Hart et al. 1999). The annual risk for thromboembolic events increases with the CHA2DS2-VASc score in patients not on OAC. For moderate-risk patients (CHA2DS2-VASc score 1), the annual stroke risk is 1.3%, and for high-risk patients (CHA2DS2-VASc score >=2) 2.2-15.2% (Lip et al. 2010). According to the ESC 2016 clinical practice guidelines, there is strong evidence that patients with the CHA2DS2-VASc score of 2 or more in men and 3

or more in women, benefit from OAC, and these patients should be anticoagulated. On the other hand, patients at a low risk (CHA2DS2-VASc score 0) do not benefit from OAC therapy and should not be anticoagulated (Kirchhof et al. 2016). The evidence based on recent studies indicate that patients with only one additional risk factor (CHA2DS2-VASc score of 1 for men and 2 for women) may benefit from OAC, but the rates of thromboembolic events vary due to differences in population (Olesen et al. 2011, Chao et al. 2015 (A), Lip et al. 2015 (B)).

In AF patients with an indication for anticoagulation therapy, the bleeding risk should also be evaluated. The Finnish multicenter register study (FibStroke) showed that ischemic stroke is the predominant complication compared to intracranial bleeding, regardless of the CHA2DS2-VASc score level, also in patients in anticoagulation therapy. Intracranial bleeds outweighed ischemic strokes only in patients with a HAS-BLED score of over 4. (Jaakkola et al. 2018) A high HAS-BLED score should not firmly lead to withholding anticoagulation therapy, but emphasize the improvement of treatment or the elimination of bleeding risk factors (Kirchhof et al. 2016).

2.3 Mortality and cardiovascular morbidity in patients with atrial fibrillation

2.3.1 Cardiovascular and all-cause mortality

All-cause mortality in patients with AF compared to those with no AF is two times higher in females and 1.5 times higher in males (Benjamin et al. 1998). In the Swedish cohort, patients with incident AF had a significant increase in all-cause mortality compared with the controls; the risk remained significant after adjustment for comorbidities. Without adjustment for concomitant diseases, the actual mortality

rate was lower in females compared with males in all age groups, but the age-adjusted relative mortality risk in AF patients was higher in women than in men compared with controls in all age categories during the 14 years follow-up period. (Andersson et al. 2013) In the meta-analysis by Edmin et al., AF was associated with a stronger relative risk of all-cause and cardiovascular mortality in women compared with men (2016).

2.3.2 Myocardial infarction

Coronary artery disease (CAD) and AF have a close relationship and interact with each other (Violi et al. 2016). They share many common cardiovascular risk factors. CAD is not only a risk factor for AF, but also a disease which outcome is modulated by AF (Pang et al. 2017, Almendro-Delia et al. 2014). Myocardial infarction (MI) is a well-established risk factor for the development of AF (Lip et al. 2010, Goranek et al. 2012), and AF is associated with an increased risk of MI (Shahid et al. 2018). The high prevalence of MI in patients with AF has been demonstrated in the REGARDS study, which found that AF was associated with a double increase in MI (Soliman et al. 2014). Further support for the independent role of AF in patient MI risk was seen in the study by Chao et al., which showed that AF patients with a CHA2DS2-VASc score of 0 or 1 were at a greater risk of MI than those without AF (Chao et al. 2014). Furthermore, the coexistence of the two diseases dramatically increases the risk of future cardiovascular events and stroke (Akao 2014). Thus, early detection of AF is important not only to start OAC therapy in order to prevent stroke, but also for the introduction of cardiovascular prevention strategies. The 2MACE score was proposed to help in the risk stratification of AF patients who would benefit from preventive strategies the most. The 2MACE score included the metabolic syndrome and age of over 75 years (2 points), prior MI/revascularization (1 point), congestive heart failure (1 point), and prior thromboembolism (1 point). The score was validated in > 2000 AF patients, and a 2MACE score of 3 or more identified patients

at the highest risk for MACE. (Pastori et al. 2016) However, it would be compelling to use the same risk score in assessing thromboembolic and cardiovascular risk. The CHA2DS2-VASc score has been shown to positively correlate with the AMI rate in patients with AF and was suggested to be used as a risk score in cardiovascular risk stratification (Kim et al. 2015, Pang et al. 2017).

2.3.3 Heart failure

AF and heart failure (HF) are linked to similar cardiovascular risk factors. HF may predispose to the development of AF – and vice versa – AF may cause HF. The proposed mechanisms for HF-induced AF include impaired left ventricular filling and atrial remodeling (Melenowsky et al. 2015). High ventricular rate during AF causes rate-related impairment of left ventricular (LV) ejection fraction (EF) (Van Gelder et al. 2016). Heart failure with both preserved EF (HFpEF) or reduced EF (HFrEF) increases the risk of AF (Mamas et al. 2009). The relative risk of AF is greater in patients with HFpEF, reflecting the greater burden of such AF risk factors as advanced age, obesity and hypertension in that group. Moreover, HFpEF is more often characterized by increased left atrium stiffness and HFrEF by greater eccentric left atrium remodeling, further explaining the uneven AF burden between the two HF subtypes. Over 35% of patients diagnosed with AF will subsequently be diagnosed with HF and vice versa (Brown et al. 2017). According to the meta-analysis of Kotecha et al., there is no significant difference in the risk of stroke between patients with HFpEF and HFrEF, but all-cause mortality seems to be higher in patients with HFrEF (Kotecha et al. 2016).

2.4 Oral anticoagulation therapy

2.4.1 Mechanism of action

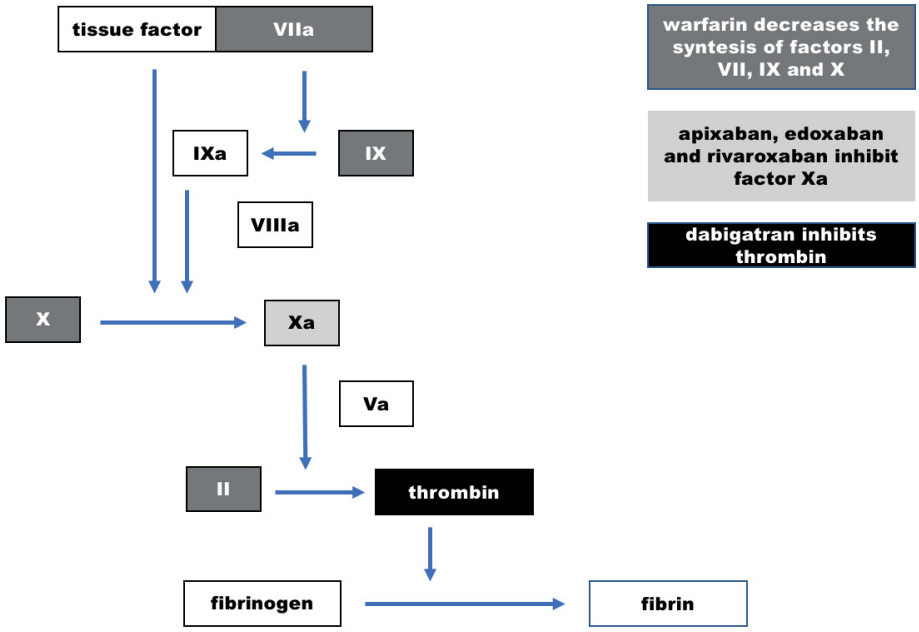
2.4.1.1 Warfarin

Warfarin is a 4-hydroxycoumarin residue, which acts as a vitamin K antagonist (VKA). It affects several vitamin K-dependent reactions in the liver (Figure 1) and decreases the capacity of factors II, VII, IX and X to activate coagulation sequences. There is a large genetic variation in the metabolism of warfarin, and it has several clinically significant food and drug interactions. Its antithrombotic effect should be monitored regularly. (Wessler et al. 1986)

2.4.1.2 Direct oral anticoagulants

Direct oral anticoagulants (DOACs), also called non-vitamin K antagonists (NOACs), have emerged as an alternative to VKAs for the prevention of thromboembolic complications in patients with non-valvular AF. Dabigatran is a direct thrombin (factor II) inhibitor, whereas apixaban, edoxaban and rivaroxaban inhibit activated factor Xa (Heidbuchel et al. 2015) (Figure 1). Their clinical efficacy and safety compared with warfarin in stroke prevention in AF has been studied in large controlled randomized studies (Connolly et al. 2009, Patel et al. 2011, Granger et al. 2011, Giuliano et al. 2013).

Figure 1. Blood coagulation cascade. Warfarin decreases the capacity of factors II, VII, IX and X to activate blood coagulation sequence. Dabigatran is a direct thrombin inhibitor. Apixaban, edoxaban and rivaroxaban inhibit activated factor Xa (Figure modified from Lassila 2011).



2.4.2 INR and the time in therapeutic range (TTR)

The intensity of anticoagulation with warfarin is followed by measuring prothrombin time (PT). The values are reported as an International Normalized Ratio (INR), which makes measurements performed in different laboratories comparable (Hirch et al. 1998). INR is a marker of the intensity of anticoagulation at the moment of the

blood test. It does not describe the quality of warfarin therapy in a longer period of time.

The time in therapeutic range (TTR) is a calculated value used in clinical practice and trials to estimate the quality of warfarin therapy during a longer follow-up. The most commonly used method is the linear extrapolation method by Rosendaal (1993). It assumes that the INR between two measurements varies linearly. TTR is reported as a percentage of time the INR was on a therapeutic level. The results of recent studies indicate that the higher the TTR, the better the outcome with regard to the incidence of stroke and mortality (Lehto et al. 2017, Liu et al. 2017, Senoo et al. 2016, Pokorney et al. 2015).

2.4.3 Effect of oral anticoagulation on the risk of thromboembolic complications

In patients with AF, VKA therapy reduces the risk of stroke by 64% compared with placebo and 39% compared with antiplatelet agents. It also reduces the risk of all-cause mortality by 25% compared with controls. (Hart et al. 2007) The quality of warfarin therapy is crucial. It has previously been suggested to aim for at least TTR 60-70%, but recent data indicate that the risk of stroke is reduced linearly up to TTR >80%. In the FinWAF study, the stroke rate was 3.1/100 patient years in patients with TTR60 >80% compared with 9.3/100 patient years in patients with TTR60 <40%. (Lehto et al. 2017)

All currently available DOACs have been shown to be at least as effective as warfarin in the prevention of stroke in randomized controlled trials. Their safety profile is better or at least on the same level as that of warfarin. (Connolly et al. 2009, Patel et al. 2011, Granger et al. 2011, Giuliano et al. 2013) The results from studies in a real-world setting have confirmed the main findings of the randomized controlled trials

(Ruff et al. 2014, Ntaios et al. 2017). However, no trial has directly compared different DOACs with each other.

2.4.4 Effect of oral anticoagulation on mortality and cardiovascular morbidity

2.4.4.1 Mortality

In the analysis by Roskell et al., the median all-cause mortality in randomized controlled trials in AF patients treated with warfarin was 4.5 per 100 patient years (2.9-8.0 per 100 patient years), and the incidence of vascular mortality 2.6 per 100 patient years (1.5-6.7 per 100 patient years). About half (52%) of the deaths were classified as vascular. (Roskell et al. 2013)

In the ARISTOTLES and the RE-LY trials, apixaban was associated with 11% and dabigatran 150 mg bid. with a 10% mortality reduction, respectively (Connolly et al. 2009, Granger et al. 2011). Edoxaban significantly reduced the incidence of cardiovascular mortality compared with warfarin in the ENGAGE-AF trial (Guigliano et al. 2013). Rivaroxaban was not associated with a reduction in mortality in the ROCKET-AF trial (Patel et al. 2011). In the meta-analysis of Ntaios et al., apixaban and dabigatran were associated with a lower risk of mortality and rivaroxaban with a similar risk of mortality compared with warfarin (Ntaios et al. 2017). In a meta-analysis of Lopez-Lopez et al., the all-cause mortality was lower with all DOACs than with warfarin (Lopez-Lopez et al. 2017).

2.4.4.2 Bleeding events

OAC is effective in reducing the risk of stroke and mortality. On the other hand, it increases clinically significant bleeding events, which diminishes its net clinical benefit. The fear of major bleeding events commonly leads to an underuse of OAC in patients at a high thromboembolic risk (Palomäki et al. 2016). Therefore, a proper assessment of the risk of both thromboembolic and bleeding events should be done individually (Gallego et al. 2013).

Roskell et al. have studied the bleeding risk of patients with AF during VKA therapy. The systematic review of literature included randomized controlled trials (RCT) and observational studies with a cumulative follow-up of 61563 patient years for RCTs and 484241 patient years for observational studies. The overall median incidence of major bleeding was 2.1 per 100 patient years (0.9-3.4 per 100 patient years) for RCTs and 2.0 per 100 patient years (0.2-7.6 per 100 patient years) for observational studies. Additionally, a trend towards an increasing incidence of major bleedings over time was noted. The differences in the definition of major bleeding events between studies and heightened awareness of major bleeding, and therefore increased reporting, may explain this trend. There may also be more interactions with VKA and contemporary medications, leading to increased bleeding risk over time. (Roskell et al. 2013) In the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE-AF trials, hazard ratios (HR) for major bleeding events compared with warfarin were 0.80-0.94 (0.69-0.93), 1.04 (0.90-1.20), 0.69 (0.60-0.80), and 0.80 (0.71-0.91), respectively (Connolly et al. 2009, Patel et al. 2011, Granger et al. 2011, Giuliano et al. 2013).

2.4.4.3 Myocardial infarction

Warfarin therapy lowers the risk of MI recurrence in patients without AF and previously documented acute coronary syndrome (ACS) (Cohen et al. 1994, Hurlem

et al. 2002). However, the impact of the quality of warfarin therapy on the incidence and outcome on MI has not been studied previously in patients with AF in detail.

In the RE-LY trial, dabigatran was associated with an increased risk of MI compared with warfarin (Connolly et al. 2009); this finding has also been supported by the meta-analysis of Douxfils et al. It has been speculated, that warfarin might be more protective against MI than dabigatran (Douxfils et al. 2014). In contrast, the Danish register study of over 30000 AF patients on OAC that investigated the risk of MI associated with the use of apixaban, dabigatran, rivaroxaban, and warfarin found no significant differences in the risk of MI in direct comparisons of DOACs. All DOACs were associated with a significant risk reduction of MI compared with warfarin (Lee et al. 2018).

2.5 Antiarrhythmic medication in patients with atrial fibrillation

2.5.1 Classification of antiarrhythmic drugs according to Vaughan-Williams

AADs are commonly classified by the Vaughan-Williams classification first introduced in 1970 (Table 1). The classification is based on the mechanism of action of a given AAD (Vaughan-Williams 1970, Vaughan-Williams 1984).

Table 1. Classification of antiarrhythmic drugs by Vaughan-Williams.

Classification	Agents	Mechanism of action	Notes
IA	Disopyramide Quinidine Procainamide	Sodium channel blockade with intermediate association/dissociation and potassium channel blockade	Contraindicated in patients with structural heart diseases
IB	Lidocaine Mexiletine	Sodium channel blockade with rapid association/dissociation	Not indicated for AF
IC	Flecainide Propafenone	Sodium channel blockade with slow association/dissociation	Contraindicated in patients with structural heart diseases
II	Atenolol Asebutolol Betaxolol Bisoprolol Carvedilol Metoprolol Nebivolol Pindolol Propranolol Seliprolol	Beta adrenergic receptor blockade	Can be used also in patients with structural heart disease More effective in rate than rhythm control
III	Amiodarone Dronedarone Sotalol Vernakalant	Potassium channel blockade Amiodarone and dronedarone have also class I, II and IV activity Sotalol has also class II activity Vernakalant blocks sodium and potassium channels in atria but not in ventricles	Dronedarone is contraindicated in severe heart failure and permanent AF Extra cardiac adverse events (e.g., liver and pulmonary toxicity and thyroid dysfunction) are common with amiodarone Vernakalant is available only for acute intravenous use
IV	Verapamil Diltiazem	Calcium channel blockade	Should be avoided in patients with congestive heart failure
Others	Digoxin	Variable mechanisms	May have adverse effect on the prognosis of patients with AF

2.5.2 Mechanisms of action

Class I AADs slow the rapid influx of sodium ion (Na+) into the cell by blocking fast Na+ channels in the cardiomyocyte membrane. As a result, they slow the fast

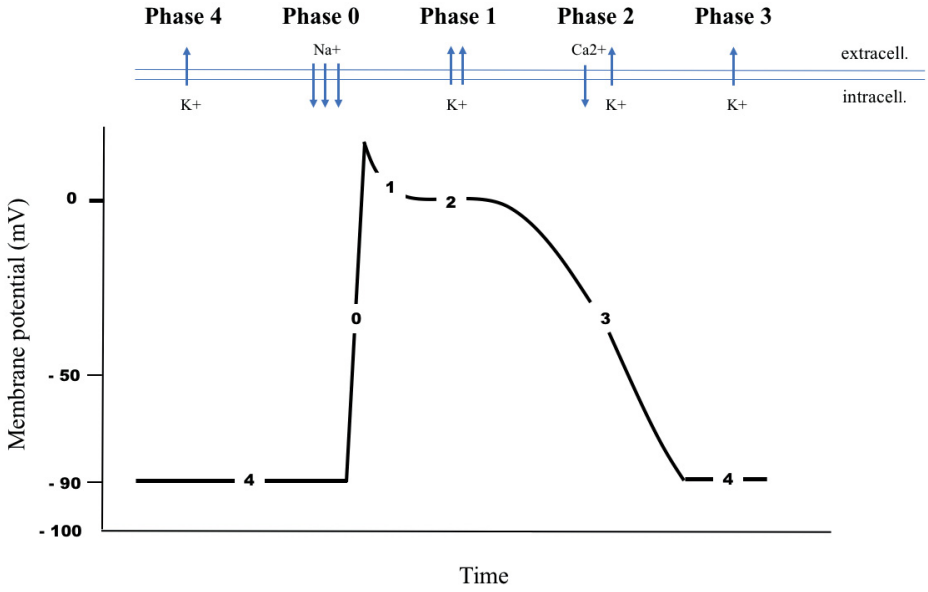
upstroke of action potential phase 0 and depolarization. Class IC agents (flecainide, propafenone) have a significant effect on slowing action potential phase 0 upstroke, but little effect on action potential duration (APD) and repolarization. Class IA agents (quinidine, procainamide, disopyramide) have a minor effect on slowing phase 0 action potential, but they prolong more APD and repolarization (Ng 2017).

