Turun yliopisto
University of Turku

# SAFETY AND EFFICACY OF CARDIOVERSION OF ACUTE ATRIAL FIBRILLATION

## - The FinCV (Finnish CardioVersion) Study

Toni Grönberg

TURUN YLIOPISTON JULKAISUJA - ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1326 | Medica - Odontologica | Turku 2017

Turun yliopisto
University of Turku

# SAFETY AND EFFICACY OF CARDIOVERSION OF ACUTE ATRIAL FIBRILLATION

– The FinCV (Finnish CardioVersion) Study

Toni Grönberg

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1326 | Medica - Odontologica | Turku 2017

## University of Turku

Faculty of Medicine

Department of Cardiology and Cardiovascular Medicine

Doctoral Programme in Clinical Research

Heart Center, Turku University Hospital

## Supervised by

Professor K. E. Juhani Airaksinen MD, PhD
Heart Center,
Turku University Hospital,
University of Turku,
Turku, Finland

Docent Ilpo Nuotio MD, PhD
Department of Medicine,
Turku University Hospital,
University of Turku,
Turku, Finland

## Reviewed by

Docent Harri Hyppölä MD, PhD
Emergency Department,
Kuopio University Hospital,
Kuopio, Finland,
and University of Tampere,
Tampere, Finland

Docent Johan Lassus MD, PhD
Heart and Lung Center,
Helsinki University Hospital,
University of Helsinki,
Helsinki,
Finland

## Opponent

Professor Tuomo Nieminen MD, PhD
Internal Medicine, University of Helsinki,
Helsinki University Central Hospital,
Helsinki, Finland,
and South Karelia Central Hospital,
Lappeenranta, Finland


The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.


ISBN 978-951-29-7064-3 (PRINT)
ISBN 978-951-29-7065-0 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy – Turku, Finland 2017

*To Sanni*

# ABSTRACT

Toni Grönberg, MD

SAFETY AND EFFICACY OF CARDIOVERSION OF ACUTE ATRIAL FIBRILLATION – THE FINCV (FINNISH CARDIOVERSION) STUDY

University of Turku, Faculty of Medicine, Department of Cardiology and Cardiovascular Medicine, Doctoral Programme in Clinical Research; Heart Center, Turku University Hospital, Turku, Finland

**Background:** The inherent risk of thromboembolism after cardioversion of atrial fibrillation with a duration of more than 48 hours is well established. However, the potential increased risk of these complications after cardioversion of recent-onset episodes of atrial fibrillation has been more controversial. Thus, the aim of this dissertation was to evaluate the safety and efficacy of cardioversion of acute (< 48 hours) atrial fibrillation.

**Methods:** The FinCV study is a multicenter (n=3) retrospective study of 3143 patients who underwent 7660 cardioversions for acute atrial fibrillation. Of those procedures, 5362 were performed without, and 2298 with, anticoagulation protection.

**Results:** The success rate of electrical cardioversions was 94.2%. After successful procedures, atrial fibrillation recurred in 17.3% of cases within 30 days. The rate of thromboembolic events (mainly ischemic strokes) was 0.7% in non-anticoagulated patients after successful cardioversion of acute atrial fibrillation. Significant independent predictors of these complications were old age, female sex, heart failure and diabetes, along with a cardioversion delay of 12 hours or longer. The risk of thromboembolism was as high as 9.8% in patients with both heart failure and diabetes. The incidence of thromboembolic complications also increased significantly from 0.4% in non-anticoagulated patients with $CHA_2DS_2VASc$ score of $\leq 1$ to 2.3% in those with a score of $\geq 5$. Overall, the incidence of thromboembolism was significantly lower after cardioversions performed during anticoagulation (0.1% vs. 0.7%). Altogether, 0.9% of electrical cardioversions resulted in bradyarrhythmia, and 44.4% of those patients underwent pacemaker implantation later.

**Conclusions:** The cardioversion of acute atrial fibrillation does not increase the risk of thromboembolism in anticoagulated patients. However, this risk is unacceptably high in non-anticoagulated patients with conventional risk factors for stroke. High $CHA_2DS_2VASc$ score and a delay to cardioversion of 12 hours or longer are significant predictors of thromboembolism. Overall, electrical cardioversion is an effective procedure and immediate arrhythmic complications are rare after these procedures.

**Keywords:** atrial fibrillation, cardioversion, anticoagulation, stroke

# TIIVISTELMÄ

LL Toni Grönberg

AKUUTIN ETEISVÄRINÄN KARDIOVERSION TURVALLISUUS JA TEHO – FINCV-TUTKIMUS

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja kardiovaskulaarilääketiede, Turun kliininen tohtoriohjelma; Sydänkeskus, Turun yliopistollinen keskussairaala, Turku, Suomi.

**Tausta:** Yli 2 vuorokautta kestäneen eteisvärinän kardioversioon liittyvä kohonnut aivohalvauksen riski on hyvin tiedossa. Sen sijaan, akuutin eteisvärinän kääntöön liittyvä aivohalvauksen riski on aikaisemmin ollut kiistanalaisempi. Tästä syystä väitöskirjatutkimuksen tarkoituksena oli selvittää akuutin (kesto alle 48 tuntia) eteisvärinän rytminsiirron turvallisuus ja teho.

**Menetelmät:** FinCV-tutkimuksen aineisto on kerätty retrospektiivisesti kolmesta tutkimuskeskuksesta. Se sisältää tiedot 3143 potilaalle tehdystä 7660:stä akuutin eteisvärinän kardioversiosta. Näistä 2298 tehtiin antikoagulaatiohoidon aikana ja 5362 ilman vastaavaa hoitoa.

**Tulokset:** Sähköisistä kardioversioista 94,2 % onnistui, mutta 17,3 %:lla potilaista eteisvärinä uusiutui 30 päivän seurannassa. Antikoaguloimattomilla potilailla 0,7 % onnistuneista kardioversioista johti tromboemboliseen komplikaatioon (pääosa aivoinfarkteja). Näiden komplikaatioiden itsenäisiä riskitekijöitä olivat korkea ikä, naissukupuoli, diabetes ja sydämen vajaatoiminta, yhdessä akuutin eteisvärinän käännön viivästymiseen yli 12 tuntiin kohtauksen alusta. Kardioversioon liittyvä tromboembolian riski oli erityisen suuri samanaikaisesti diabetesta ja sydämen vajaatoimintaa sairastavilla potilailla – 9,8 prosenttia. Tromboembolisten komplikaatioiden ilmaantuvuus antikoaguloimattomilla potilailla oli 2,3 prosenttia CHA2DS2VASc-riskipisteiden ollessa yli neljä, kun taas potilailla, joilla riskipisteitä oli vähemmän kuin kaksi, riski oli ainoastaan 0,4 prosenttia. Antikoaguloiduilla potilailla tromboembolisten komplikaation esiintyvyys kardioversion jälkeen oli selvästi vähäisempää verrattuna antikoaguloimattomiin potilaisiin (0,1 % vs. 0,7 %). Sähköisistä kardioversioista 0,9 % johti välittömästi käännön jälkeen ilmenevään bradyarytmiaan ja 44,4 %:lle näistä potilaista asennettiin myöhemmin tahdistin.

**Päätelmät:** Akuutin eteisvärinän rytminsiirtoon liittyy huomattava tromboembolisten komplikaatioiden vaara tietyillä potilasryhmillä. Korkea $CHA_2DS_2VASc$ -pistemäärä ja rytminsiirron viivästyminen yli 12 tuntiin oireiden alusta lisäävät selvästi tätä riskiä. Antikoagulaatiohoidon aikana tehty kardioversio ei näyttäisi kuitenkaan lisäävän tromboembolian vaaraa. Sähköinen kardioversio on tehokas toimenpide ja käännön yhteydessä ilmenevät arytmiset komplikaatiot ovat harvinaisia ja hyvänlaatuisia.