Class II AADs are beta blockers; they decrease sympathetic activity by blocking β-receptors. Metoprolol and bisoprolol are the most used β-receptor blockers in AF patients. They are β1-selective, which means they are cardio selective and have a minor effect on β2-receptors. Propranolol has an effect on both β1- and β2-receptors. Carvidilol additionally effects α-receptors (Singh 2005).

Class III AADs prolong APD and repolarization mostly by blocking outward potassium ion (K+) channels. Sotalol blocks β1- and β2-receptors on a low dosage, but have a class III effect on higher dosages by prolonging the action potential phase 3 and decreasing the slope of action potential phase 4 (Singh 2005, Ng 2017). Amiodarone prolongs action potential phase 3, but also has class I, II, and IV activity. Dronedarone is a synthetic analogue of amiodarone with no iodine, and it has similar electrophysiological properties to amiodarone (Kozlowski et al. 2012).

Class IV AADs are calcium channel blockers. They slow the calcium ion (Ca2+) channel and prolong action potential phase 2. They can be used in rate control of AF to relieve symptoms associated with rapid ventricular rate and to improve the quality of life associated with AF (Ng 2017).

Figure 2. Cardiac cell action potential. In phase 0 (depolarization), there is a rapid Na+ influx through open fast Na+ channels. In phase 1 (early repolarization), transient K+ channels open and the K+ efflux returns transmembrane potential (TMP) to 0 mV. In phase 2 (the plateau phase), the influx of Ca2+ through L-type Ca2+ channels is electrically balanced by K+ efflux through delayed rectifier K+ channels. In phase 3 (repolarization), Ca2+ channels close but delayed rectifier K+ channels remain open and return TMP to -90 mV. In phase 4 (the resting phase), Na+ and Ca2+ channels are closed, and open K+ rectifier channels keep TMP stable at -90 mV (Nerbonne et al. 2005, figure modified from Ikonnikow & Wong).



2.5.3 Indications and efficacy of antiarrhythmic drugs in AF

2.5.3.1 Rate control

Antiarrhythmic medication is used to decrease ventricular rate during AF (rate control strategy) and to prevent AF recurrence episodes (rhythm control strategy) in symptomatic patients. Rate control therapy should be considered for all patients with AF, if needed, both in rate and rhythm control strategies (Kirchhof et al. 2016). The efficacy and safety of beta blockers (class II) and calcium channel blockers (class IV) are well established in acute and long-term rate control. Beta blockers are often the first-line therapy in AF rate control (Segal et al. 2000); they reduce ventricular rate and relief symptoms associated to AF, but have not been shown to reduce all-cause mortality compared with placebo in patients with AF (Kotecha et al. 2014). In another register study, AF patients using beta blockers had lower mortality during a 4.9 year follow-up period compared with AF patients without rate control medication (Chao et al. 2015).

Non-dihydropyridine calcium channel blockers verapamil and diltiazem reduce ventricular rate in AF and alleviate AF-related symptoms (Nikolaidou et al. 2009). However, they should not be used on patients with reduced ejection fraction because of their negative inotropic effects (Elkayam 1998).

Digoxin reduces resting heart rate in AF, but has only minor efficacy in rate control during exercise and emotional stress. Digoxin can be used as a second-line rate control agent in patients with heart failure, who tolerate other rate control medications poorly (Van Gelder et al. 2016). The meta-analysis by Vamos et al. suggested that digoxin use could be associated with an increased mortality risk among patients with AF (Vamos et al. 2015); according to a recent meta-analysis by Sethi et al., its clinical effects on all-cause mortality, serious adverse events, quality

of life, heart failure, and stroke are unclear based on currently available evidence (Sethi et al. 2018).

Amiodarone should not be used as a first-line rate control agent, but could be considered under certain circumstances. It is effective in reducing heart rate during AF, but it can potentially cause serious extra cardiac adverse effects, which limits its long-term use (Kumar et al. 2013). Dronedarone is contraindicated as a rate control drug during persistent or chronic AF (Connolly et al. 2011).

2.5.3.2 Rhythm control

A rhythm control strategy with long-term AAD should be considered for patients with highly symptomatic AF. It has not been shown to reduce mortality (Noheria et al. 2016); therefore, the severity of symptoms related to AF is the main factor in the selection of treatment strategy (Rolf et al. 2015). Age, presence of structural heart disease and other co-morbidities, the type of AF and contraindications to AADs should also be taken into account, when selecting AAD therapy in a rhythm control strategy (Piccini et al. 2016).

Class I and III AADs are more effective than placebo in maintaining sinus rhythm in patients with symptomatic AF (Van Gelder et al. 1989, Hohnloser et al. 2009, Roy et al. 2000, Singh et al. 2005, Singh et al. 2007, Kirchhof et al. 2016). Most widely used AADs had moderate efficacy in preventing AF episodes in the meta-analysis by Lafuente-Lafuente. The number needed to treat (NNT) to avoid one recurrence of AF for one year was 4, 3, 8, and 9 for flecainide, amiodarone, sotalol, and dronedarone, respectively. However, pooled recurrence rates of AF were high: 69-84% in controls not receiving antiarrhythmic medication and 43-67% in patients treated with AADs at a one-year follow-up. (Lafuente-Lafuente et al. 2015)

2.6 Use of medical therapy in prior studies

2.6.1 Oral anticoagulation therapy

In prior studies of AF, the use of OAC was less common with more frequent therapy interruptions in females compared with males (Gomberg-Maitland et al. 2006); the quality of OAC therapy in females could have been suboptimal compared with males (Sullivan et al. 2012). It has been speculated that these differences could explain why female patients were at a higher stroke risk and worse outcome in these studies. However, the knowledge about AF and its complications has increased. In the worldwide multicenter GARFIELD registry with over 17000 patients with newly diagnosed AF and at least one additional risk factor for stroke, the use of OAC was similar for both sexes. The rates of anticoagulant use were not different overall (61% of men vs. 61% of women) or in patients with a CHADS2 score of two or more (OR 1.00; 95% confidence interval 0.92-1.09). In the high-risk category (CHA2DS2-VASc >=2), 35% of men and 38% of women did not receive OAC therapy. On the other hand, in the low-risk category (CHA2DS2-VASc 0 in men and 1 in women), 42% of men and 41% of women received OAC therapy. Thromboprophylaxis was suboptimal in substantial proportions of men and women, with underuse in those at a moderate-to-high risk of stroke and overuse in those at a low risk. (Lip et al. 2015 (A)) In the Euro Heart Survey on Atrial Fibrillation, OAC therapy was used similarly in both sexes (65% for males vs. 65% for females, p=NS), but the quality of OAC therapy was not reported (Dagres et al. 2007). In the HERMES study with over 3000 AF patients in EDs, 75% of patients at a high thromboembolic risk were anticoagulated (Coll-Vinent et al. 2015).

The Finnish retrospective FibStroke register study included 3404 patients with previously diagnosed AF, who suffered a stroke or TIA. Of the high-risk patients

for thromboembolic complications (CHADS2 >=2), only 55% used OAC before an event (Palomäki et al. 2016).

2.6.2 Antiarrhythmic drug therapy

In the Euro Heart Survey on Atrial Fibrillation, there were no sex-related differences in the choice between rhythm and rate control strategy in patients with symptomatic AF (rhythm control 72% for men and 69% for women, p=NS). Similarly, there were no differences in the use of AADs between the sexes. Beta blockers were prescribed for 51% of males and 49% of females (p=NS). Class IC antiarrhythmic medication was used by 10% of males and 9% of females (p=NS). Class III AAD, mostly amiodarone, was used by 32% of males and 29% of females (p=NS) (Dagres et al. 2007).

The RACE study compared rate and rhythm control strategies in patients with persistent AF. At the end of the study, the rate control medications used were beta blockers (males 36%, females 35%), calcium channel blockers (males 32%, females 42%), and digoxin (males 57%, females 67%). In the rhythm control group, 18% of both sexes were on class I AADs. Class III AAD sotalol was used by 24% of males and 31% of females, and amiodarone by 19% of males and 20% of females. (Rienstra et al. 2005)

2.7 Efficacy and safety of medical therapy compared with invasive procedures

2.7.1 Anticoagulation vs. left atrial appendage closure

LAA has been identified to be an important anatomical structure predisposing thrombus formation in patients with AF (Blackshear et al. 1996). It has become a target for invasive percutaneous occlusion procedures in AF patients at a high thromboembolic risk and contraindication to OAC therapy. It can also be occluded surgically as a concomitant procedure during a heart surgery. The percutaneous Watchman device has been studied in randomized controlled trials (Holmes et al. 2009, Holmes et al. 2014) and nonrandomized registries (Reddy et al. 2011), comparing the occlusion of LAA to warfarin therapy for a composite primary endpoint of stroke, systemic embolism, and cardiovascular death. A meta-analysis of these studies demonstrated that LAA closure with the device had similar efficacy to warfarin in preventing the composite efficacy endpoint. All-cause stroke rates were identical between LAA closure and warfarin groups, but patients in the warfarin group experienced more hemorrhagic strokes and patients in the device group experienced more ischemic strokes. The long-term bleeding rates were significantly higher in patients treated with chronic warfarin therapy (Holmes et al. 2015); the long-term result from a 5-year follow-up seems to be consistent with these data (Reddy et al. 2017). Other devices for percutaneous LAA closure have not been studied in randomized controlled studies against warfarin (Baman et al. 2018). As invasive procedures predispose patients to procedure-related complications, contemporary ESC guidelines recommend that percutaneous LAA occlusion may be considered in stroke prevention for AF patients at a high thromboembolic risk and contraindication for long-term OAC therapy (class IIb, level B) (Kirchhof et al. 2016).

2.7.2 Antiarrhythmic drug therapy vs. catheter ablation

Catheter ablation of AF has established its position in the treatment of paroxysmal atrial fibrillation. The main target in the procedure is to isolate the pulmonary veins electrically from the left atrium to prevent triggers from pulmonary veins to initiate AF (Haissaguerre et al. 1998). According to ESC guidelines, it is indicated as a part of the rhythm control strategy for symptomatic patients after failure of AAD therapy (class I, level A) or as first-line therapy in selected patients (class IIa, level B) (Kirchhof 2016). In patients with drug refractory paroxysmal AF, the results of clinical trials have demonstrated the superiority of catheter ablation over AAD therapy in the maintenance of sinus rhythm after failure of AAD (Hakalahti et al. 2015). The MANTRA-PAF trial was a prospective randomized multicenter study comparing the efficacy of radiofrequency catheter ablation (RFA) and AAD therapy in patients with symptomatic paroxysmal AF as a first-line therapy. It found no significant difference between RFA and AAD groups in the cumulative burden of AF over a period of 2 years (90th percentile of arrhythmia burden, 13% and 19%, respectively, p=0.11) (Cosedis Nielsen et al. 2012). However, after 5 years of follow-up, more patients in the RFA group were free of AF (86% vs. 71%, p=0.001) and the burden of AF was significantly lower in the RFA group than in the AAD group (Cosedis Nielsen et al. 2017). There have been similar results in smaller RAAFT-1 and -2 studies (Wazni et al. 2005, Morillo et al. 2014).

In persistent AF, catheter ablation has demonstrated to be superior compared with AAD therapy in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac-related hospitalizations (Nyong et al. 2016). Patients with AF and reduced left ventricular ejection fraction had a lower rate of composite endpoint of death from any cause or hospitalization for worsening heart failure (29% vs. 45%, HR 0.62, 95% CI 0.43-0.87, p=0.007) after RFA compared with AAD therapy alone in the CASTLE-AF study (Marrouche et al. 2018). This is an important finding, as it is the first time that a rhythm control strategy has reduced

mortality. According to preliminary results from the CABANA study, there was a non-significant 15% reduction in all-cause mortality with RFA compared with AAD therapy, as assessed by Intention-to-Treat (ITT), and a significant benefit of ablation for mortality in analyses by treatment (nonpublished data).

The efficacy of AF catheter ablation via cryoballoon is comparable with the RFA technique (Kuck et al. 2016). The cryotechnique is also indicated for ablation of paroxysmal and persistent AF.

Avoiding complications is important in both AAD therapy and catheter ablation. Data on the long-term safety of AAD therapy are scarce. Class IA drugs quinidine and disopyramide and class III sotalol were associated with increased all-cause mortality in patients with AF in a meta-analysis by Lafuente-Lafuente et al. (Lafuente-Lafuente et al. 2015). The class IC drug flecainide, which is most widely used AAD in patients with AF, has been shown to increase proarrhythmias and mortality in patients with structural heart disease. Therefore, its use is limited to patients without structural heart disease (Tamargo et al. 2012). Class III dronedarone has been shown to cause increased mortality and morbidity in patients with permanent AF and/or heart failure (Adlan et al. 2013). Amiodarone (class III) is the most efficacious AAD in AF, but its long-term use is limited due to an unfavorable safety profile; it increases the risk of extra cardiac adverse effects in the thyroidea, liver, lungs, skin, eyes, and nervous system. Amiodarone has several pharmacokinetic interactions with other drugs, which further complicate its use. It inhibits the clearance of warfarin, potentiating its anticoagulant effect (Viles-Gonzales et al. 2014).

Catheter ablation of AF carries a risk of severe complications, the concerns about its safety being raised repeatedly. Data about the safety of catheter ablation indicate that it causes rare but more severe major complications compared with AAD therapy.

This underlines the importance of patient selection and operator experience (Hakalahti et al. 2015).

3 AIMS OF THE STUDY

The aims of the present study were:

1. To characterize the baseline cardiovascular risk factors in patients with an ED visit due to symptomatic AF (I and II).
2. To characterize the cardiovascular risk factors of AF patients using warfarin (III and IV).
3. To evaluate the use of OAC and AAD and changes made in medications during an ED visit due to symptomatic AF (I and II).
4. To evaluate the association between warfarin control and the incidence and outcome of myocardial infarction (III).
5. To assess the predictive value of the CHA2DS2-VASc score for MI in AF patients using warfarin (III).
6. To compare the residual risk of stroke, bleeding events, and cardiovascular and all-cause mortality among female and male AF patients using warfarin (IV).

4 MATERIALS AND METHODS

4.1 The FinFib2 population

The FinFib2 data were used in articles I and II. Data were collected in 35 EDs around Finland. Finland is divided into five university hospital districts, and patients from all of them were enrolled in order to avoid any bias due to geographical differences. Patients from health care centers and local, central, and university hospitals were included. All patients who were admitted to the ED due to palpitations or other arrhythmia-related symptoms within a two-week period (November 11-23, 2013) were screened, and those with ECG documentation of AF or atrial flutter were enrolled into the study (n=1013). The study protocol was approved by the Pirkanmaa Hospital District Ethical Committee. Written informed consent was not required because no information allowing for later identification of the patients was included in the database.

Data on underlying diseases and other risk factors, as well as information on utilization of OAC therapy, other antithrombotic drugs, and AADs were collected from patient medical records using a predefined internet-based case report form. OAC therapy included warfarin and DOACs. Subcutaneous low molecular weight heparin (LMWH) use was included in the OAC therapy in all statistical analyses. The use of antiplatelet agent aspirin (ASA) was reported separately. The risk of thromboembolic events and bleeding complications was evaluated by calculating the CHA2DS2-VASc and HAS-BLED scores for every patient, as recommended by the contemporary AF management guidelines of the European Society of Cardiology (ESC) (Camm et al. 2012). In study I, the patients were divided into two groups

based on the AF history, i.e., those with previously and with newly diagnosed AF. In study II, the patients were divided into groups according to treatment strategy (rate and rhythm control groups). The baseline characteristics of FinFib2 population are shown in Table 2.

The data were analyzed using IBM SPSS Statistics software package version 22 (IBM SPSS Inc., Armonk, NY, USA). Missing data values were excluded from the statistical analysis. Continuous variables were expressed as mean ± standard deviation and compared with independent variables t-test or Mann-Whitney U-test, when appropriate. Categorical variables were expressed as numbers and percentages and compared using Fisher's exact test. All tests were two-sided, and a P value of <0.05 was considered statistically significant.

Table 2. Baseline characteristics of the FinFib2 population.

	Total n (%)	Prior AF n (%)	New AF n (%)	P-value
Patients	1013	780 (78.2%)	217 (21.8%)	
Age mean (range)	70.0±13.1 (19-103)	70.1±12.5 (23-96)	70.0±14.8 (19-103)	0.904
Female	482 (47.6)	369 (47.3)	110 (50.7)	0.399
Congestive heart failure	176 (17.4)	140 (18.0)	31 (14.3)	0.222
Hypertension	658 (65.1)	513 (65.9)	136 (62.7)	0.376
Diabetes	214 (21.2)	172 (22.1)	39 (18.1)	0.222
Stroke	81 (8.1)	66 (8,5)	15 (7.0)	0.573
TIA1	53 (5.3)	43 (5.6)	9 (4.2)	0.494
Other thromboembolic events	24 (2.4)	23 (3.0)	1 (0.5)	0.041
Coronary artery disease	235 (23.2)	183 (23.5)	50 (23.0)	0.928
ASO2	39 (1.3)	28 (3.6)	10 (4.6)	0.547
Previous AMI3	126 (12.5)	107 (13.7)	18 (8.3)	0.036
Dyslipidemia	441 (43,9)	356 (46.1)	79 (36.6)	0.013
Ongoing or ex-smoking	254 (31.8)	200 (32,4)	45 (26,8)	0.189
Valvular disease	128 (12.6)	105 (13.5)	20 (9.2)	0.105
Pacemaker	68 (6.7)	65 (8.3)	2 (0.9)	<0.001
Thyroid dysfunction	112 (11.1)	88 (11.4)	23 (10.6)	0.809
Lung disease	135 (13.4)	106 (13.7)	26 (12.0)	0.573
Anemia	103 (10.4)	79 (10.3)	24 (11.2)	0.706
History of major bleeding	34 (3.4)	30 (3.8)	4 (1.8)	0.266
Renal insufficiency	100 (9.9)	78 (10.0)	19 (8.8)	0.698
Liver insufficiency	18 (1.8)	13 (1.7)	5 (2.3)	0.565

[1] TIA = transient ischemic attack

[2] ASO = arteriosclerosis

[3] AMI = acute myocardial infarction

4.2 The FinWAF population

The FinWAF data was used in articles III and IV of this study. Data from seven Finnish nationwide population registries and six laboratory databases were linked together by using unique personal civil registration numbers (Table 3). The permits for data collection and linkage were received from the Social Insurance Institute, the National Institute for Health and Welfare, Population Register Center, and Statistics Finland. The International Statistical Classification of Diseases (10th revision, ICD-10) was used to code and classify the underlying diagnosis and causes of hospitalization and death.

Table 3. Registries used in the FinWAF data.

Register	Register Holder	Information obtained
National Prescription Register	The Social Insurance Institution of Finland (Kela)	Drug purchases (ATC codes)
National Reimbursement Register	Kela	Reimbursement decisions 207 for chronic arrhythmias
Finnish Care Register, HILMO	National Institute for Health and Welfare	Diagnoses (ICD10 codes)
National Causes of Death Register	Statistics Finland	Deaths and causes of deaths
Laboratory databases	HUSLAB, Helsinki; TYKSLAB, Turku; FIMLAB, Tampere and FIMLAB, Central Finland; ISLAB, Kuopio; and NORLAB Oulu.	INR and other relevant laboratory measurements
Population Register	Population Register Center	Places of domicile 12 months prior to and on index dates.
Social HILMO	National Institute for Health and Welfare	Information (dates) about institutionalization (other than hospitalization)

The study was performed in accordance with the Declaration of Helsinki and the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance

code of conduct. The ethical committee of the Hospital District of Helsinki and Uusimaa and the five university laboratories providing the INR data accepted the protocol.

All patients included in the study fulfilled three criteria: 1) AF diagnosis (ICD-10 code I48) between January 1, 2005 and December 31, 2009, 2) at least one warfarin purchase, and 3) at least one INR measurement between January 1, 2007 and December 31, 2009. We found 161 271 patients with a diagnosis code of atrial fibrillation during the study period. After implementing the inclusion and exclusion criteria (age under 18 years, permanent residence outside Finland during the follow-up period), 54 568 patients were eligible for the study.

The follow-up period began at the date of the first warfarin purchase after January 1, 2007, and continued until the first outcome event or death occurred, or until the end of study period (December 31, 2011).

Information on age, sex, comorbidities, and medications were collected from the national registries. The basic characteristics of the FinWAF population are shown in Table 4. The diagnosis codes for concomitant diseases were collected from the Finnish Care Register (HILMO) and the National Causes of Death Register. In study IV, the stroke risk score was calculated for each patient without assigning a point for the female sex as a CHA2DS2-VA score: congestive heart failure (1 point), hypertension (1 point) (ICD-10 codes I10-I15), age ≥ 75 years (2 points), diabetes mellitus (1 point) (ICD-10 codes E10-E40), stroke or transient ischemic attack (TIA), or systemic thromboembolism (2 points) (ICD-10 codes I63, I64, I63.9-I69.8, G45), vascular disease (1 point) (ICD-10 codes I20-I25, I65-I66, I67.2, I70), and age 65-74 years (1 point).

Table 4. Baseline characteristics of the FinWAF population.

	All, n (%)	Women, n (%)	Men, n (%)	P-value
Patients	54568	25846 (47.0)	28722 (53.0)	
Age, mean±SD	73.1±10.8	76.8± 9.5	69.8±10.9	<0.001
<65	11573 (21.2)	2813 (10.9)	8760 (30.5)	<0.001
65–74	15333 (28.1)	6053 (23.4)	9280 (32.3)	<0.001
≥75	27662 (50.7)	16980 (65.7)	10682 (37.2)	<0.001
Congestive heart failure	9727 (17.8)	5141 (19.9)	4586 (16.0)	<0.001
Cardiomyopathy	1505 (2.8)	342 (1.3)	1163 (4.1)	<0.001
Hypertension	13166 (24.1)	7184 (27.8)	5982 (20.8)	<0.001
Pulmonary embolism	815 (1.5)	445 (1.7)	370 (1.3)	<0.001
Stroke or TIA	6669 (12.2)	3466 (13.4)	3203 (11.2)	<0.001
Thyrotoxicosis	426 (0.8)	296 (1.2)	130 (0.5)	<0.001
Vascular disease	13708 (25.1)	6255 (24.2)	7453 (26.0)	<0.001
Coronary artery disease	12480 (22.9)	5694 (22.0)	6786 (23.6)	<0.001
Peripheral arterial disease	2237 (4.1)	946 (3.7)	1291 (4.5)	<0.001
Venous thromboembolism	1637 (3.0)	959 (3.7)	678 (2.4)	<0.001
Bleeding	2549 (4.7)	958 (3.7)	1591 (5.5)	<0.001
Myocardial infarction	2410 (4.4)	1111 (4.3)	1299 (4.5)	0.211
Intracranial haemorrhage	320 (0.6)	129 (0.5)	191 (0.7)	0.013
Anemia	11887 (21.8)	4871 (18.9)	7016 (24.4)	<0.001
Renal impairment	10823 (19.8)	4941 (19.1)	5882 (20.5)	<0.001
Diabetes	5301 (9.7)	2358 (9.1)	2943 (10.3)	<0.001
Cancer	10408 (19.1)	5182 (20.1)	5226 (18.2)	<0.001
CHA2DS2-VA score (without a point for female gender)	2.3±1.5	2.6±1.5	2.0±1.5	<0.001
0	6732 (12.3)	1648 (6.4)	5084 (17.7)	<0.001
1	9951 (18.2)	3573 (13.8)	6378 (22.2)	<0.001
2	16253 (29.8)	8464 (32.8)	7789 (27.1)	<0.001
3-4	16721 (30.6)	9238 (35.7)	7483 (26.1)	<0.001
5-8	4911 (9.0)	2923 (11.3)	1988 (6.9)	<0.001

The results of the INR measurements were collected from the databases of six accredited regional central laboratories, which cover about two-thirds of the Finnish population.

The main predictor variable in studies III and IV was time-dependent TTR. It was calculated and updated daily via linear interpolation using the Rosendaal method (Rosendaal et al. 1993), as the percentage of days that the INR values were between 2.0 and 3.0 within the previous 60 days (TTR60). If the cap between consecutive INR measurements was more than 60 days, the most recent INR value was carried forward. Any time periods exceeding 60 days from the previous measured INR value were removed from the analysis. The robustness of the 60-day window in the time-dependent TTR definition was further investigated by using sensitivity analyses, in which the time-dependent TTR was calculated based on continuous 30-, 90-, 180-, and 360-day windows. In addition, a summary TTR capturing the entire follow-up period as a single TTR value (sTTR) was calculated for both sexes to sum up the overall quality of warfarin therapy.

The endpoints of the study were categorized according to the 10th revision of the International Statistical Classification of Diseases (ICD-10). The primary endpoints of study III included: 1) first hospitalization due to MI (ICD-10 codes I21-I22), 2) MI mortality (ICD10 codes I21-I22), and 3) cardiovascular mortality (ICD-10 codes I00-I83, I99, Q20-Q28). In addition, we evaluated whether the CHA2DS2-VASc score was associated with the risk and outcome of MI. The endpoints of study IV study were: 1) any stroke or transient ischemic attack (TIA) (ICD-10 codes I63, I64, I69.3-I69.8, G45), 2) bleeding event leading to hospitalization (ICD-10 codes D68.3, I60-I62, J942, K221, K223, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K274, K276, K280, K282, K284, K286, K290, K631, K633, K920-K922, R04, R31, S064-S066, S068), 3) death due to cardiovascular cause (ICD-10 codes I00-I83, I99, Q20-Q28), and 4) death due to any cause (any ICD-10 code).

When evaluating the association between the accomplishment of warfarin therapy and the incidence and outcome of MI and cardiovascular mortality in study III, the patients were divided into six groups according to the TTR60 values (i.e., < 40%, 40-50%, 50-60%, 60-70%, 70-80%, and > 80%). A summary value (sTTR) covering the entire study period was calculated for each patient to sum up the overall quality of warfarin therapy with a single numeral. In substudy IV, sex differences in endpoints were investigated in the whole population and according to the TTR60 levels of <40%, 40-50%, 50-60%, 60-70%, 70-80%, >80% and age groups of < 65, 65-74, and ≥ 75 years.

The baseline characteristics are reported as the mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Data management and all statistical analysis were performed using the R language. Stratified incidence rates were estimated in each time-dependent TTR60 category, and the 95% confidence intervals (CIs) were captured according to the Poisson assumption. Hazard ratios for different time-dependent TTR60 levels compared with the reference group of a TTR60 of 60–70% (in study III) were estimated using the Cox proportional hazards model adjusted for age, sex (not in substudy IV), and time-varying comorbidities, including a history of MI, congestive heart failure, hypertension, diabetes, previous stroke, previous TIA, renal impairment (serum creatinine > 90 μmol/l in women, and > 100 μmol/l in men), vascular disease and any previous hospitalization. In study III, hazard ratios were accompanied by expected cumulative hazards, derived for an average study patient assumed to have a time-fixed TTR and used to evaluate the predicted cumulative incidences as recommended by Therneau and Grambsch (Therneau et al. 2000).

To test for sensitivity, the results were re-derived using the Cox proportional hazards model with 30-, 90-, 180-, and 360-day timeframes to calculate the time-dependent TTR and by excluding patients who did not have at least two separate warfarin

purchases within 120 days from the CED. Sensitivity analyses were also performed for previous and new warfarin users, and on cohorts that excluded patients with an AF diagnosis only after the first purchase of warfarin and with a diagnosis of any valve disorder accompanied with their diagnosis of AF.

5 RESULTS

5.1 Characteristics of atrial fibrillation patients in Finland (I and IV)

The mean age of patients admitted to the ED due to symptomatic AF in the FinFib2 study was 70.0±13.1 years. Of these, 67.7% were 65 years old or older, and 39.5% were 75 years old or older. In the FinWAF register population, the mean age of AF patients was 73.1±10.8 years; 78.8% of them were 65 years old or older, and 50.7% were 75 years old or older. Slightly fewer than half of the patients were female in both studies (47.6% in FinFib2 and 47.4% in FinWAF).

The most common underlying diseases were hypertension (65.1% in FinFib2 and 24.1% in FinWAF), vascular disease (23.2% in FinFib2 and 25.1% in FinWAF), congestive heart failure (17.4% in FinFib2 and 17.8% in FinWAF), and diabetes (21.1% in FinFib2 and 9.7% in FinWAF). 13.4% of patients in the FinFib2 study and 12.2% in the FinWAF study had a previous stroke or TIA diagnosis. In the FinWAF study, hypertension, congestive heart failure, and prior stroke or TIA were more common among women, but in contrast, vascular disease, diabetes, and prior bleeding events were more common in men. The mean CHA2DS2-VASc score was 3.1±2.1 in the FinFib2 study and 2.8±1.7 in the FinWAF study. In the FinWAF study, the risk score without a point for the female sex (CHA2DS2-VA score) was higher for women than men (2.6±1.5 vs. 2.0±1.5, $p<0.001$).

5.2 Risk stratification of stroke and other cardiovascular outcomes

5.2.1 The CHA2DS2-VASc score and a risk of myocardial infarction

In study III, we found a strong association between the CHA2DS2-VASc score and the risk of MI. Among patients with no risk factors, the incidence of MI (2.88 per 1000 patient years, 95% CI 1.82-4.58) was lower than in any other group ($P<0.001$). In comparison, among patients with a CHA2DS2-VASc score of >5, the incidence rate was 39-64 per 1000 patient years. A high CHA2DS2-VASc score was also a strong predictor of MI mortality and cardiovascular death. (Table 5)

Table 5. Number of events and event rates (per 1000 person years) stratified by the CHA2DS2-VASc score in study III.

CHA2DS2-VASc score		Number of patients	Number of events	Time at risk (years)	Event rate (95% CI)
Myocardial infarction	0	4780	18	6244	2.9 (1.8 - 4.6)
	1	9495	90	13790	6.5 (5.3 – 8.0)
	2	15301	240	23087	10.4 (9.2 – 11.8)
	3	19852	433	29055	14.9 (13.6 – 16.4)
	4	17694	560	24394	23.0 (21.1 – 24.9)
	5	13087	529	17241	30.7 (28.2 – 33.4)
	6	7771	380	9544	39.8 (36.0 – 44.0)
	7	3506	162	4136	39.2 (33.6 – 45.7)
	8	1165	74	1199	61.7 (49.1 – 77.5)
	9	234	16	251	63.9 (39.1 – 104.2)
Myocardial infarction mortality	0	4780	3	6244	0.5 (0.2-1.5)
	1	9507	9	13824	0.7 (0.3 – 1.3)
	2	15368	47	23222	2.0 (1.5 – 2.7)
	3	20026	149	29366	5.1 (4.3 – 6.0)
	4	18056	270	24873	10.9 (9.6 – 12.2)
	5	13533	281	17908	15.7 (14.0 – 17.6)
	6	8136	259	10067	25.7 (22.8 – 29.1)
	7	3750	126	4411	28.6 (24.0 – 34.0)
	8	1268	60	1322	45.4 (35.3 – 58.5)
	9	263	10	283	35.4 (19.0 – 65.7)
Cardiovascular mortality	0	4780	43	6244	6.9 (5.1 – 9.3)
	1	9507	116	13824	8.4 (7.0 – 10.1)
	2	15368	307	23222	13.2 (11.8 – 14.8)
	3	20026	736	29366	25.1 (23.3 – 26.9)
	4	18056	1440	24873	57.9 (55.0 – 61.0)
	5	13533	1648	17908	92.0 (87.7 – 96.6)
	6	8136	1419	10067	141.0 (133.8 – 148.5)
	7	3750	820	4411	185.9 (173.6 – 199.1)
	8	1268	384	1322	290.6 (262.9 – 321.1)
	9	263	86	283	304.0 (246.1 – 375.6)

5.2.2 The female sex as a risk factor for stroke, bleeding events, and mortality

In the FinWAF study, the crude unadjusted incidence rate per 1000 patient years for stroke or TIA and cardiovascular and all-cause mortality were higher among female than male patients. In contrast, the unadjusted incidence rate of bleeding events was lower in women than in men. (Table 6)

Table 6. Number of adverse events and unadjusted incidence rates per 1000 patient years with 95% CI of study endpoints for both sexes in study IV.

Endpoint	Gender	N patients Females 25846 Males 28722	N events	Person years	Rate	95% CI
Stroke or TIA	female		3224	60470	53.32	51.51–55.19
	male		2893	61720	46.87	45.20–48.61
Bleeding	female		2198	62720	35.04	33.61–36.54
	male		3214	62541	51.39	49.64–53.20
Cardiovascular mortality	female		3680	65123	56.51	54.71–58.36
	male		3319	66397	49.99	48.32–51.72
All-cause mortality	female		5876	65123	90.23	87.95–92.57
	male		5723	66397	86.19	83.99–88.46

After adjusting for baseline characteristics, there were no difference in the risk of stroke or TIA between the sexes (HR 0.97, 95% CI 0.91-1.03, p=0.304). The adjusted risk for bleeding events (HR 0.52, 95% CI 0.49-0.56, p<0.001), cardiovascular mortality (HR 0.82, 95% CI 0.78-0.88, p<0.001), and all-cause mortality (HR 0.79, 95% CI 0.75-0.83, p<0.001), were lower in women than in men.

In pre-specified age-groups of <65, 65-74, and ≥75 years, there were no sex-specific differences in rate of stroke or TIAs, but the incidence of bleeding events,

cardiovascular and all-cause mortality were lower in women irrespective of age (Table 7).

Table 7. Incidence rates per 1000 patient years for the study outcomes by age group for both sexes in study IV.

Outcome	Age group	Incidence rate: Female	Incidence rate: Male	p-value
Stroke or TIA	<65	34.22 (29.21, 40.1)	33.89 (30.86, 37.22)	0.9025
	65-74	41.51 (38.02, 45.32)	39.54 (36.89, 42.37)	0.405
	75 and over	58.48 (56.26, 60.78)	57.97 (55.24, 60.83)	0.789
Bleeding events	<65	18.74 (15.19, 23.13)	31.75 (28.84, 34.95)	<0.001
	65-74	26.08 (23.40, 29.08)	44.45 (41.66, 47.43)	<0.001
	75 and over	39.15 (37.38, 41.01)	65.28 (62.40, 68.30)	<0.001
Cardiovascular mortality	<65	9.90 (7.44, 13.18)	17.80 (15.69, 20.19)	<0.001
	65-74	17.02 (14.91, 19.43)	28.66 (26.50, 31.00)	<0.001
	75 and over	71.86 (69.49, 74.31)	78.99 (75.92, 82.18)	<0.001
All-cause mortality	<65	19.81 (16.18, 24.24)	32.15 (29.27, 35.30)	<0.001
	65-74	36.21 (33.07, 39.65)	50.75 (47.84, 53.83)	<0.001
	75 and over	111.90 (108.93, 114.95)	134.64 (130.62, 138.78)	<0.001

5.3 The quality of warfarin therapy and clinical outcome

5.3.1 The overall quality of oral anticoagulation therapy

In the FinFib2 study, INR was over 2 on admission to the ED in 81.1% of patients. However, during the month before the ED admission, INR was out of the therapeutic range in 41.9% of patients who had been receiving longstanding warfarin therapy.

In the FinWAF study, during the follow-up period (mean 3.2±1.6 years), the mean and median summary TTR (sTTR) for the whole population was 61.1%±25% and

67.0% (49.7-78.7), respectively. The mean sTTR was significantly higher among women than men (62.5%±23.6% vs. 59.8%±26.4%, p<0.001). The mean annual number of INR measurements was 18.5±14.5 (median 16.6) in the whole FinWAF population. The number of annual INR measurements was higher for females compared with males (19.3±14.5 vs. 17.9±14.5, p<0.001).