Avainsanat: eteisvärinä, kardioversio, antikoagulaatio, aivohalvaus

**CONTENTS**

Contents

# ABBREVIATIONS

| | |
|---|---|
| AF | atrial fibrillation |
| ASA | acetylsalicylic acid |
| CI | confidence interval |
| ESC | European Society of Cardiology |
| FinCV | The Finnish CardioVersion study |
| INR | international normalized ratio |
| NOAC | non-vitamin K antagonist oral anticoagulant |
| OR | odds ratio |
| ROC | receiver-operating characteristic |
| TIA | transient ischemic attack |
| TTR | time in therapeutic range |

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to throughout the text by their Roman numerals.

I. Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Vasankari T, Hartikainen JE, Airaksinen KE. Arrhythmic complications after electrical cardioversion of acute atrial fibrillation: the FinCV study. Europace. 2013 Oct;15(10):1432-5.

II. Airaksinen KE, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, Hartikainen JE. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. J Am Coll Cardiol. 2013 Sep 24;62(13):1187-92.

III. Nuotio I, Hartikainen JE, Grönberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. JAMA. 2014 Aug 13;312(6):647-9. (Letter)

IV. Grönberg T, Hartikainen JE, Nuotio I, Biancari F, Vasankari T, Nikkinen M, Ylitalo A, Airaksinen KE. Can we predict the failure of electrical cardioversion of acute atrial fibrillation? The FinCV study. Pacing Clin Electrophysiol. 2015 Mar;38(3):368-75.

V. Grönberg T, Hartikainen JE, Nuotio I, Biancari F, Ylitalo A, Airaksinen KE. Anticoagulation, $CHA_2DS_2VASc$ score, and thromboembolic risk of cardioversion of acute atrial fibrillation (from the FinCV Study). Am J Cardiol. 2016 Apr 15;117(8):1294-8.

# 1. INTRODUCTION

Atrial fibrillation (AF) affects 46 million people globally (Chugh et al. 2014). Due to its potentially asymptomatic nature and transient paroxysms, the prevalence of AF may even be higher. Hence, it is a major burden to the modern health care system. The rhythm disorder is associated with an increased risk of thromboembolic complications and all-cause mortality, decrease in quality of life, heightened risk of decompensated heart failure and hospitalizations (Wolf et al. 1991, Dries et al. 1998, Thrall et al. 2006).

The cornerstone in AF treatment is the prevention of thromboembolic complications with oral anticoagulation. The efficacy of anticoagulation has been shown in numerous studies. It can decrease the risk of ischemic stroke and systemic embolism by more than two-thirds (Hart et al. 2007). Thus, all clinical practice guidelines of AF emphasize the use of anticoagulation in patients with AF (January et al. 2014, Kirchhof et al. 2016).

The risk of thromboembolism is not heterogeneous in patients with AF. Therefore, various stroke risk stratification schemes have been developed to aid the systemic evaluation of stroke risk and the justified initiation of oral anticoagulation. Current guidelines recommend omitting the initiation of anticoagulation only in patients with a truly low risk for thromboembolism. In all others, stroke risk outweighs the risk of bleeding related to anticoagulation (January et al. 2014, Kirchhof et al. 2016).

The heightened risk of ischemic stroke in patients undergoing cardioversion of persistent or unknown duration AF is well established (Bjerkelund et al. 1969, Arnold et al. 1992). Hence, anticoagulation is recommended for three weeks before and four weeks after cardioversion for these patients (January et al. 2014). However, the optimum anticoagulation management for cardioversion of acute AF (duration < 48 hours) has been unclear. Therefore, in Finland, performing these cardioversions without anticoagulation used to be common practice, but that all changed when the European Society of Cardiology (ESC) recommended effective anticoagulation during and after the cardioversion of acute AF (Camm et al. 2010). The evidence behind this recommendation was scarce, however.

Rhythm control therapy denotes restoration and maintenance of the sinus rhythm. Cardioversion of AF, i.e., restoration of the sinus rhythm, is a common and efficient procedure. Although rhythm control is not superior to the rate control strategy in respect to the quality of life and survival of patients (Wyse et al. 2002, Van Gelder et al. 2002, Opolski et al. 2004), it is justified in both young and selected symptomatic patients during persistent AF paroxysms. In addition to an increased risk of thromboembolism, cardioversion of AF also carries a potential risk for arrhythmic complications (Gallagher

et al. 2008, Morani et al. 2009). However, only a small number of studies have shed light on arrhythmic complications related to cardioversion of acute AF.