5.3.2 The Association between TTR and the risk of myocardial infarction and cardiovascular mortality

In study III, the quality of warfarin therapy was assessed continuously by calculating the time in therapeutic range within a 60-day window (TTR60) using the Rosendaal method. Stratified incidence rates were estimated in six different TTR60 categories. During the 3.2±1.6-year follow-up, the annual incidence of MI (95% CI) was 3.3% (3.0-3.5%), 2.9% (2.6-3.3%), 2.4% (2.1-2.7%), 1.9% (1.7-2.2%), 1.7% (1.5-2.0%), and 1.2% (1.1-1.3%) among patients with TTR60 <40%, 40-50%, 50-60%, 60-70%, 70-80%, and ≥80%, respectively. The hazard ratio (HR) for MI was more than 1.5 times higher among patients with TTR60<40% than in the reference population (TTR60 60-70%). In patients with TTR60 over 80%, the risk of MI (HR 0.7, 95% CI 0.6-0.8) and MI mortality and cardiovascular mortality (HR 0.8, 95% CI 0.7-0.9) were significantly lower than in any other group. Hence, well-managed warfarin therapy was also associated with a lower MI mortality and cardiovascular mortality. (Table 8)

Table 8. Number of events, incidence rates and HRs of myocardial infarction, myocardial infarction mortality, and cardiovascular mortality among patients in different time-dependent TTR60 categories in study III. HRs were adjusted for age, sex, congestive heart failure, hypertension, diabetes, stroke, TIA, vascular disease, previous hospitalization, and renal impairment.

	TTR60 (%)	Number of events	Rate / 100 patient years (95% CI)	HR (95% CI)	P-value
Myocardial infarction	≤40	859	3.3 (3.0 – 3.5)	1.6 (1.4 – 1.8)	<0.001
	40-50	265	2.9 (2.6 – 3.3)	1.5 (1.2 – 1.7)	<0.001
	50-60	248	2.4 (2.1 – 2.7)	1.2 (1.0 – 1.5)	0.033
	60-70	218	1.9 (1.7 – 2.2)	1 (reference)	
	70-80	203	1.7 (1.5 – 2.0)	0.9 (0.8 – 1.1)	0.447
	>80	709	1.2 (1.1 – 1.3)	0.7 (0.6 – 0.8)	<0.001
Myocardial infarction mortality	≤40	486	1.8 (1.6 – 2.0)	1.8 (1.5 – 2.2)	<0.001
	40-50	144	1.5 (1.3 – 1.8)	1.6 (1.2, 2.0)	<0.001
	50-60	105	1.0 (0.8 – 1.2)	1.0 (0.8 – 1.4)	0.783
	60-70	107	0.9 (0.8 – 1.1)	1 (reference)	
	70-80	91	0.8 (0.6 – 0.9)	0.9 (0.7 – 1.1)	0.316
	>80	281	0.5 (0.4 – 0.5)	0.6 (0.5 – 0.8)	<0.001
Cardiovascular mortality	≤40	3162	11.7 (11.3 –12.1)	2.0 (1.8 – 2.2)	<0.001
	40-50	714	7.6 (7.1 – 8.2)	1.3 (1.2 – 1.5)	<0.001
	50-60	670	6.2 (5.8 –6.7)	1.1 (1.0 – 1.2)	0.084
	60-70	647	5.5 (5.1 – 6.0)	1 (reference)	
	70-80	497	4.1 (3.8 – 4.5)	0.8 (0.7 – 0.9)	<0.001
	>80	1309	2.2 (2.0-2.3)	0.5 (0.4-0.5)	<0.001

5.3.3 Impact of the female sex on the association between TTR and the risk of stroke, bleeding events, and mortality

In study IV, the quality of warfarin therapy was estimated by calculating TTR 60 days before each index event (TTR60). The risk of stroke or TIA and cardiovascular mortality were higher in women than in men among patients with TTR60 less than 50%. In other TTR60 groups, there was no difference in the incidence of these endpoints. In TTR60 group of < 40%, all-cause mortality was higher in women, but in the other TTR60 groups, the risk did not differ between the sexes. The risk of bleeding events was significantly lower among women in all TTR60 groups. The patient outcome improved in both sexes linearly along TTR60. (Table 9)

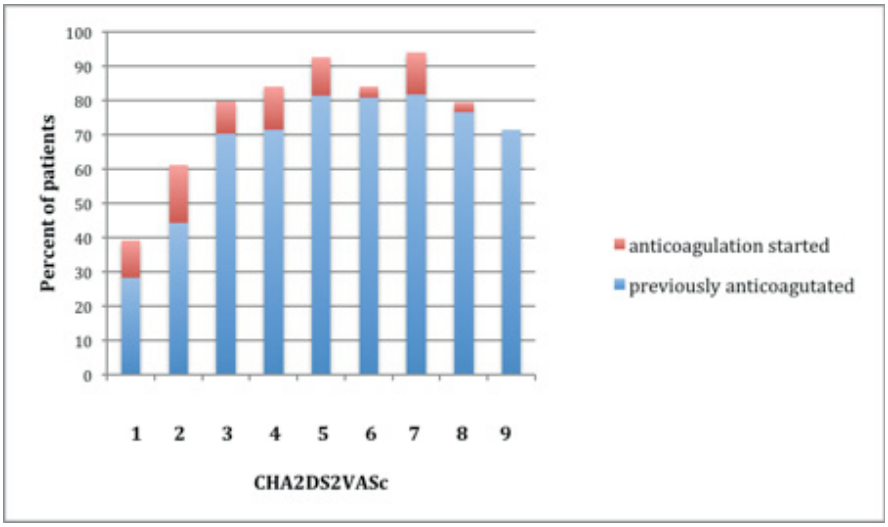
Table 9. Incidence rates per 1000 patient years for the study outcomes by sex and TTR60 with p-values in study IV.

Outcome	TTR60	Incidence rate: Female	Incidence rate: Male	p-value
Stroke or TIA	<40%	107.4(101.65, 113.48)	79.75(75.09, 84.69)	<0.001
	40-50%	63.23(56.22, 71.12)	51.75(45.36, 59.05)	0.028
	50–60%	54(47.96, 60.8)	48.88(43.03, 55.51)	0.268
	60–70%	48.79(43.31, 54.98)	44.64(39.29, 50.71)	0.328
	70–80%	46.74(41.43, 52.73)	44.77(39.48, 50.77)	0.657
	>80%	31.07(29.08, 33.21)	31.29(29.31, 33.41)	0.886
Bleeding events	<40%	57.9(53.78, 62.34)	90.05(85.07, 95.32)	<0.001
	40-50%	45.95(40.14, 52.6)	67.06(59.77, 75.24)	<0.001
	50–60%	39.36(34.35, 45.1)	63.14(56.5, 70.56)	<0.001
	60–70%	35.59(31.03, 40.81)	54.09(48.22, 60.67)	<0.001
	70–80%	37.01(32.41, 42.26)	49.98(44.43, 56.22)	<0.001
	>80%	22.49(20.83, 24.28)	29.42(27.52, 31.45)	<0.001
Cardiovascular mortality	<40%	133.75(127.57, 140.24)	101.49(96.4, 106.85)	<0.001
	40-50%	83.51(75.7, 92.13)	68.36(61.22, 76.32)	0.008
	50–60%	64.65(58.25, 71.75)	60.13(53.85, 67.14)	0.354
	60–70%	54.45(48.85, 60.69)	56.05(50.24, 62.53)	0.724
	70–80%	42.25(37.4, 47.73)	40.65(35.81, 46.15)	0.686
	>80%	21.08(19.49, 22.78)	22.11(20.5, 23.84)	0.392
All-cause mortality	<40%	228.76(220.62, 237.19)	191.15(184.11, 198.45)	<0.001
	40-50%	131.98(122.06, 142.71)	118.32(108.81, 128.67)	0.062
	50–60%	100.08(92.04, 108.82)	104.65(96.26, 113.78)	0.469
	60–70%	82.01(75.07, 89.59)	89.05(81.64, 97.12)	0.195
	70–80%	62.56(56.59, 69.16)	65.32(59.1, 72.19)	0.563
	>80%	29.95(28.05, 31.97)	32.69(30.72, 34.77)	0.057

5.4 Use of oral anticoagulation therapy

AF patients at a high thromboembolic risk are well-recognized in emergency departments in Finland. In the FinFib2 study, only 11 of 1013 patients were recognized incorrectly as low thromboembolic risk patients despite the CHA2DS2-VASc score being at least 2. Of the patients with the CHA2DS2-VASc score being at least 2 and having previously diagnosed AF, 76.3% used OAC when admitted to the ED. At discharge from the ED or the hospital ward, the use of OAC among these patients increased to 85.5%. Of the patients with newly diagnosed AF during an ED visit and the CHA2DS2-VASc score being at least 2, OAC therapy was started for 79.6% of patients. The main reasons not to start OAC were a history of major bleeding (24 patients), patient refusal (27 patients), and malignancy (11 patients). According to the HAS-BLED score, 27.5% of patients were at a high risk of bleeding. Most of them (81.8%) were discharged with anticoagulation therapy, which is in line with the ESC guidelines. (Figure 3)

Figure 3. Oral anticoagulation therapy among patients with previously diagnosed AF in study I (study period November 11-23, 2013). The patients were divided into groups according to the CHA2DS2-VASc score. Previously anticoagulated patients are shown in the blue column. Percentage of anticoagulated patients increased when discharged (red column).

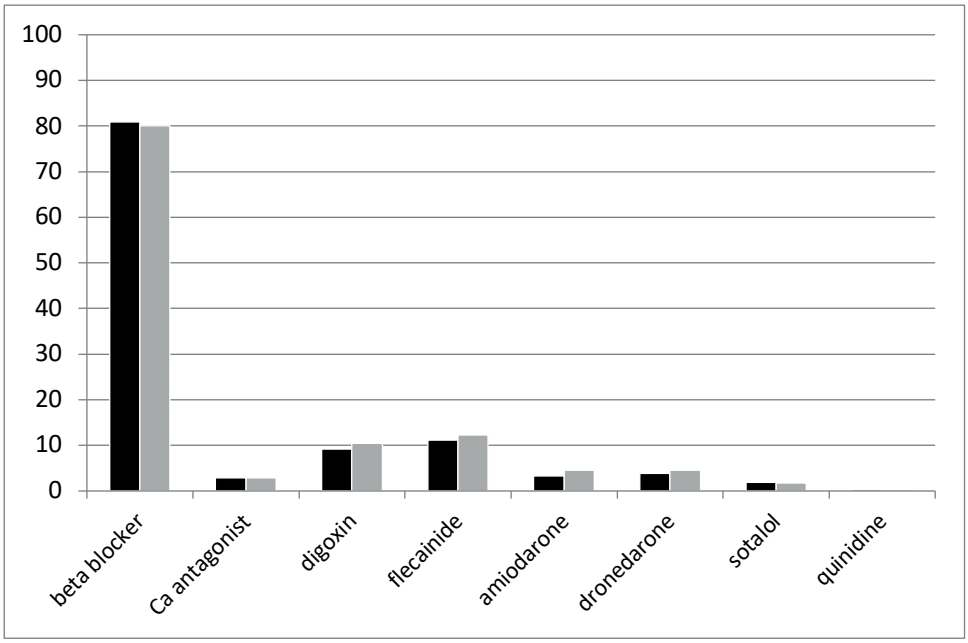


5.5 Use of antiarrhythmic medication

Most patients (85.3%) with previously diagnosed AF were using AAD for rhythm or rate control when admitted to the ED in the FinFib2 study. A majority of these AADs were rate control agents. As rate control therapy, beta blockers were used by 80.9%, digoxin by 9.2%, and verapamil or diltiazem by 2.9% of these patients. At discharge from the ED or hospital ward, 80.1% of these patients were on beta blocker medication. In patients with newly diagnosed AF during the ED visit, a beta blocker was prescribed for 71.0%, a calcium channel antagonist for 24.0%, and digoxin for 3.7% of patients.

AADs recommended for rhythm control (Kirchhof et al. 2016) were used infrequently upon admission to the ED. In patients with previously diagnosed AF, class I AADs were used by 11.4% of patients (mostly flecainide 11.2%). Of class III AADs, amiodarone was used by 3.3%, dronedarone by 3.8%, and sotalol by 1.9% of patients. Upon discharge from the ED or hospital ward, despite recurrent AF symptoms, a change in AAD was done only in 12.4% of patients. Class I or III AAD was started or the dosage of the drug used was adjusted in 7.4% of the patients with a previous diagnosis of AF and a rhythm control strategy. In patients with a new diagnosis of AF during the ED visit, amiodarone was started for 2 patients, and flecainide was not prescribed to anyone. (Figure 4)

Figure 4. The use of antiarrhythmic drugs among patients with previously diagnosed AF upon admission to the ED (black column) and at discharge (light grey column) in study II.



6 DISCUSSION

6.1 Main findings of the study

The main finding of the study was that the risk factors of AF in Finnish patients do not vary from those in previously published data from Western countries. Hypertension was the most common cardiovascular risk factor, and its role is highlighted in symptomatic AF patients admitted to the ED. The CHA2DS2-VASc score predicted the risk of myocardial infarction and cardiovascular mortality in AF patients on OAC therapy well.

TTR-related quality of warfarin therapy was important not only in order to prevent strokes, but also to decrease the risk of myocardial infarction, bleeding events, and cardiovascular and all-cause mortality. There was no sex-related difference in the risk of stroke with adequate OAC therapy, but female patients in warfarin therapy were at a lower risk of bleeding and mortality than males in all age and TTR groups. AF patients at a high thromboembolic risk were well-recognized in EDs. The use of OAC therapy was on a good level compared with prior studies, but there were major concerns about the quality of warfarin therapy.

Rate control therapy with beta blockers is prescribed for most AF patients in the ED, but the use of class I and III AADs is rare in rhythm control strategy.

6.2 Risk factors of atrial fibrillation

Recognizing the risk factors of AF is crucial when aiming towards the primary prevention of AF. According to the ARIC study, which included 14500 patients and a 17-year follow-up, more than 50% of AF cases were related to at least one known risk factor of AF, meaning that theoretically a large proportion of AF burden could be avoided by eliminating the risk factors in an early phase (Huxley et al. 2011).

We used two different populations of AF patients in our studies. In the FinFib2 study, patients were admitted to the ED due to a symptomatic AF. In contrast, the FinWAF population was constructed by linking data from several registries, including patients with a diagnosis of AF and in anticoagulation therapy. In the FinWAF study, no data on the symptoms of the patients were available. Comparing the risk factors with previously published data and highlighting potential differences with those reported from other regions of the world was of special interest.

The mean age of the patients was 70 years in the FinFib2 population and 73 years in the FinWAF population. In the worldwide RE-LY Atrial Fibrillation Registry of AF patients admitted to the ED, the age of patients varied from 57 years in Africa up to 70 years in North America (Oldgren et al. 2014). Female patients were older than males in the FinWAF population (77 vs. 70 years, $p<0.001$), which has also been seen in prior AF studies (Overvad et al. 2014, Piccini et al. 2016, Gomberg-Maitland et al. 2006, Pancholy et al. 2014).

Hypertension is a globally common risk factor for AF and thromboembolic complications in addition to age (Oldgren et al. 2014). In our FinFib2 population from the EDs, 65% of the patients had a previous diagnosis of hypertension, 23% had coronary artery disease, 21% had diabetes, and 17% congestive heart failure. In comparison, in the FinWAF population, a diagnosis of hypertension was only in 24%, coronary artery disease 23%, diabetes 10%, and congestive heart failure in 18%

of patients. The low proportion of patients with a diagnosis of hypertension in the FinWAF data could be explained by inappropriate documentation of hypertension diagnoses in the Finnish Care Registry. However, in the prospective Danish Diet, Cancer and Health register study, a diagnosis of hypertension was in 27% of males and 28% of females (Overvad et al. 2014), which is equal to our FinWAF population. Our findings about the concomitant diseases in patients admitted to the ED due to AF in the FinFib2 population are also in agreement with previous data for AF patients in EDs in Western Europe. There is a large variation in the incidence of hypertension in AF patients in different populations and different regions of the world. In the RE-LY Atrial Fibrillation Registry with AF patients admitted to the ED, hypertension varied from 42% in India up to 81% in Eastern Europe (Oldgren et al. 2014). The role of hypertension is highlighted in patients admitted to hospital due to symptomatic AF (An et al. 2015, Tran et al. 2016). It emphasizes the importance of treating hypertension not only in the prevention of AF, but also in reducing symptoms associated with AF and probably reducing the AF burden in the EDs.

One limitation of our study is that we were only able to identify cardiovascular risk factors, but data on modifiable lifestyle risk factors were not available. It is well-known that, for example, excessive alcohol consumption (Kodama et al. 2011, Larsson et al. 2014), physical activity, cardiovascular fitness, and smoking are closely associated with the risk of AF development (Boriani et al. 2018). We also could not study the influence of obesity on the risk of AF. Obesity is a growing risk factor for cardiovascular diseases and AF worldwide, and systematic weight loss programs have been found to reduce AF burden and symptoms associated with AF in patients with and without other rhythm control strategies (Pathak et al. 2015).

Early treatment of underlying diseases and management of precipitating factors is important in the prevention of AF. It also offers an overall cardiovascular risk

reduction, stroke risk reduction, and improved life expectancy in patients with AF (Kirchhof et al. 2009, Kirchhof et al. 2013).

6.3 Risk stratification of stroke and other cardiovascular outcomes

6.3.1 The CHA2DS2-VASc score and myocardial infarction

The CHA2DS2-VASc score has previously been validated to estimate stroke risk in AF patients without anticoagulation (Lip et al. 2010). However, a number of the components in the CHA2DS2-VASc score are also known to be related to the risk of MI and cardiovascular mortality. Considering that, our aim in study III was to evaluate the CHA2DS2-VASc score as a predictor of MI and cardiovascular mortality in anticoagulated AF patients.

The mean CHA2DS2-VASc score in the population of study III was 2.8±1.7. There was a strong association between the CHA2DS2-VASc score and the risk of MI. Among patients with no risk factors, the incidence of MI (2.88 per 1000 patient years, 95% CI 1.82-4.58) was lower than in any other group ($P<0.001$). In comparison, among patients with the CHA2DS2-VASc score above 5, the incidence rate varied from 39 to 64 per 1000 patient years. A high CHA2DS2-VASc score was also a strong predictor of MI mortality and cardiovascular death.

The coexistence of AF and MI dramatically increases the risk of future cardiovascular events and stroke (Akao 2014). Thus, early detection of AF is important not only to start OAC therapy to prevent stroke, but also to introduce cardiovascular prevention strategies. Using the same risk score in assessing thromboembolic and cardiovascular risk would be compelling in daily clinical

practice. Our findings support the results of Pang et al., where the CHA2DS2-VASc score positively correlated with the MI rate in patients with AF (2017). The CHA2DS2-VASc score could be used in risk stratification of cardiovascular outcome in anticoagulated AF patients, and it could help identify patients who would benefit from a strict treatment of cardiovascular risk factors.

6.3.2 Female sex as a risk factor for stroke, bleeding events, and mortality

The impact of sex on the risk of stroke is controversial. In older studies, female AF patients were at an increased risk of stroke compared with males (Hart et al. 1999B, Wang et al. 2003); thus, the female sex has been included into the CHA2DS2-VASc score. However, in many studies, the number of female patients was low, and they had more concomitant diseases, which may have biased the results (Fang et al. 2005, Gomberg-Maitland et al. 2006, Wang et al. 2003). According to a recent meta-analysis, the risk of stroke was elevated in women compared with men, particularly in the age group of over 75 years (Wagstaff et al. 2014). In contrast, Renoux et al. found no sex-related differences in stroke risk in any age group, including patients over 75 years of age, after proper multivariate adjustment in the population-based cohort study (2017). In a recent Danish register study, the increased risk of stroke for women was especially evident among those with more than two non-sex-related stroke risk factors. The female sex seems to be a risk modifier rather than a risk factor for stroke in patients with AF. (Nielsen et al. 2018)

In study IV, the unadjusted risk of stroke or TIA and mortality were elevated in women, which was seen previously in the SPORTIF trials (Gomberg-Maitland et al. 2006) and in the meta-analysis by Pancholy (Pancholy et al. 2014). However, in our and in previous studies, female patients were older and had more concomitant diseases compared with males. Thus, we estimated the hazard ratios for the study endpoints in women compared with men by using the Cox proportional hazards

model, adjusted for age, congestive heart failure, hypertension, diabetes, previous stroke or TIA, renal impairment, vascular disease, and any previous hospitalization. After data adjustments, we found no sex difference in stroke risk, and the risk of bleeding events and mortality was lower in females. Similar results have also been seen in other recent studies (Senoo et al. 2016 and Renoux et al. 2017). The residual risk for stroke or TIA increased with age, but there were no significant differences between the sexes in any age group, not even in patients >75 years old.

If the female sex is a risk factor for stroke, this elevated risk is not seen in properly anticoagulated AF patients in any age group, not even in patients over 75 years old. The female sex does not affect the decision to start anticoagulation therapy according to ESC guidelines (Kirchhof et al. 2016). The results from recent studies indicate that the role of the "female point" in CHA2DS2-VASc score should be reconsidered. The use of the CHA2DS2-VA score instead would not lead to underuse of anticoagulation, but in clinical practice, patients and physicians might be confused if the score is changed (Nielsen et al. 2018).

6.4 Quality of warfarin therapy and clinical outcome

6.4.1 Association between TTR and the risk of myocardial infarction and cardiovascular mortality

Study III showed that well-managed warfarin therapy reduced the risk of MI, MI mortality and cardiovascular mortality. The risk of these endpoints was significantly lower among AF patients with individual TTR60 over 80% than in the lower TTR60 groups. In the current study, the risk of MI clearly decreased among patients with TTR60 over 80% compared with the other TTR60 groups. It was estimated that an average patient with poor INR control (TTR60<40%) would have an almost 10%

absolute risk of developing MI within the next 5 years. In contrast, in those with TTR above 80%, the risk of MI would have been almost half (i.e., 5.2%).

In patients with acute coronary syndrome, concomitant AF predicts an adverse outcome (Almendro-Delia et al. 2014, Goranek et al. 2012), but the impact of warfarin therapy on the outcome of MI in general is sparsely characterized. In our study, the rate of MI mortality and cardiovascular mortality correlated inversely with the quality of warfarin therapy. That is, in patients with TTR60 over 80%, the outcomes were superior to any other TTR group, including TTR60=70-80%. The estimated risk of dying from MI within the next 5 years was 5.6% in an average patient with poor INR control (TTR60 less than 40%) compared with 2.1% in a patient with good INR control (TTR>80%). The corresponding number for cardiovascular mortality was 37.8% vs. 10.1%, respectively.

The results of our study are in line with previously published smaller series. In the SPORTIF III and IV studies, AF patients with poor-quality warfarin therapy (TTR<60%) were at a significantly higher risk of MI compared with patients with well-managed warfarin therapy (TTR>75%) (White et al. 2007). In the RE-LY trial, which compared warfarin therapy to dabigatran therapy in patients with nonvalvular AF, the patients with well-controlled VKA with TTR ≥65% had a lower MI rate compared with TTR <65%. More recently, in their study of a small cohort of 627 patients, Pastori et al. showed that TTR was an independent predictor of MACE (including MI and cardiovascular mortality) in patients with AF and warfarin therapy (Pastori et al. 2015).

Hence, aiming for high TTR is important not only to avoid strokes, but also in relation to the risk and outcome of MI and overall cardiovascular mortality.

The limitation of this study was that some important risk factors for MI, such as smoking status and alcohol consumption, were not available in the registries. The

use of aspirin and other over-the-counter drugs is not included in the registries in Finland, and therefore, data of their use was not available and could influence the results.

6.4.2 Impact of the female sex on the association between TTR and the risk of stroke, bleeding events, and mortality

Study IV showed no difference in the adjusted risk of stroke between male and female patients, who were anticoagulated with warfarin. The risk of bleeding events and cardiovascular and all-cause mortality were lower in women than in men.

Assessing the quality of anticoagulation therapy is crucial when evaluating the outcome of anticoagulated AF patients. In many previous studies, INR control during warfarin therapy has been worse in women compared with men (Senoo et al. 2016, Sullivan et al. 2012, Vinereanu et al. 2015). We used a continuously calculated TTR value 60 days before an index event (TTR60) to evaluate the quality of warfarin therapy. It describes not only the quality of oral anticoagulation therapy, but also depicts temporal associations between the quality of warfarin therapy and clinical outcomes. Poor TTR60 was associated with an increased risk of stroke and impaired cardiovascular outcome in both sexes. When dividing the patients into groups according to their TTR60 level, no sex-related differences were found in the risk of stroke and cardiovascular and all-cause mortality in patients with TTR60 over 50%.

Consistent with prior data (Renoux et al. 2017, Senoo et al. 2016), our study showed that female patients were at a lower risk for bleeding events leading to hospitalization compared with men both before and after adjusting for baseline characters in all pre-specified age and TTR60 groups; the reasons for this are unclear. The summary TTR over the whole study period was slightly better in females (62%) than in males (60%). Sensitivity analyses, investigating the effects of any previous hospitalizations, which

could have affected the quality of warfarin therapy, found no impact on the overall results. The use of aspirin and other over-the-counter drugs is unclear, as in study III. The main indication to combine aspirin to warfarin therapy would be prior myocardial infarction (MI). However, there were no sex difference in prior MIs or those during the study period in any TTR60 group. Additionally, as our data were adjusted for prior stroke or TIA and vascular disease, which are the other common indications for aspirin, it is unlikely that our results were related to a difference in the use of aspirin between the sexes. Clopidogrel was used more by male patients prior and during a follow-up. However, in the sensitivity analysis, where time periods of clopidogrel use were excluded, there were no changes in the results in any endpoint according to age or TTR60 groups.

Hence, in this population, the female sex was not a risk factor for an adverse outcome in patients with AF when treated properly with warfarin.

6.5 Use of medical therapies in patients with atrial fibrillation in the emergency department

6.5.1 Oral anticoagulation therapy

Study I indicates that physicians in the EDs in Finland recognized AF patients at a high thromboembolic risk well. Patients with the CHA2DS2-VASc score of at least 2 were categorized as high thromboembolic risk patients. Only 11 patients out of 1013 were categorized incorrectly as low-risk patients, despite the CHA2DS2-VASc score being at least 2. According to ESC guidelines, during the study period, AF patients with the CHA2DS2-VASc score of at least 2 were recommended to use OAC, if not contraindicated. In the FinFib2 study, ESC guidelines were followed well. OAC therapy was prescribed to 80% of the high-risk patients with newly

diagnosed AF, and 86% of the high-risk patients with previously diagnosed AF were anticoagulated when discharged from the ED. In previous studies, 71-75% of high-risk patients received OAC therapy, and the use of ASA has been much more common than in our study (Coll-Vinent et al. 2015, Lip et al. 2014).

However, our data indicated severe problems in the quality of warfarin therapy. In the FinFib2 study, most high-risk patients received warfarin therapy, but INR had been at a therapeutic level during the preceding month in only 58% of these patients. In comparison, a mean TTR was 55-65% in large phase 3 DOAC studies (Connolly et al. 2009, Giuliano et al. 2013, Granger et al. 2011, Patel et al. 2011) and 61% in the FinWAF study (Lehto et al. 2017).

Physicians in the ED play an important role in starting anticoagulation therapy for high-risk patients with AF. Our findings indicate, poor-quality warfarin therapy was a major problem, whereas the underuse of OAC in AF patients seems to be declining (Lehto et al. 2011). The use of DOACs is increasing due to education and better reimbursement, which may diminish the problem of labile INR values. Patients with labile INR levels and low TTR without any apparent reason should be switched to DOACs. The use of DOACs among patients with newly diagnosed AF should be encouraged.

6.5.2 Antiarrhythmic drug therapy

The aim of study II was to evaluate the use of antiarrhythmic drug therapy in AF patients being admitted to the emergency department due to symptomatic AF. The results of the study demonstrated that rate control therapy with beta blockers was used for most (80%) of the patients. However, despite recurrent symptoms and ESC guideline recommendations (Kirchhof et al. 2016), prior use and initiation of rhythm

control therapy with class I and III AAD were rare in patients being admitted to the ED with symptomatic AF.

Rate control therapy should be considered for all AF patients, if the ventricular rate during AF is rapid (Kirchhof et al. 2016). The efficacy of beta blockers to reduce ventricular rate in patients with AF is well-established, but their efficacy in the prevention of AF is only modest (Lafuente-Lafuente et al. 2015, Kühlkamp et al. 2000). In our study, 81% of patients with a prior diagnosis of AF were using beta blocker medication when admitted to the ED. Digoxin (9.2%) and calcium channel blockers (2.9%) were also used as rate control therapy. When discharged from the ED, 80% of these patients used beta blockers. In patients with newly diagnosed AF, a beta blocker was prescribed for 71% and a calcium channel blocker for 24% of patients. The need for rate control medication is well-recognized in EDs, and the use of beta blockers is at the same level as reported previously by Kuang et al. (2016), yet more frequent than in the Euro Heart Survey on Atrial Fibrillation (Dagres et al. 2007) and in the RACE study (Rienstra et al. 2005).

In patients with acute AF, normal sinus rhythm can effectively be restored by electrical or pharmacological cardioversion (Kirchhof et al. 2009). After cardioversion, the likelihood of AF recurrence is highest during the following weeks (Lafuente-Lafuente et al. 2015). It has been shown that 56% of the patients admitted to the ED with symptomatic AF will have a repeat visit due to AF recurrence within one year (Tran et al. 2016). Using AADs as a rhythm control therapy is indicated for patients with repeated episodes of AF and disturbing symptoms (Kirchhof et al. 2016). AADs are expected not only to improve the quality of life, but also to reduce the ED burden associated with AF. However, in our study, class I or III medication was started or the dosage of these drugs was changed only in 7% of patients with previously diagnosed AF. The use of class I and III AADs was rare compared with other studies (Dagres et al. 2007, Rienstra et al. 2005). It is well-established that early

intervention is crucial for the long-term efficacy of AAD or catheter ablation of AF. Therefore, the decision to start class I or III AAD therapy should be made in the ED, if structural heart disease has been excluded by recent examinations and clinical history.

The rate control therapy of AF patients is well-established in Finnish EDs. However, the use of class I and III AADs in rhythm control strategies is scarce. More education is needed to improve the use of these rhythm control medications to reduce the recurrence of symptomatic AF, to diminish the AF burden on the EDs, to avoid increasing costs associated with AF, and to improve the quality of life in AF patients. If a decision of AAD therapy cannot be made in the ED, patients should be electively referred for a cardiologist evaluation.

7 LIMITATIONS

The FinFib2 cohort provided a snapshot of AF patient management in an emergency department setting; therefore, no follow-up data were available. For example, many patients were electively referred to a cardiologist, but the results of further examinations and therapies were not available. Likewise, it was not possible to assess the rationality of all individual treatment decisions. The diagnoses of concomitant diseases were collected from patient medical records, which may have led to an underestimation of concomitant diseases and may have affected the CHA2DS2-VASc and HAS-BLED scores. The results of studies I and II may not be directly extrapolated to different health care systems, as in Finland, all inhabitants are covered by national health insurance, and patients need to pay only a nominal fee for ED admission and hospitalization. During the study period, the use of DOACs in Finland was rare. The main obstacle for this during the time of the study was the lack of reimbursement.

The FinWAF was retrospective register study, in which the data were collected as part of real-world healthcare activities. All the nationwide registries used in the FinWAF cohort have been validated, and the diagnoses have proved to be accurate (Furu et al. 2010, Rapola et al. 1997, Sund et al. 2012). Nevertheless, some secondary diagnoses, like hypertension, may have been underused in hospital discharge documents and death certificates, which may have influenced the CHA2DS2-VASc score. No information on the severity of concomitant diseases or cardiovascular risk factors, such as smoking, alcohol consumption, and dietary habits, were available. Individual treatment decisions by physicians might have excluded some AF patients

from the cohort, e.g. some fragile elderly female patients could have been left without OAC therapy and not included the cohort.

Data on some concomitant drugs that may have influenced the outcome were not available either because they were over the counter (e.g. aspirin and non-steroid anti-inflammatory drugs) or not included in the data collection permission (e.g. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers). The main indication to combine aspirin with warfarin therapy would be prior MI. However, there were no sex difference in prior MIs or those during the study period in any TTR60 group. Additionally, as our data were adjusted for prior stroke or TIA and vascular disease, which are the other common indications for aspirin, it is unlikely that our findings were related to a difference in the use of aspirin between the sexes in study IV. Clopidogrel was used more by male patients prior to (male 4.6%, female 3.5%, $P<0.001$) and during the follow-up period (male 4.7%, female 3.1%, $P<0.001$); however, the results were adjusted for prior stroke or vascular disease. Additionally, in the sensitivity analyses, where time periods of clopidogrel use were excluded, there were no changes in the results in any endpoint according to age or TTR60 group.

The exact reasons behind poor TTR remain to be established. Although the overall findings remained in the sensitivity analysis, investigating the effects of previous hospitalizations, it is possible that, in some cases, TTR was low because warfarin was discontinued on purpose (e.g. due to surgical interventions, cancer, bleeding).

8 SUMMARY AND CONCLUSIONS

AF is a growing health concern worldwide; the incidence and prevalence of AF is increasing rapidly. There is an urgent need for primary prevention strategies of AF; the risk factors of AF should be recognized, and we have to be aware of their local characteristics. There is also a need for a more detailed risk stratification of stroke and other complications associated with AF. A more detailed risk stratification is the basis for an individually tailored treatment of concomitant diseases predisposing to AF, stroke, and other adverse events associated with AF. It is also important to evaluate the use of treatment recommended by clinical practice guidelines and the effect of these therapies on the clinical outcome. The principal findings and conclusions are as follows:

1. The cardiovascular risk factors predisposing to AF are similar in Finland compared with previous reports from other Western countries. Hypertension is the most common cardiovascular risk factor, and its influence is highlighted in symptomatic AF patients admitted to the ED. The clinical interpretation is that the treatment of hypertension and other cardiovascular risk factors is important in patients with AF in order to reduce the AF burden and symptoms associated with AF.
2. The CHA2DS2-VASc score was good at predicting the risk of myocardial infarction and cardiovascular mortality in AF patients on OAC therapy. Hence, it could be used to identify patients who could benefit from strict treatment of cardiovascular risk factors.
3. TTR-related quality of warfarin therapy was important not only in order to prevent strokes, but also to decrease the risk of myocardial infarction,

bleeding events, and cardiovascular and all-cause mortality. There was no sex-related difference in the risk of stroke in patients with adequate OAC therapy, but female patients with warfarin therapy were at a lower risk of bleeding events and mortality rates than males in all age and TTR groups.
AF patients at a high thromboembolic risk were well-recognized in the EDs. The use of OAC therapy was on a good level compared with prior studies, but there were major concerns about the quality of warfarin therapy. In warfarin therapy, TTR up to 80% should be targeted, and patients with inadequate warfarin control without any apparent reason should be switched to DOAC therapy.

4. Rate control therapy with beta blockers is prescribed for most AF patients in the ED, but the use of class I and III AADs is rare in rhythm control strategies. There is a need for more education of physicians in the future in order to improve the use of AADs and to reduce AF burden and symptoms associated with AF.

9 ACKNOWLEDGEMENTS

This study was carried out at the Heart Center, Tampere University Hospital, and Tampere University.

First, I want to express my gratitude to my supervisors, Docent Pekka Raatikainen, M.D., and Docent Heikki Mäkynen, M.D. Pekka introduced me to the scientific part of cardiovascular medicine; he taught me the basics of electrophysiology and writing scientific articles and encouraged me at every step of this project. Pekka's enthusiasm in AF research has been vital for this project, like in many other AF studies. Heikki gave me the opportunity to learn electrophysiology in 2012 and has supervised me since then, both in scientific and clinical work. I could not think of a better colleague and supervisor.