AF tends to recur after cardioversion (Osmanagic et al. 2015). Hence, repeated clinical evaluations and interventions are needed after the primary successful procedure, which leads to rising healthcare costs and patients' exposure to the increased risk of thromboembolic complications related to cardioversion. By knowing the clinical characteristics leading to the recurrence of AF and primary unsuccessful cardioversion, we can more accurately choose patients who will benefit from rhythm control therapy (Jaakkola et al. 2017) and lower costs of our health care system.

The Finnish CardioVersion (FinCV) study is a retrospective multicenter study of patients undergoing cardioversion for recent-onset AF. Our aim was to provide new information about the safety and efficacy of cardioversion in acute AF. The purpose was also to evaluate the efficacy of anticoagulation and the feasibility of $CHA_2DS_2VASc$ score in these patients.

# 2. REVIEW OF THE LITERATURE

## 2.1 General aspects of AF

### *2.1.1 Definition of AF*

AF is a supraventricular tachycardia, a heart rhythm disorder characterized by rapid, irregular mechanical and electrical activity of the atrial chambers. It results in irregular contractions of the heart's ventricular chambers due to heterogenic conduction through the atrioventricular node. Fibrillation of the atria and irregular contraction of the ventricles is seen on electrocardiogram as a loss of normal P waves, a presence of fibrillatory waves of different shape and amplitude, associated with irregular rate and timing of the QRS complex. Irregular and often rapid ventricular response causes AF symptoms such as palpitations.

### *2.1.2 Prevalence*

With a prevalence of 1–2% in the general population, AF is the most common sustained arrhythmia (Go et al. 2001, Davis et al. 2012). It is estimated that 46 million individuals worldwide had AF in 2010 (Chugh et al. 2014). More often, these people lived in developed countries (Collila et al. 2013). It also anticipated that the prevalence of AF will rise up to 3% in individuals aged 20 or older (Haim et al. 2015); Aged people suffer from AF more often (Chugh et al. 2014): Kannel et al. (1998) reported a prevalance of almost 9% in octogenarians in 1998. The incidence and prevalence is even higher in aged people with cardiovascular diseases and other conditions, such as diabetes mellitus (Oldgren et al. 2014, Jabre et al. 2011, McManus et al. 2009). Such conditions and diseases are major risk factors for both the development of AF and stroke (Chyou et al. 2015). The increase in AF prevalence will consequently result in a growing number of strokes if patients are not appropriately treated according to contemporary guidelines (Björck et al. 2013). Subclinical atrial tachyarrhythmias are associated with increased risk of thromboembolism (Healey et al. 2012). Undiagnosed AF is common (Davis et al. 2012), and there is growing evidence that some of the strokes previously labeled as cryptogenic are caused by undiagnosed AF (Gladstone et al. 2014). Hence, new ESC guidelines encourage opportunistic screening for AF in patients older than 65 years (Kirchhof et al. 2016).

### *2.1.3 Types of AF*

The current ESC guidelines on AF management distinguish five types of AF: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF (Kirchhof et al. 2016).

First diagnosed AF is defined as an AF episode that has not been diagnosed before. The duration of the episode or any other aspects are irrelevant. Paroxysmal AF is classified as a rhythm disorder that self-terminates, in most cases within 48 hours after onset of the episode, or is cardioverted within a week. An episode lasting longer than 7 days but less than a year is called persistent AF. Long-standing persistent AF is in question when rhythm control therapy is applied a year after the onset of continuous AF. When AF is accepted and the rhythm control strategy is not pursued, AF is defined as permanent (Kirchhof et al. 2016). AF can also be classified according to symptoms and underlying diseases associated with AF (January et al. 2014). Clinically, it is practical to distinguish recent onset, defined as a duration of 48 hours or less, as an AF episode as its own entity. Based on retrospective studies, the first 48 hours from onset of an AF episode have been regarded as a safe period to perform cardioversion of the AF episode without prior anticoagulation (Weigner et al. 1997, Michael et al. 1999, Burton et al. 2004; Gallagher et al. 2002, Stiell et al. 2010, Xavier Scheuermeyer et al. 2010).