Secondly, I want to thank Docent Mika Lehto, M.D., who had great influence on all the studies of this thesis. Mika has many years' experience in AF research and a strong clinical view on this topic. He has always given rapid, exact answers to my questions and helped me through any difficult steps in the writing process. I also want to thank my co-authors – Professor Riitta Lassila, M.D., Jussi Niiranen, M.D., Juha Lund, M.D., Ph.D., Timo Lauri, M.D., Ph.D., Professor Juha Hartikainen, M.D., Docent Markku Mäkijärvi, M.D., and Docent Harri Hyppölä, M.D. for their collaboration. Further, I would like to thank Pasi Korhonen, Juha Mehtälä, and Houssem Khanfir from EPID Research for the statistical analyses of the FinWAF data.

I am grateful to TAYS Heart Hospital, who gave me the possibility to enter into scientific work. Special thanks to Docent Kari Niemelä, CEO and Medical Director of the TAYS Heart Hospital, M.D., Docent Vesa Virtanen, M.D., Pasi Lehto, M.D., Ph.D., and Professor Kjell Nikus, M.D. for said opportunity.

It is a privilege to work in TAYS Heart Hospital with so many intelligent and wonderful colleagues. Special thanks to my teammates in EP team: Olli Arola, Jaakko Inkovaara, Harri Saarinen, Pavels Sipacovs, Sinikka Yli-Mäyry, and to our highly skilled EP nurses in the rhythm cardiology team.

My gratitude goes to the official reviewers of this thesis, Docent Tuomas Kiviniemi, M.D., and Professor Jari Laukkanen, M.D., for their evaluation of the manuscript and criticism, which helped improve it.

I wish to express my deepest gratitude to my mother Raija, father Olli, brother Jere, and sister Paula, who have given their everlasting support in all my decisions since childhood.

I want to thank Antti to being a great friend for a long time and for being my technical support 24/7.

Thank you Sari, the love of my life, for your love, support, and opinions which have kept me grounded. Your positive attitude to life is inspiring. Eeva, Anna and Eero, you are the stars, the priority, and the meaning of my life.

This study was financially supported by the Finnish Cardiac Society, TAYS Heart Center, Bristol-Myers Squibb & Pfizer Alliance, and Boehringer Ingelheim Finland.

10 REFERENCES

Adlan AM, Lip GY. Benefit-risk assessment of dronedarone in the treatment of atrial fibrillation. Drug Saf. 2013;36:93-110.

Akao M. Atrial fibrillation and coronary artery disease: Resembling twins? J Cardiol 2014;63:169-170.

Almendro-Delia M, Valle-Caballero MJ, Garcia-Rubira JC, Munoz-Calero B, Garcia-Alcantara A, Reina-Toral A, Benitez-Parejo J, Hidalgo-Urbano R. Prognostic impact of atrial fibrillation in acute coronary syndromes: results from the ARIAM registry. Eur Heart J Acute Cardiovasc Care 2014;3(2):141-148.

An J, Niu F, Lang DT, Jazdzewski KP, Le PT, Rashid N, Meissner B, Mendes R, Dills DG, Aranda Jr. G, Bruno A. Stroke and bleeding risk associated with antithrombotic therapy for patients with nonvalvular atrial fibrillation in clinical practice. J Am Heart Assoc 2015;4:e001921, doi: 10.1161/JAHA.115.001921.

Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. Eur Heart J 2013;1061-1067.

Baman JR, Mansour R, Heist K, Huang DT, Biton Y. Percutaneous left atrial appendage occlusion in the prevention of stroke in atrial fibrillation: a systematic review. Heart Fail Rev 2018;23:191-208.

Benjamin EJ, Levy D, Vaziri SM, D´Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840-844

Benjamin EJ, Wolf PA, D´Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-952.

Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755-759.

Boriani G, Proietti M. Atrial fibrillation prevention: an appraisal of current evidence. Heart 2017;0:1-6.

Brown L, Boos CJ. Atrial fibrillation and heart failure: Factors influencing the choice of oral anticoagulant. Int J Cardiol 2017;227:863-868.

Camm AJ, Accetta G, Al Mahmeed W, et al. Impact of gender on event rates at 1 year in patients with newly diagnosed non-valvular atrial fibrillation: contemporary perspective from the GARFIELD-AF registry. BMJ Open 2017;7:e014579. doi: 10.1136/bmjopen-2016-014579.

Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser S, Hindricks G, Kirchhof P. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719-2747.

Chao TF, Huang YC, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Hsieh MH, Lip GY, Chen SA. Acute myocardial infarction in patients with atrial fibrillation with a CHA2DS2-VASc score of 0 or 1: a nationwide cohort study. Heart Rhythm 2014;11:1941-1947.

Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, et al. Rate-Control Treatment and Mortality in Atrial Fibrillation. Circulation 2015;132:1604-1612.

Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, et al. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive anticoagulation? J Am Coll Cardiol 2015;65:635-642. (A)

Chimenti C, Russo MA, Capri A, Frustaci A. Histological substrate of human atrial fibrillation. Biomed Pharmacother 2010;64:177-183.

Chugh SS, Havmoeller R, NarayananK, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 2014;120(8):837-47.

Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, Fox KA, Chasebro JH, Strain J, Keller C, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic therapy in acute coronary syndromes research group. Circulation 1994;89:81-88.

Coll-Vinent B, Martin A, Malagon F, Suero C, Sanchez J, Varona M, et al. HERMES-AF Investigators. Stroke prophylaxis in atrial fibrillation: searching for management

improvement opportunities in the emergency department: the HERMES-AF study. Ann Emerg Med 2015;65:1-12.

Connolly SJ, Camm AJ, Halperin JL, et al for the PALLAS Investigators. Dronedarone in high risk permanent atrial fibrillation. N Engl J Med 2011;365:2268-2276.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikolboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151.

Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012;367:1587-1595.

Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson SM, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised controlled trial. Heart;103:368-376.

Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S, Kramastinos D, Breithardt G, Cokkinos DV, Crijns HJ. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe. A report from the Euro Heart Survey on Atrial Fibrillation. J Am Coll Cardiol 2007;49:572-577.

Douxfils J, Buckinx F, Mullier F, Minet V, Rabenda V, Reginster J, Hainault P, Bruyere O, Dogne J. Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2014;3:e000515. doi: 10.1161/JAHA.113.000515.

Du X, Dong J, Ma C. Is atrial fibrillation a preventable disease? J Am Coll Cardiol 2017;69:1968-1982

Edmin CA, Wong CX, Hsioao AJ, Altman DG, Peters SA, Woodward M, Odutayo A. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ 2016;532:h7013. doi: 10.1136/bmj.h.7013.

Elkayam U. Calcium channel blockers in heart failure. Cardiology 1998;89:38-46.

Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation:

the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2005;112:1687-1691.

Ferrari R, Bertini M, Blomstom-Lundqvist C, Dobrev D, Kirchhof P, Pappone C, Ravens U. An update on atrial fibrillation in 2014: From pathophysiology to treatment. Int J Cardiol 2014;203:22-29.

Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet 2016;388:806-817.

Friberg LF, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. BMJ 2012;344:e3522 doi: 10.1136/bmj.e3522.

Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 2010;106:505-515.

Gallego P, Lip GY, Lane DA. Bleeding risk during oral anticoagulation therapy for atrial fibrillation. Europace 2013;15:773-774.

Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110:364-367.

Giuliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Phil D, Weitz JI, Spinar J, Ruzyllo W, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-2104.

Go AS, Hylek EM, Philips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implication for rhythm management and stroke prevention. The Anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 2001;285:2370-2375.

Gomberg-Maitland M, Wenger NK, Feyzi J, Lengeyel M, Volgman AS, Peterssen P, Frison L, Halperin JL. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. Eur Heart J 2006;27:1947-1953.

Gorenek B, Kudaiberdieva G. Atrial fibrillation in acute ST-elevation myocardial infarction: clinical and prognostic features. Curr Cardiol Rev 2012;8(4):281-289.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.

Haissaguerre M, Jais P, Shah D, Takahashi A, Hocini M, Quiniou G, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666.

Hakalahti A, Biancari F, Cosedis Nielsen J, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace 2015;17:370-378.

Hart RG, Benavente O, Mc Bride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.

Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-867.

Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) investigators. Stroke 1999;30;1223-1229. (B)

Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015; 17:1467-1507.

Hirch J, Dalen J, Anderson D, Poller L, Bussey H, Ansell J, Deykin D, Brandt J. Oral anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. Chest 1998;114:445S-469S.

Hohnloser SH, Crijns HJ, Van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668-678.

Holmes DR, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation. A patient-level meta-analysis. J Am Coll Cardiol 2015;65:2614-1623.

Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman left atrial appendage closure

device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1-12.

Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation, a randomized non-inferiority trial. Lancet 2009;374:534-542.

Hughes M, Lip GY, et al. Stroke and thromboembolism in atrial fibrillation: A systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. Thromb Haemost 2008;99:295-304.

Hurlem M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin or both after myocardial infarction. N Engl J Med 2002;347:969-974.

Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loetr RL, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011;123:1501-1508

Jaakkola S, Kiviniemi TO, Nuotio I, Hartikainen J, Mustonen P, Palomäki A, Jaakkola J, Ylitalo A, Hartikainen P, Airaksinen KEJ. Usefulness of the CHA2DS2-VASc and HAS-BLED scores in predicting the risk of stroke versus intracranial bleeding in patients with atrial fibrillation (from the FibStroke study). Am J Cardiol 2018;121:1182-1186).

Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982;306:1018-22.

Kannel W, Wolf P, Benjamin E. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population based estimates. Am J Cardiol 1998;82:2N-9N.

Kim KH, Kim W, Hwang SH, Kang WY, Cho SC, Kim W, Jeong MH. The CHA2DS2-VASc score can be used to stratify the prognosis of acute myocardial infarction patients irrespective of presence of atrial fibrillation. J Cardiol 2015;65:121-127.

Kirchhof P, Bax J, Blomstrom-Lundqvist C, Calcins H, Camm AJ, Cappato R, et al. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference research perspectives in AF. Eur Heart J 2009;30:2969-2977.

Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration With EACTS. Eur Heart J 2016;37:2893-2962.

Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, Bailleul C, Bax J, Benninger G, Blomström-Lundqvist C, Boersma L, Boriani G, Brandes A, Brown H, Brueckmann M, Calcins H, et al. Personalized management of atrial fibrillation: proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. Europace 2013;15:1540-1556.

Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2011;57:427-436.

Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. Int J Cardiol. 2016;203:660-666.

Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, et al. Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384:2235-2243.

Kozlowski D, Budrejko S, Lip GY, Mikhailidis D, Rysz J, Raczak G, Banach M. Dronedarone: an overview. Ann Med 2012;44:60-72.

Kuang P, Mah ND, Barton CA, Miura AJ, Tanas LR, Ran R. Achieving ventricular rate control using metoprolol in β-blocker-naïve patients vs patients on chronic β-blocker therapy. Am J Emerg Med 2016;34:606-608.

Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374:2235-2245.

Kumar K, Zimetbaum P. Antiarrhythmic Drugs 2013: State of the Art. Curr Cardiol Rep 2013;15:410.

Kühlkamp V, Schirdewan A, Strangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after cardioversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 2000;36:139-146.

Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database SystRev 2015; doi:10.1002/14651858.CD005049.pub4.

Lane DA, Lip GY. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. Thromb Heamost 2009;101:802-805.

Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol 2014;64:281-289.

Lau D, Linz D, Schotten U, Mahjan R, Sanders P, Kalman J. Pathophysiology of Paroxysmal and Persistent Atrial Fibrillation: Rotors, Foci and Fibrosis. Heart, Lung and Circulation 2017;26:887-893.

Lau D, Nattel S, Kalman J, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. Circulation 2017;136:583-596.

Lee CJ, Gerds TA, Carlson N, Bonde AN, Gislason GH, Lamberts M, Olesen JB, Pallisgaard JL, Hansen ML, Torp-Pedersen C. Risk of myocardial infarction in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2018;72:17-26.

Lehto M, Niiranen J, Korhonen P, Mehtälä J, Khanfir H, Hoti F, Lassila R, Raatikainen P. Quality of warfarin therapy and risk of stroke, bleeding, and mortality among patients with atrial fibrillation: results from the nationwide FinWAF registry. Pharmacoepidemiol Drug Saf. 2017;26:657-665.

Lehto M, Raatikainen P, Mäkynen H, Peiponen M, Kyhälä-Valtonen H, Hartikainen J, Lund J, Ahonen J, Mäkijärvi M. Eteisvärinän hoito Suomessa - FinFib-tutkimus. SLL 2011;45:3401-3407.

Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. "Real-world" antithrombotic treatment in atrial fibrillation: the EORP-AF pilot survey. Am J Med 2014;127:519-529.

Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-272.

Lip GY, Ruston-Smith SK, Goldhaber SZ, Fitzmaurice DA, Mantovani LG, Goto S, Haas S, Bassand JP, Camm AJ, Ambrosio G, Jansky P, Al Mahmeed W, Oh S, van Eickels M, Raatikainen P, Steffel J, Oto A, Kayani G, Accetta G, Kakkar AK. Does sex affect

anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. Circ Cardiovasc Qual Outcomes 2015;8:12-20. (A)

Lip GY, Skjøth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with non-valvular atrial fibrillation with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. J Am Coll Cardiol 2015;65:1385-1394. (B)

Liu S, Li X, Shi Q, Hamilton M, Friend K, Zhao Y, Horblyuk R, Hede S, Shi L. Outcomes associated with warfarin time in therapeutic range among US veterans with nonvalvular atrial fibrillation. Curr Med Res Opin 2017;34:1-7.

Lopez-Lopez J, Sterne J, Thom H, Higgins J, Hingorani A, Okoli G, Davies P, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359:j5058.

Magnani JW, Rienstra M, Lin H, Siiner MF, Lubitz SA, McManus DD, et. al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. Circulation 2011;124:1982-1993.

Mahnkopf C, Badger TJ, Burgon NS, et al. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: implications for disease progression and response to catheter ablation. Heart Rhythm 2010;7:1475-1481.

Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 2009;11:676-683.

Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-427.

McDonald AJ, Pelletier AJ, Ellinor PT, Camargo CA. Increasing US emergency department visit rates and subsequent hospital admissions for atrial fibrillation from 1993 to 2004. Ann Emerg Med 2008;51:58-65.

Melenowsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ. Heart Fail. 2015;8:295-303.

Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. J Thromb Haemost 2012;10:1745-1751.

Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA 2014;311:692-700.

Murphy NF, Simpson CR, Jhund PS, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart 2007;93:606-612.

Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol 2008;1:62-73.

Nattel S, Guasch E, Savelieva I, et al. Early management of atrial fibrillation to prevent cardiovascular complications. Eur Heart J 2014;35:1448-1456.

Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev 2005;85:1205-1253.

Ng GA. Feasibility of selection of antiarrhythmic drug treatment on the basis of arrhythmogenic mechanism – Relevance of electrical restitution, wavebreak and rotors. Phamacol Ther 2017;176:1-12.

Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GY. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: Should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation 2018;137:832-840.

Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of Medical heart rate control management. Postgrad Med J 2009;85:303-312.

Noheria A, Shrader P, Piccini JP, Fonarow GC, Kowey PR, Mahaffey KW, Naccarelli G, Noseworthy PA, Reiffel JA, Steinberg BA, Thomas LE, Peterson ED, Gersh BJ; ORBIT-AF Investigators and patients. Rhythm control versus rate control and clinical outcomes in patients with atrial fibrillation: Results from the ORBIT-AF Registry. JACC Clin Electrophysiol 2016;2:221-229.

Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GY. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke 2017;48:2494-2503.

Nyong J, Amit G, Adler AJ, Owolabi OO, Perel P, Prieto-Merino D, Lambiase P, Casa JP, Morillo CA. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. Cochrane Database Syst. Rev. 2016;11:CD012088.

Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P, Sigamani A, Morillo CA, Liu L, Damasceno A, Grinvalds A, Nakamya J, Reilly PA, Keltai K, Van Gelder IC, Yusufali AH, Watanabe E, Wallentin L, Connolly SJ, Yusuf S. Variations in cause and management of atrial fibrillation in a prospective registry of 15 400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. Circulation 2014;129:1568-1576.

Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolsrup JS, Lindhardsen J, Selmer C, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.

Overvad TF, Rasmussen LH, Skjøth F, et al. Female sex as a risk factor for thromboembolism in patients with atrial fibrillation. The prospective Danish Diet, Cancer and Health study. Thromb Haemost 2014;112:789-795.

Palomäki A, Mustonen P, Hartikainen JE, Nuotio I, Kiviniemi T, Ylitalo A, Hartikainen P, Airaksinen KE. Underuse of anticoagulation in stroke patients with atrial fibrillation – the FibStroke Study. Eur J Neurol 2016;23:133-139.

Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of Gender Differences in Residual Stroke Risk and Major Bleedings in Patients with Nonvalvular Atrial Fibrillation Treated with Oral Anticoagulants. Am J Cardiol 2014;113:485-490.

Pang H, Han B, Fu Q, Zong Z. Predictive value of CHADS2 and CHA2DS2-VASc scores for acute myocardial infarction in patients with atrial fibrillation. Sci Rep 2017;7:4730.

Pastori D, Farcomeni A, Poli D, Antonucci E, Angelico F, Del Ben M, Cangemi R, Tanzilli G, Lip GY, Pignatelli P, Violi F. Cardiovascular risk stratification in patients with non-valvular atrial fibrillation: the 2MACE score. Intern Emerg Med 2016;11:199-204.

Pastori D, Pignatelli P, Saliola M, Carnevale R, Vicario T, Del BM, Cangemi R, Barilla F, Lip GY, Violi F. Inadequate anticoagulation by Vitamin K Antagonists is associated with Major Adverse Cardiovascular Events in patients with atrial fibrillation. Int J Cardiol 2015;201:513-516.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hanke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-891.

Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65:2159-2169.

Piccini JP, Fauchier L. Rhythm control in atrial fibrillation. Lancet 2016;388:829-840.

Piccini JP, Simon DN, Steinberg BA, Thomas L, Allen LA, Fonarow GC, Gersh B, Hylek E, Kowey PR, Reiffel JA, Naccarelli GV, Chan PS, Spertus JA, Peterson ED. Differences in clinical and functional outcomes of atrial fibrillation in women and men: Two-year results from the ORBIT-AF registry. JAMA Cardiol 2016;3:282-291.