Given that AF remodels atrial substrate, it propagates itself (Heijman et al. 2014), and thus it is thought that AF begets AF. The natural history of AF is characterized by a gradual shift from paroxysmal episodes of AF to more persistent episodes and finally to permanent AF (Sakamoto et al. 1995;, Abe et al. 1997). However, there are ways to prevent this progression, such as catheter ablation, which may reduce AF progression to its permanent form (Scaglione et al. 2014).

## 2.2 Treatment strategies for AF

There are two main treatment strategies for AF: rhythm and rate control. In rate control, strategy restoration of sinus rhythm is not pursued. AF is accepted, and the aim is to control ventricular rate, or heart rate. In rhythm control, the treatment aims to restore and maintain sinus rhythm. The restoration of sinus rhythm is aspired with cardioversion (electrical or pharmacological) and the maintaining of sinus rhythm with antiarrhythmic agents and catheter ablation, or both.

### *2.2.1 Rate control*

According to common sense, one would assume that maintaining sinus rhythm is much more beneficial and would result in a better outcome in all aspects. However, numerous studies have compared rhythm and rate control strategies in respect to quality of life and survival of patients, and these studies have resulted in neutral or even negative outcomes (Wyse et al. 2002, Van Gelder et al. 2002, Opolski et al. 2004). There is no clear evidence in the superiority of rhythm control strategy. However, rhythm control therapy may offer some advantages for younger patients, which may favor it as the initial approach for these patients (Chatterjee et al. 2013). The lack of decent ways to prevent AF recurrence

might be one reason for the evenness of these two strategies. During a follow-up of 1.7 to 3.5 years, only 39% to 64% of patients remain in sinus rhythm (Van Gelder et al. 2002, Opolski et al. 2004). Regardless of the strategy chosen, anticoagulation therapy is recommended and must be seen as paramount, since the restoration of sinus rhythm does not eliminate the risk of thromboembolic complications (Wyse et al. 2002).

Rate control therapy aims to minimize the clinical consequences of AF via ventricular rate regulation during the rhythm disorder (Wyse 2008). The absence of the normal contraction of atrias reduces stroke volume by 15–25% (Linderer et al. 1983, Shapiro et al. 1968, Orlando et al. 1979), and this is often accompanied by a fast ventricular rate, which also reduces stroke volume (Kerr et al. 2001). Fast, irregular and uncontrolled heart rate can lead to tachycardia-induced cardiomyopathy (Shinbane et al. 1997, Gopinathannair et al. 2015).

Current guidelines recommend a resting heart rate between 80 and 110 beats per minute as an initial heart rate target (Kirchhof et al. 2016, January et al. 2014, Verma et al. 2014). The most lenient recommendation is from the ESC (Kirchhof et al. 2016). The optimal heart rate during AF is somewhat unclear since there is only one prospective randomized study assessing this matter The RACE II study compared strict rate control strategy to a more lenient rate control strategy for preventing cardiovascular morbidity and mortality. The lenient heart rate target was proven to be as effective as and easier to achieve than strict rate control (Van Gelder et al. 2010). The RACE II study findings are backed up with pooled analyses of the AFFIRM and RACE studies (Van Gelder et al. 2006). To affirm the physiological demands of the body, heart rate during AF needs to be faster than in sinus rhythm because atrial contraction does not contribute to cardiac output (Daoud et al. 1996). However, a lower limit for resting heart rate is not defined in clinical practice guidelines.

Rate control strategy can be carried out pharmacologically and non-pharmacologically. The following pharmacological agents are widely used to reduce the heart rate during AF: beta-blockers, digoxin, diltiazem and verapamil. These drugs are recommended for acute and long-term rate control according to the new ESC guidelines (Kirchhof et al. 2016). Beta-blockers block β1-receptors in the atrioventricular node, and hence reduce the ventricular rate. Diltiazem and verapamil block calcium channels in the atrioventricular node, consequently increasing the refractory period, which results in the same final outcome as with beta-blockers. Due to negative inotropic effects, verapamil and diltiazem are contraindicated in patients with low ejection fraction (Goldstein et al. 1991, Elkayam et al. 1998). These drugs, however, have other advantageous effects. Like beta-blockers, non-dihydropyridine calcium-channel antagonists reduce blood pressure and treat ischemic heart disease (Agbor-Etang et al. 2015). Beta-blockers are also proven to be beneficial to patients with heart failure in large randomized controlled trials

(Hjalmarson et al. 2000, Packer et al. 2001), and these agents may prevent AF recurrences in patients suffering from paroxysmal AF (Camm et al. 2010).

Digoxin is often seen as a secondary option in rate control therapy after previously mentioned drugs, and it is used concomitantly with beta-blockers. Digoxin has a narrow therapeutic window and is cleared through the kidneys (Beller et al. 1971), which limits its use in patients with renal failure. It is an effective rate-controlling drug in rest, but the effect is modest during exercise (Khand et al. 2003). It may also be associated with increased mortality risk in patients with AF (Turakhia et al. 2014), but this finding is somewhat controversial (Gheorghiade et al. 2013, Lee et al. 2015). Of note, digoxin users are often older and have more comorbidities than others (Ziff et al. 2015).

When drugs fail or develop drug-related adverse effects, atrioventricular node ablation and implantation of a permanent pacemaker are used as non-pharmacological rate control treatments. Atrioventricular node ablation is a simple procedure with low long-term mortality risk (Queiroga et al. 2003). After ablation of the atrioventricular node, patients are dependent on the pacemaker, but the treatment is seen as the best option for patients whose symptoms cannot be managed with other treatment strategies (Kirchhof et al. 2016). It might even improve ventricular function in selected patients (Wood et al. 2000).

The rate control strategy is often sufficient to improve AF-related symptoms (Kirchhof et al. 2016) and is a crucial part of AF management. All patients need rate control regardless of the treatment strategy chosen. Aimless pursuit of sinus rhythm will, however, result in an increase in hospitalizations (Carlsson et al. 2003) and predispose patients to an increased risk of thromboembolism related to cardioversion (January et al. 2014).

### *2.2.2 Rhythm control*

The rhythm control strategy denotes restoration and maintenance of the sinus rhythm. As stated before, rhythm control is not superior in respect to the patient's prognosis compared to rate control (Wyse et al. 2002, Van Gelder et al. 2002, Opolski et al. 2004). However, there is some evidence that in patients younger than 65 years, rhythm control might be more beneficial (Chatterjee et al. 2012, Prystowsky et al. 2015). Hence, young age, patient's preference and severe symptoms during rate control therapy drive the decision to choose the rhythm control strategy. Hemodynamic instability of the patient demands an urgent restoration of sinus rhythm via electrical cardioversion (Kirchhof et al. 2016). There is also evidence that early rhythm control strategy might prevent changes in atrial structure and cellular dysfunction, and thus in the progression of AF (Piña et al. 2017).

The restoration of sinus rhythm can be performed with electrical and pharmacological cardioversion; electrical cardioversion is more effective than pharmacological cardioversion (Gitt et al. 2013, Cristoni et al. 2011). Cardioversion exposes patients to an increased risk of thromboembolism (Bjerkelund et al. 1969, Arnold et al. 1992), which is highest in the first 72 hours after the procedure (January et al. 2014). However, the risk of thromboembolism can be dramatically reduced by anticoagulation (Hansen et al. 2015, Renda et al. 2016).