Pisters R, Lane D, Nieuwlaat R, De Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. Chest 2010;138:1093-1100.

Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, Singer DE, Ansell J, Blanco RG, Gersh B, Mahaffey KW, Hylek EM, Go AS, Piccini JP, Peterson ED. Patients´ time in therapeutic range, and clinical outcomes in atrial fibrillation patients taking warfarin. Stroke 2016;47:1665-1668.

Rapola JM, Virtamo J, Korhonen P, Haapakoski J, Hartman AM, Edwards BK, Heinonen OP. Validity of diagnoses of major coronary events in national registries of hospital diagnoses and deaths in Finland. Eur J Epidemiol 1997;13:133-138.

Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. J Am Coll Cardiol 2017;24:2964-2975.

Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from PROTECT AF and the Continued Access Registry. Circulation 2011;123:417-424.

Renoux C, Coulombe J, Suissa S. Revisiting sex differences in outcomes in non-valvular atrial fibrillation: a population-based cohort study. Eur Heart J 2017;38:1473-1479.

Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, Van Gelder IC. Gender-related differences in rhythm control treatment in persistent atrial

fibrillation. Data of the rate control versus electrical cardioversion (RACE) study. J Am Coll Cardiol 2005;46:1298-1306.

Rolf S, Komej J, Dagres N, Hindricks G. What can rhythm control therapy contribute to prognosis in atrial fibrillation? Heart 2015;101:842-846.

Rosendaal F, Cannegieter S, van der Meer F, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Heamost 1993;69:236-239.

Roskell NS, Samuel M, Noack H, Monz BU. Major bleeding in patients with atrial fibrillation receiving vitamin K antagonists: a systematic review of randomized and observational studies. Europace 2013;15:787-797.

Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian trial of atrial fibrillation investigators. N Engl J Med 2000;342;913-920.

Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadaylu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamasita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-962.

Schnabel R, Yin X, Gona P, Larson M, Beiser A, McManus D, et al. Fifty-Year Trends in Atrial Fibrillation Prevalence, Incidence, Risk Factors, and Mortality in the Community. Lancet 2015;386:154-162.

Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. The evidence regarding the drugs used for ventricular rate control. J Fam Pract 2000;49:47-59.

Senoo K, Lip GY. Female sex, Time in Therapeutic Range, and Clinical Outcomes in Atrial Fibrillation Patients Taking Warfarin. Stroke 2016;47:1665-1668.

Sethi NJ, Nielsen E, Safi S, Feinberg J, Gluud C, Jakobsen J. Digoxin for atrial fibrillation and flutter: A systematic review meta-analysis and trial sequential analysis of randomized clinical trials. PLoS One 2018;13: e0193924.

Shahid F, Pastori D, Violi F, Lip GY. Prognostic and therapeutic implications of vascular disease in patients with atrial fibrillation. Pharmacol Res. 2018;132:149-159.

Singh BN. β-Adrenergic Blockers as Antiarrhythmic and Antifibrillatory Compounds: An overview. J Cardiovasc Pharmacol Therapeut 2005;Vol 10 supplement 1:S3-S14.

Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987-999.

Singh BN, Singh SN, Reda DJ, Tang XC, Lopez P, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861-1872.

Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. JAMA Internal Med 2014;174:107-114.

Stroke in AF working group 2007. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69:546-554.

Sullivan RM, Zhang J, Zamba G, Lip GY, Olhansky B. Relation of gender specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from Affirm). Am J Cardiol 2012;110:1799-1802.

Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health 2012;40:505-515.

Tamargo J, Capucci A, Mabo P. Safety of flecainide. Drug Saf. 2012;35:273-289.

Therneau T, Grambsch P. Modelling survival data: Extending the Cox model. Springer: New York, ISBN 0-387-98784-3. Chapter102000;261-287.

Tran C, Bennell MC, Qiu F, Ko DT, Singh SM, Dorian P, et al. Predictors and clinical outcomes of inpatients versus ambulatory management after an emergency department visit for atrial fibrillation: a population based study. Am Heart J 2016;173:161-169.

Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Herat J 2015;36:1831-1838.

Van Gelder IC, Crijns HJ, Van Gilst WH, Van Wijk LM, Hamer HP, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or flutter. Am J Cardiol 1989;64:1317-1321.

Van Gelder I, Rienstra M, Crijns H, Olshansky B. Rate control in atrial fibrillation. Lancet 2016;388:818-828.

Vaughan-Williams EM. The experimental basis for the choice of an anti-arrhythmic drug. Adv Cardiol 1970;4:275-289.

Vaughan-Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 1984;24:129-147.

Viles-Gonzales JF, Halperin JL. Efficacy and safety of amiodarone in patients with atrial fibrillation in the era of target-specific anticoagulants. J Am Coll Cardiol 2014;64:1551-1553.

Vinereanu D, Stevens SR, Alexander JH, et al. Clinical outcomes in patients with atrial fibrillation according to sex during anticoagulation with abixaban or warfarin: a secondary analysis of randomized controlled trial. Eur Heart J 2015;36:3268-3275.

Violi F, Soliman EZ, Pignatelli P, Pastori D. Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. J Am Heart Assoc 2016;5:e003347.

Voigt N, Heijman J, Wang Q, et al. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. Circulation 2014;129:145-156.

Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D`Agostino RB, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290:1049-1055.

Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM 2014;107:955-967.

Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005;293:2634-2640.

White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007;167(3):239-245.

Wessler S, Gitel S. Pharmacology of Heparin and Warfarin. JACC 1986;8:10B-20B.

Wolf PA, Abbott R, Kannel W. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. Arch Intern Med 1987;147:1561-1564.

Zoni-Berisso M, Lercari F, Carazza T, Dominicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-20.

11 PUBLICATIONS

Penttilä et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2017) 25:81
DOI 10.1186/s13049-017-0424-7

Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

ORIGINAL RESEARCH Open Access

Antiarrhythmic drug therapy among patients presenting to emergency department with symptomatic atrial fibrillation – a prospective nationwide cohort

Tero Penttilä[1*], Heikki Mäkynen[1], Juha Hartikainen[2], Harri Hyppölä[3], Timo Lauri[4], Mika Lehto[5], Juha Lund[6], MJ Pekka Raatikainen[5] and for the FinFib2 investigators

Abstract

Background: Atrial fibrillation (AF) is a common arrhythmia that causes numerous visits to emergency departments (ED). The aim of the FinFib2 study was to evaluate whether treatment of patients with AF in ED is consistent with the contemporary European Society of Cardiology (ESC) management guidelines. Here we report the results of antiarrhythmic drug therapy (AAD) in ED.

Methods: All patients within the two-week study period whose primary reason for the ED visit was symptomatic AF were included into this prospective multicentre study. Comprehensive data on factors contributing to the treatment of AF were collected, including a data of previous use of ADDs, and changes made for them during a visit in ED.

Results: The study population consisted of 1013 consecutive patients (mean age 70 ± 13 years, 47.6% female). The mean European Heart Rhythm Association (EHRA) symptom score was 2.2 ± 0.8. Rhythm control strategy was opt for 498 (63.8%) and 140 (64.5%) patients with previously and newly diagnosed AF, respectively. In patients with previously diagnosed AF the most frequently used AAD was a beta blocker (80.9%). Prior use of class I (11.4%) and III (9.1%) AADs as well as start or adjustment of their dosage (7.4%) were uncommon. Most of the patients with newly diagnosed AF were prescribed a beta blocker (71.0%) or a calcium channel antagonist (24.0%), and only two of them received class I or class III AADs.

Conclusions: Our data demonstrated that in patients presenting to the ED with recurrent symptomatic AF and aimed for rhythm control strategy, the use of class I and class III AADs was rare despite ESC guideline recommendations. It is possible that early adaptation of a more aggressive rhythm control strategy might improve a quality of life for symptomatic patients and alleviate the ED burden associated with AF. Beta blockers were used by majority of patients as rate control therapy both in rate and rhythm control groups.

Trial registration: NCT01990105. Registered 15 November 2013.

Keywords: Atrial fibrillation, Emergency department, Antiarrhythmic medication, Rhythm control, Rate control, EHRA score

* Correspondence: tero.penttila@sydansairaala.fi
[1]Heart Center Co. Tampere University Hospital, P.O. Box 2000, -33521 Tampere, FI, Finland
Full list of author information is available at the end of the article

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia [1]. Given the predicted increase in the incidence of AF it has been estimated that in 2030 there will be 14–17 million patients with AF in Europe [2–4]. Consequently, the amount of AF related visits to the emergency departments (ED) is likely to rise extensively in near future [5].

Emergency departments play a key role in management of AF [6]. In patients with acute AF the decision between rhythm and rate control is done in the ED. The severity of symptoms related to AF is the main factor in selection of the treatment strategy [7]. Age, presence of structural heart disease and other co-morbidities, the type of AF and contraindications to antiarrhythmic drugs (AAD) should also be taken into account when evaluating the need and reasonability of cardioversion, and how to prevent recurrent AF episodes [8]. The efficacy and safety of beta blockers and calcium channel antagonists are well established in acute and long-term rate control [9]. Rate control therapy should consider for all patients with AF if needed, both in a rate and a rhythm control strategies [10, 11]. In a rhythm control strategy, additionally class I and III AADs are recommended to maintain sinus rhythm [12–17]. Regardless of the chosen treatment strategy the need of oral anticoagulation (OAC) along with risk factors for thromboembolic complications and bleeding must be evaluated [10, 11].

The results of previous studies indicate that there is large variation in the management of AF in the ED [18, 19]. The FinFib2 study was designed to evaluate whether the treatment of patients with symptomatic AF in the ED is in line with the European Society of Cardiology (ESC) treatment guidelines valid at the study period 2013 [10, 11]. We report real life data on the selection of the treatment strategy, symptoms and risk factors of AF, and use of antiarrhythmic medication in these patients.

Methods

Study design and patient population

This prospective snapshot study was conducted in 35 EDs around Finland. There were a large variation of size and facilities of EDs; units from small heath care centers to big university hospitals were participating. Finland is divided into five university hospital districts, and patients from all of them were enrolled in order to avoid any bias due to geographical differences. All patients whose primary reason for the ED visit was symptomatic AF during a two-week study period (November 11–23, 2013) were included.

Data on concomitant diseases, risk factors for AF, and a history of thromboembolic complications, treatment strategy, and use of antiarrhythmic medication was collected using predefined internet based case report form. A rhythm control strategy means a physician's aim to maintain a sinus rhythm. A rate control strategy means a physician's decision to accept a permanent AF. Symptoms associated to AF were ranked using European Heart Rhythm Association (EHRA) score [10] (Fig. 1). Antiarrhythmic drugs were classified according to the Vaughan Williams classification (Table 1).

A data of prior use and changes made for AADs in ED were collected. A physician in ED made an independent decision to choose a rate control strategy or a rhythm control strategy for each patient. We evaluated the use of AAD therapy during an ED visit to support that decision; if the rhythm control was chosen, were a class I or III AAD started or a dosage of these drugs changed. We also evaluated a use of rate control drugs (beta and calcium channel blockers) for all patients, both in a rate and a rhythm control groups.

Statistical analysis

The data were analysed using IBM SPSS Statistics software package version 22 (IBM SPSS Inc., Armonk, NY, USA). Missing data values were excluded from the statistical analysis. Continuous variables are expressed as mean ± standard deviation and compared with independent variables t-test or Mann-Whitney U-test when appropriate. Categorical variables are expressed as numbers and percentages and compared by Fisher's exact test. All tests were two-sided and a P value of <0.05 was considered statistically significant.

Results

Baseline characteristic of the study population

A total of 1013 consecutive patients with symptomatic AF were enrolled into the study. In 217 (21.4%) patients AF was diagnosed for the first time in the ED, whereas 780 (77.0%) patients had recurrent AF. The mean age of the patients was 70.0 ± 13.1 years (19–103 years) - 67.7% of them were 65 years or older, and 39.5% were 75 years or older. Slightly less than half of them (47.6%) were female. The most common underlying diseases were hypertension (65.0%), dyslipidaemia (43.5%), coronary artery disease (23.2%), and diabetes (21.1%) (Table 2).

The mean EHRA score was 2.2 ± 0.8. The most frequent symptom was palpitation (620 patients, 61.2%). Other AF related symptoms included dyspnoea (270 patients, 26.7%), dizziness (197 patients, 19.4%), and chest pain (125 patients, 12.3%). Eighteen patients (1.8%) had had syncope. Almost half of the patients with previously diagnosed AF (354 patients, 45.4%) had had at least one visit to the ED because of AF within the preceding

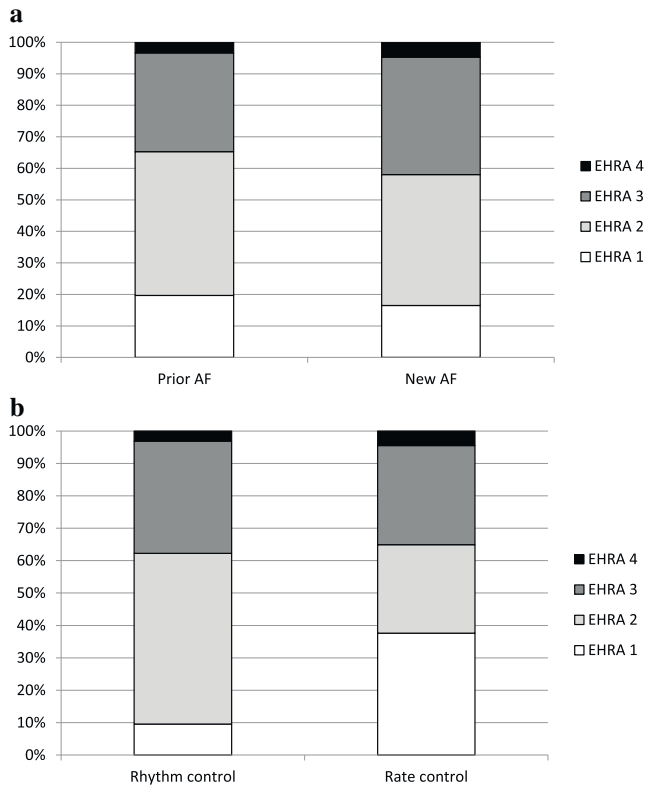


Fig. 1 Classification of AF related symptoms according to the European Heart Rhythm Association (EHRA) score in patients with prior (n = 780) and newly diagnosed AF (n = 217) (**a**) and in patients with rhythm control (n = 659) and rate control strategy (n = 336) (**b**). EHRA 1 = no symptoms, EHRA 2 = mild symptoms (normal daily activity not affected), EHRA 3 = severe symptoms (normal daily activity affected), EHRA IV = disabling symptoms (normal daily activity discontinued)

12 months. For these patients, the mean number of prior ED admissions per patient was 2.7 ± 3.6 (range 1–30).

Prior antiarrhythmic therapy

Most of the patients (85.3%) with previously diagnosed AF were using antiarrhythmic medication for rhythm or rate control when admitted to the ED. Beta blockers were used by 631 (80.9%), digoxin by 72 (9.2%), and verapamil or diltiazem by 23 (2.9%) of these patients. Class I AADs were used by 89 (11.4%) patients. The majority of them were using flecainide (87 patients, 11.2%), and two patients were on quinidine (0.3%). The other AADs included amiodarone (26 patients, 3.3%), dronedarone (30 patients, 3.8%) and sotalol (15 patients, 1.9%).

Treatment strategy and initial management in the ED

In patients with previously diagnosed AF the rhythm disorder was paroxysmal in 282 (36.5%), persistent in 298 (38.7%) and permanent in 191 (24.8%) patients. Rhythm control strategy was chosen by ED physicians in 498 of the 580 (85.9%) patients with paroxysmal or persistent AF. Among them 287 and 62 patients underwent successful acute electrical or pharmacological cardioversion, respectively. Sinus rhythm restored spontaneously or an elective cardioversion were planned in 149 patients. The AADs used for pharmacological cardioversion included flecainide (17 patients), amiodarone (7 patients), vernakalant (6 patients), and a beta blocker or digoxin (32 patients).

There were 217 patients with newly diagnosed AF in the study population. The rhythm control strategy was chosen for 140 (64.5%) of them. Normal sinus rhythm resumed spontaneously in 51 patients. Electrical or pharmacological cardioversion was performed in 43 and 21 (beta blocker 17, digoxin 1, flecainide 3, amiodarone 1) patients, respectively. An elective cardioversion was planned for 25 patients.

Table 1 Antiarrhythmic drugs according to the Vaughan Williams classification. None of the patients received drugs which are presented in parenthesis

Classification	Agents	Mechanism of action	Notes
IA	(Disopyramide) Quinidine (Procainamide)	Sodium channel blockade with intermediate association/dissociation and potassium channel blockade	Contraindicated in patients with structural heart diseases
IB	(Lidocaine) (Mexiletine)	Sodium channel blockade with rapid association/dissociation	Not indicated for AF
IC	Flecainide (Propafenone)	Sodium channel blockade with slow association/dissociation	Contraindicated in patients with structural heart diseases
II	(Atenolol) (Asebutolol) (Betaxolol) Bisoprolol Carvedilol Metoprolol (Nebivolol) (Pindolol) Propranolol (Seliprolol)	Beta adrenergic receptor blockade	Can be used also in patients with structural heart disease More effective in rate than rhythm control
III	Amiodarone Dronedarone Sotalol Vernakalant	Potassium channel blockade Amiodarone and dronedarone have also class I, II and IV activity Sotalol has also class II activity Vernakalant blocks sodium and potassium channels in atria but not in ventricles	Dronedarone is contraindicated in severe heart failure and permanent AF Extra cardiac adverse events (e.g., liver and pulmonary toxicity and thyroid dysfunction) are common with amiodarone Vernakalant is available only for acute intravenous use
IV	Verapamil Diltiazem	Calcium channel blockade	Should be avoided in patients with congestive heart failure
Others	Digoxin	Variable mechanisms	May have adverse effect on the prognosis of patients with AF

The patients in whom rate control strategy was chosen were significantly older than those with rhythm control strategy (78.6 ± 10.1 vs. 65.7 ± 12.4 years, $P < 0.001$). The EHRA score was significantly higher among patients with rhythm control strategy (2.3 ± 0.7 vs. 2.0 ± 0.9, $P < 0.001$), whereas the CHA_2DS_2VASc (4.4 ± 1.8 vs. 2.4 ± 1.9, $P < 0.001$) and HAS-BLED (2.6 ± 1.2 vs. 1.5 ± 1.1, $P < 0.001$) scores were higher among those with rate control strategy (Table 2).