A major problem in rhythm control strategy is the high recurrence rate of AF (Fetsch et al. 2004). Sinus rhythm maintenance can be achieved with long-term antiarrhythmic therapy, catheter ablation and surgery. Amiodarone, dronedarone, flecainide, propafenone, quinidine, disopyramide and sotalol are antiarrhythmic drugs used in Europe (Kirchhof et al. 2016). Amiodarone and dronedarone are categorized as class III antiarrhythmic agents according to the Vaughan-Williams classification. These agents are multichannel blockers. Amiodarone is the most effective antiarrhythmic drug (Qin et al. 2016), but its use is limited by a number of extracardiac side effects (Wolkove et al. 2009). However, it is suitable for patients with heart failure (Singh et al. 1995). The current ESC guidelines recommend amiodarone as a second-line treatment in patients with whom other antiarrhythmic agents cannot be used (Kirchhof et al. 2016). Dronedarone is better tolerated than amiodarone, but less effective (Piccini et al. 2009a). Sotalol is also a class III antiarrhythmic agent. The problem with using sotalol is that it exposes patients to torsades de pointes, a life-threatening rhythm disorder, due to prolongation of the QT interval (Soyka et al. 1990). The recurrence rate after cardioversion at the one-year follow-up for AF during sotalol therapy was 67% in one multicenter double-blind randomized trial (the PAFAC trial) (Fetsch et al. 2004). Flecainide and propafenone are IC class drugs, which block sodium channels in the heart. These agents are fairly effective and safe (Roy et al. 2000, Kirchhof et al. 2012), but their use should be avoided in patients with coronary artery disease and heart failure (Cardiac Arrhythmia Suppression Trial [CAST] Investigators 1989). The use of beta-blockers concomitantly with these agents is recommended in order to avoid conversion of AF to atrial flutter with 1:1 conduction (Kirchhof et al. 2016). Two Vaughan-Williams class IA agents, quinidine and disopyramide, are not so commonly used.

Overall, the efficacy of all antiarrhythmic agents is only modest, since the recurrence rate of AF during antiarrhythmic drug therapy ranges from 36% to 68% at follow-up (Freemantle et al. 2011). Pro-arrhythmias and extra-cardiac side effects are quite common in long-term antiarrhythmic drug therapy (Wolkove et al. 2009, Koike et al. 2016, Soyka et al 1990). The 2010 ESC guidelines outlined appositely that clinically successful antiarrhythmic drug treatment may reduce rather than eliminate the recurrence of AF (Camm et al. 2010).

Luckily, in addition to antiarrhythmic drug therapy, there are other ways to maintain sinus rhythm. Catheter ablation of AF is more effective than antiarrhythmic drug therapy in terms of sinus rhythm maintenance in patients with failure of drug therapy (Wilber el al. 2010, Calkins et al. 2009, Piccini et al. 2009b). As a first-line therapy, the benefit of catheter ablation is not so clear (Cosedis Nielsen et al. 2012, Hakalahti et al 2015). Surgical techniques include the Cox-Maze procedure and thoracoscopic pulmonary vein isolation.

## 2.3 Stroke prevention in AF

### *2.3.1 Risk factors for thromboembolism*

It is well recognized that AF carries an inherent risk of stroke (Wolf et al. 1991). The risk for ischemic stroke is fivefold compared with the general population (Kannel et al. 1998). In patients with mitral stenosis, this risk is 17 times higher (Wolf et al. 1978). Cardioversion of AF increases this risk and is especially high within 10 days following the procedure (January et al. 2014). Paroxysmal AF might be associated with slightly lower thromboembolic risk compared to permanent and persistent ones (Ganesan et al. 2016). Overall, AF is responsible for roughly 15–40% of all ischemic strokes (Dulli et al. 2003, Marini et al. 2005, Friberg et al. 2014). It is not reassuring that the stroke can be the first manifestation of AF (Jaakkola et al. 2016).

The risk of stroke and systemic embolism is not equal in all patients suffering from AF, and it depends on various additional risk factors. There are systematic reviews conducted to identify independent risk factors for stroke (Hughes et al. 2008, Stroke Risk in AF Working Group. 2007, Pisters et al. 2012a). The evidence is most consistent with a history of previous stroke and transient ischemic attack (TIA), increasing age, diabetes and hypertension (Hughes et al. 2008, Stroke Risk in AF Working Group 2007). Even though studies have shown a clear association with stroke and significant impairment of left ventricular function or recent decompensated heart failure (Olesen et al. 2012a, Agarwal et al. 2014), the heterogeneity of a clinical diagnosis results in a history of heart failure that is not consistently defined as risk factors for thromboembolism (Stroke Risk in AF Working Group 2007). In addition to classic stroke risk factors, a Swedish study of 182 678 patients found peripheral artery disease, vascular disease, prior myocardial infarction and female sex to be significant predictors of stroke (Friberg et al. 2012b). Anandasundaram and colleagues (2013) also found a significant association between atherosclerotic vascular disease and stroke. The female sex is especially associated with an increased risk of stroke in the presence of other additional risk factors (Wagstaff et al. 2014). However, the female sex plays a limited role as a risk factor in young patients without comorbidities (Friberg et al. 2012a, Mikkelsen et al. 2012). Renal failure has

also been reported to increase the risk of stroke in some studies (Friberg et al. 2012b, Olesen et al. 2012b).