Antiarrhythmic drug therapy at discharge

At discharge from the ED 625 (80.1%) patients with prior AF diagnosis were prescribed beta blocker medication. Despite recurrent AF symptoms a change in antiarrhythmic medication was done only in 97 of these patients (12.4%). Class I or III antiarrhythmic medication was started or the dosage of the drug used was adjusted in 37 (7.4%) of the patients with previous AF diagnosis and rhythm control strategy. The reasons for the changes in AAD therapy included inadequate antiarrhythmic efficacy (68 patients), adverse effects (11 patients), change into rate control strategy (19 patients) and lack of compliance (1 patient).

In patients with newly diagnosed AF a beta blocker was prescribed for 154 (71.0%), a calcium channel antagonist for 52 patients (24.0%), and digoxin for 8 patients (3.7%). Amiodarone was started for 2 patients, but no class I drugs were prescribed for the patients with newly diagnosed AF.

Discussion

The results of the FinFib2 study demonstrated that despite recurrent symptoms and ESC guideline recommendations prior use and initiation of class I and class III antiarrhythmic medication are rare in patients presenting to the ED with symptomatic AF (Fig. 2).

At admission to the ED class I or III antiarrhythmic drugs were used only by 20.5% of the patients with prior AF diagnosis, and at discharge 36.5% of the patients in the rhythm control group were prescribed class I or III antiarrhythmic medication. With regard to the current guidelines recommending execution of "upstream" therapy and use of class I and III antiarrhythmic drugs in the early stage of the disease, these numbers appear low [20, 21]. In patients with highly symptomatic AF active rhythm control strategy is expected not only to improve the quality of life, but also to reduce ED burden associated with AF.

After cardioversion, the likelihood of AF recurrences is highest during the following weeks [22]. It has been shown that 56% of the patients presenting to the ED with symptomatic AF will have a repeat ED visit due to

Table 2 Clinical characteristics of the patients with symptomatic atrial fibrillation (AF) on admission to the emergency department in the rhythm versus rate control groups

	Total n (%)	Rhythm control n (%)	Rate control n (%)	*P*-value
Patients	1013	659 (65.1)	336 (33.2)	
Previously diagnosed AF	780	498 (63.8)	261 (33.5)	
Newly diagnosed AF	217	140 (64.5)	71 (32.7)	
Age	70.0 ± 13.1 (19–103)	65.7 ± 12.4	78.6 ± 10.1	< 0.001
Female	482 (47.6)	267 (40.5)	205 (61.0)	< 0.001
Congestive heart failure	176 (17.4)	57 (8.6)	115 (34.2)	< 0.001
Hypertension	658 (65.0)	395 (59.9)	251 (74.7)	< 0.001
Diabetes	214 (21.1)	116 (17.6)	95 (28.3)	< 0.001
Stroke	81 (8.0)	37 (5.6)	41 (12.2)	< 0.001
Transient ischemic attack	53 (5.2)	21 (3.2)	32 (9.5)	< 0.001
Other thromboembolic events	24 (2.4)	8 (1.2)	15 (4.5)	0.003
Coronary artery disease	235 (23.2)	106 (16.1)	122 (36.3)	< 0.001
Previous myocardial infarction	126 (12.4)	55 (8.3)	66 (19.6)	< 0.001
Atherosclerosis	39 (3.8))	15 (2.3)	24 (7.1)	< 0.001
Dyslipidaemia	441 (43.5)	273 (41.4)	161 (47.9)	0.042
Ongoing or ex-smoking	254 (25.1)	174 (26.4)	75 (22.3)	0.809
Valvular disease	128 (12.6)	63 (9.6)	65 (19.3)	< 0.001
Thyroid dysfunction	112 (11.1)	66 (10.0)	45 (13.4)	0.136
Lung disease	135 (13.3)	72 (10.9)	61 (18.2)	0.002
Renal insufficiency	100 (9.9)	27 (4.1)	70 (20.8)	< 0.001
Liver insufficiency	18 (1.8)	7 (1.1)	11 (3.3)	0.021
Anaemia	103 (10.2)	39 (5.9)	62 (18.5)	< 0.001
History of major bleeding	34 (3.4)	16 (2.4)	18 (5.4)	0.026
Echocardiography	508 (50.1)	353 (53.6)	152 (45.2)	0.015
EHRA score	2.2 ± 0.8	2.3 ± 0.7	2.0 ± 0.9	< 0.001
CHA2DS2-VASc score	3.1 ± 2.1	2.4 ± 1.9	4.4 ± 1.8	< 0.001
HAS-BLED score	1.9 ± 1.2	1.5 ± 1.1	2.6 ± 1.2	< 0.001

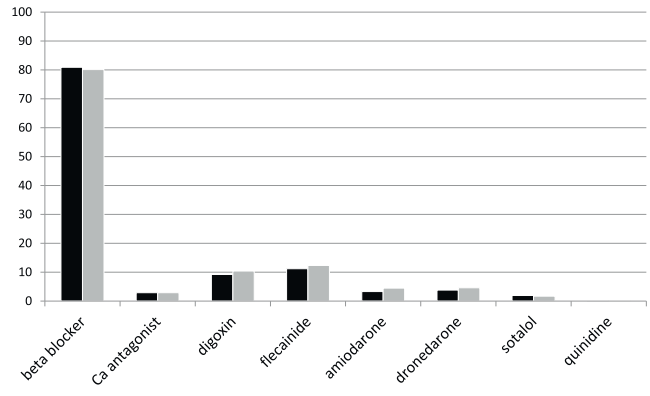


Fig. 2 The use of antiarrhythmic drugs among patients with previously diagnosed AF (*n* = 780) at admission to the ED (*black column*) and at discharge (*light grey column*)

AF recurrence within a year [18]. This was reflected in our study population by the high number of previous visits to ED. In patients with acute AF normal sinus rhythm can be effectively restored by electrical or pharmacological cardioversion [20]. However, in rhythm control strategy cardioversion alone is hardly ever enough but a physician should always try to find a way to prevent AF recurrences. In our survey, a class I or III antiarrhythmic medication was started or the dosage was optimized as a part of a rhythm control strategy only in about 7% of the patients with a previously diagnosed AF. It is well established that early intervention is crucial for the long-term efficacy of antiarrhythmic drugs and catheter ablation. Therefore, decision to start a class I or III antiarrhythmic medication should be done in the ED if structural heart disease has been excluded by recent examinations and clinical history. Echocardiography plays a key role in diagnosis of many cardiac diseases and selection of AF treatment strategy. In our study, it had been done earlier for half of the patients.

However, as the rhythm control strategy has not demonstrated a mortality benefit compared to the rate control strategy in large studies, it should be not used for all patients with AF [23–25]. In our study, patients in the rate control group were older, had more concomitant diseases, and a lower symptom score.

A rate control therapy should be considered for all patients with AF despite of a treatment strategy, if a heart rate during AF is rapid. In this study population, a rate control therapy was used by most of the patients. In line with the results of previous studies, about 80% of the patients in our study were using beta blockers [26]. The efficacy of beta blockers to reduce ventricular rate in patients with AF is well established, but their efficacy in preventing AF recurrences is only modest [22, 27].

According to the contemporary AF management guidelines class I agents should be the drug of choice for rhythm control in patients with lone AF. Despite this, significantly less effective beta blocker medication was used as a first line therapy in most of these patients, and none of them received class I antiarrhythmic medication after a first documented AF episode.

The facilities to treat patients with AF vary between different EDs in Finland. In small heath care centers it's not possible to make an electrical cardioversion, and a patient has to be sent to a bigger unit. In smaller EDs physicians experience to use AADs might not be as good as in bigger units. In Finland, we are going towards bigger ED units in near future, which is expected to improve the quality of rhythm control therapy of patients with AF, and also improve acute collaboration between ED physicians and cardiologists.

Limitations

This study provided a snapshot of the management of patient with AF in an emergency care setting. Therefore, no follow-up data are available. For example, many patients were referred to a cardiologist but the results of the further examinations and therapies were not available. Likewise, it was not possible to assess a rationality of all individual treatment decisions; therefore we assessed a treatment decisions the physicians made after choosing a treatment strategy. Finally, the results of this study may not be directly extrapolated to different health care systems. In Finland all inhabitants are covered by national health insurance and patients need to pay only a nominal fee for ED visits and hospitalization.

Clinical implications

ED physicians play a key role in treatment of acute AF. We have previously shown that patients with high risk of thromboembolic complications were recognized well by the ED physicians, and oral anticoagulation therapy (OAC) was prescribed for the majority of these patients [28]. The results of the current analysis indicate that rhythm control therapy is not understood and executed as well as OAC therapy. According to contemporary ESC clinical practice guidelines rhythm control strategy should be considered for patients with recurrent episodes of symptomatic AF [10, 11]. On the other hand, rate control strategy is a feasible choice in patients with mild symptoms. In many cases the treatment strategy can be selected and implemented in the ED. In our study the factors favouring a rate control strategy included older age, concomitant diseases and mild/moderate symptoms.

Early adaptation of an aggressive rhythm control strategy is likely to alleviate the ED burden associated with symptomatic AF. In order to be able to select the most appropriate antiarrhythmic therapy for a given patient the ED physician should evaluate the symptoms of the patient and take thorough clinical history. He/she should have enough information on the results of prior cardiac examinations (e.g., electronic nationwide patient records) and knowledge of the key features of the antiarrhythmic drugs (Table 1). Class I AADs have been shown to be safe and effective in patients with lone AF but contraindicate in patients with structural heart disease [29]. Hence, if no data on echocardiographic and other cardiac examination are available the patient should be referred to cardiologist for elective evaluation or rather a cardiologic consultation should be readily available in ED. Structured local instructions for treatment of AF patients and close collaboration with cardiologists play a key role in this process.

Conclusions

Current survey is one of the largest studies evaluating AF treatment strategy and antiarrhythmic therapy in an emergency care setting. Our data indicate that rhythm control therapy is not understood and executed adequately in the ED. That is, in contrast to contemporary AF management guidelines a beta blocker was by far the most commonly used AAD and use of more effective drugs was rare also in symptomatic patients in rhythm control group.

Abbreviations

AAD: antiarrhythmic drug; AF: atrial fibrillation; ED: emergency department; EHRA: European Heart Rhythm Association; ESC: European Society of Cardiology; FCS: Finnish Cardiac Society; OAC: oral anticoagulation therapy

Acknowledgements

The FinFib2 investigators:
Pekka Raatikainen (Heart and Lung Center, Helsinki University Hospital, Finland); Mika Lehto, Aleksi Almenoksa, Juha Koskinen, Sergei Kesonen, Jyri Veräjänkorva (Carea, Kotka, Finland); Kimmo Salmio (North Kymi Hospital, Kouvola, Finland); Juhani Metsäniitty (Peijas Hospital, Vantaa, Finland); Laura Mikkonen (Porvoo Hospital, Porvoo, Finland); Jouni Nurmi, Risto Viitanen, Jukka Vaahersalo (Lohja Hospital, Lohja, Finland); Jukka Rinne (Länsi-Uusimaa Hospital, Tammisaari, Finland); Risto Pajari, Jani Mononen, Anna-Mari Hekkala (Haartman Hospital, Helsinki, Finland); Laura Moring, Bernd Günther (Maria Hospital, Helsinki, Finland); Juha Lund (Heart Center Turku University Hospital, Turku, Finland); Jarkko Karihuhta (Satakunta Cental Hospital, Pori, Finland); Jon Holmström (Vaasa Central Hospital, Vaasa, Finland); Juho Lindberg (Tyks Loimaa Hospital, Loimaa, Finland); Anja Toljamo, Jonna Juhola (Tyks Salo Hospital, Salo, Finland); Marjatta Strandberg (Tyks Vakka-Suomi Hospital, Uusi-Kaupunki); Tuula Meinander, Heikki Mäkynen, Tero Penttilä (Heart Center Tampere University Hospital, Tampere, Finland); Ville Hällberg, Tapio Innamaa (Kanta-Häme Central Hospital, Hämeenlinna, Finland); Hanna Suurmunne (Päijät-Häme Central Hospital, Lahti, Finland); Jari Nyrhilä (Seinäjoki Central Hospital, Seinäjoki, Finland); Katja Jokela (Vammala Regional Hospital, Vammala, Finland); Peeter Kasemets (Valkeakoski Regional Hospital, Valkeakoski, Finland); Juha Hartikainen, Matti Onnela, Harri Hyppölä (Kuopio University Hospital, Kuopio, Finland); Kai Nyman, Pirjo Mustonen (Central Finland Central Hospital, Jyväskylä, Finland); Tuomas Rissanen (North Carelia Central Hospital, Joensuu, Finland); Jaana Luukkonen (Savonlinna Central Hospital, Savonlinna, Finland); Pertti Salmi, Pekka Salminen, Teemu Lasanen, Matti Kettunen (Health Center of Varkaus); Timo Lauri (Oulu University Hospital, Oulu, Finland); Ari Toppinen (Kainuu Central Hospital, Kajaani, Finland); Jussi Sia (Keski-Pohjanmaa Central Hospital, Kokkola, Finland); Hanna Tormilainen, Magnus Hagnäs (Lapland Central Hospital, Rovaniemi, Finland); Tapio Åman (Länsi-Pohja Central Hospital, Kemi, Finland); Liisa Miettinen (Oulaskangas Hospital, Oulainen, Finland); Niilo Keränen (Health Center of Kuusamo, Kuusamo, Finland).

Funding

This study was sponsored by the FCS. The FCS have received unrestricted research grants from Bayer, Biosense Webster, BMS/Pfizer Alliance, Boehringer-Ingelheim, Meda, Sanofi and St Jude Medical.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PR, HM, JH, TL, ML and JL designed the study. TP made an analysis of data and drafted the manuscript. All authors took part for a writing process, and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Pirkanmaa Hospital District Ethical Committee (R13044). According to Ethical Committee, individual approval from patients participating was not needed.

Consent for publication

Not applicable.

Competing interests

TP and PR have received research grants from the Finnish Cardiac Society (FCS). All other authors declare that there is no conflict of interest.

Publisher's Note

Author details

[1]Heart Center Co. Tampere University Hospital, P.O. Box 2000, -33521 Tampere, FI, Finland. [2]Heart Center, Kuopio University Hospital, Kuopio, Finland. [3]Emergency Department, Kuopio University Hospital, Kuopio, Finland. [4]Oulu University Hospital, Oulu, Finland. [5]Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland. [6]Turku University Hospital, Turku, Finland.

Received: 18 May 2017 Accepted: 2 August 2017
Published online: 15 August 2017

References

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982;306:1018–22.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014;129(8):837–47.
3. Zoni-Berisso M, Lercari F, Carazza T, Dominicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213–20.
4. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114:119–25.
5. Magnani JW, Rienstra M, Lin H, Siiner MF, Lubitz SA, McManus DD, et al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. Circulation. 2011;124:1982–93.
6. Kyhälä-Valtonen H, Lehto M, Rossinen J, Pajari R, Mustonen H, Koponen L, et al. Quality of emergency room care for atrial fibrillation. Scand Cardiovasc J. 2006;40:267–73.
7. Rolf S, Kornej J, Dagres N, Hindricks G. What can rhythm control therapy contribute to prognosis in atrial fibrillation? Heart. 2015;101:842–6.
8. Piccini JP, Fauchier L. Rhythm control in atrial fibrillation. Lancet. 2016; 388:829–40.
9. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. The evidence regarding the drugs used for ventricular rate control. J Fam Pract. 2000;49:47–59.
10. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation. Eur Heart J. 2010;31:2369–429.
11. Camm AJ, Lip GY, De Caterina R, et al. 2012 focuser update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European heart rhythm association. Eur Heart J. 2012;33:2719–47.
12. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Bergman JF. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2007;4:CD005049.
13. Van Gelder IC, Crijns HJ, Van Gilst WH, Van Wijk LM, Hamer HP, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. Am J Cardiol. 1989;64:1317–21.
14. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med. 2009;360:668–78.
15. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med. 2007;357:987–99.
16. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez P, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005;352:1861–72.

17. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian trial of atrial fibrillation investigators. N Engl J Med. 2000;342:913–20.
18. Tran C, Bennell MC, Qiu F, Ko DT, Singh SM, Dorian P, et al. Predictors and clinical outcomes of inpatient versus ambulatory management after an emergency department visit for atrial fibrillation: a population-based study. Am Heart J. 2016;173:161–9.
19. Rogenstein C, Kelly A-M, Mason S, Schneider S, Lang E, Clement CM, et al. An international view of how recent-onset atrial fibrillation is treated in the emergency department. Acad Emerg Med. 2012;19:1255–60.
20. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calcins H, Camm AJ, Cappato R, et al. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. Eur Heart J. 2009;30:2969–77.
21. Cosio FG, Aliot E, Botto GL, Heidbuchel H, Geller CJ, Kirchhof P, et al. Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. Europace. 2008;10:21–7.
22. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database SystRev. 2015; doi:10.1002/14651858.CD005049.pub4.
23. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–33.
24. Van Gelder IC, Hagens VE, Bosker HA, Kingma H, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834–40.
25. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–77.
26. Kuang P, Mah ND, Barton CA, Miura AJ, Tanas LR, Ran R. Achieving ventricular rate control using metoprolol in β-blocker-naive patients vs patients on chronic β-blocker therapy. Am J Emerg Med. 2016; doi:10.1016/j.ajem.2015.12.084. Epub 2016 Jan 7
27. Kühlkamp V, Schirdewan A, Strangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after cardioversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 2000;36:139–46.
28. Penttilä T, Mäkynen H, Hartikainen J, Lauri T, Lehto M, Lund J, et al. Anticoagulation therapy among patients presenting to the emergency department with symptomatic atrial fibrillation – the FinFib2 study. Eur J Emerg Med. 2016; (Epub ahead of print)
29. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012;367:1587–95.