### *2.3.2 Clinical risk stratification schemes for thromboembolism*

A number of stroke risk stratification schemes have been developed on the basis of these risk factors. The aim of these risk stratification schemes is to help evaluate the patient's individual risk of stroke and thus aid in the selection of anticoagulation therapy. The first of these schemes was developed in the late 1990s. The predictive value of the risk stratification scheme is often assessed by C-statistic, which can have values from 0.5 to 1.0. A C-statistic of 0.5 denotes that the risk stratification system is no better than chance, whereas a value of 1.0 indicates perfect discrimination.

The $CHADS_2$ score was introduced in 2001 and was formed by combining two existing classification schemes, AFI and SPAF. It proved to be better than either of the previous ones and acquired a C-statistic of 0.82 in the original validation study (Gage et al. 2001). In 2010, Lip and coworkers introduced $CHA_2DS_2VASc$. score It was developed on the basis of the $CHADS_2$ score. The C-statistic was 0.61 for the $CHA_2DS_2VASc$ score and 0.56 for the $CHADS_2$ score. Thus, the results showed a quite modest predictive value for both existing schemes (Lip et al. 2010b). The advantage of the $CHA_2DS_2VASc$ score over the $CHADS_2$ is its ability to improve risk prediction in patients deemed as low risk for stroke based on the $CHADS_2$ score (Lip et al. 2010b, Olesen et al 2012c). Olesen et al. found that patients with a $CHADS_2$ score of 0 are not all low-risk patients, since one-year thromboembolic event rates range from 0.84 ($CHA_2DS_2VASc$ score of 0) to 3.2 ($CHA_2DS_2VASc$ score of 1). Thus, the $CHA_2DS_2VASc$ score provides important information for the decision to use anticoagulation in AF patients who have a $CHADS_2$ score of 0–1. Patients with a $CHA_2DS_2VASc$ score of 0 are clearly low-risk patients (Olesen et al. 2012c). In 2013, the $R_2CHADS_2$ score was developed based on the $CHADS_2$ score, but it did not provide clinically significant improvement in the risk classification (C-statistic of 0.59 for $R_2CHADS_2$ compared to C-statistics of 0.58 for both $CHADS_2$ and $CHA_2DS_2VASc$ scores) (Piccini et al. 2013a). The score calculation of all three risk stratification schemes introduced above is depicted in Table 1.

**Table 1.** Calculation of different risk stratification schemes.

| Risk factor | $CHADS_2$ score | $CHA_2DS_2VASc$ score | $R_2CHADS_2$ score |
|---|---|---|---|
| **Congestive heart failure** | 1 | 1 | 1 |
| **Hypertension** | 1 | 1 | 1 |
| **Age 75 or older** | 1 | 2 | 1 |
| **Diabetes mellitus** | 1 | 1 | 1 |
| **Previous stroke, TIA, or thromboembolism** | 2 | 2 | 2 |
| **Vascular disease** | | 1 | |
| **Age 65–74** | | 1 | |
| **Sex category (female)** | | 1 | |
| **Renal dysfunction (creatinine clearance <60 mL/min)** | | | 2 |
| **Score sum** | **0–6** | **0–9** | **0–8** |

TIA=transient ischemic attack

Since the introduction of the $R_2CHADS_2$ score, other risk stratification schemes have been developed to improve stroke prediction. The ATRIA score was introduced in the same year as $R_2CHADS_2$, and it combined renal failure with the female sex, diabetes mellitus, congestive heart failure, hypertension, proteinuria and increasing age, which contributed differently in patients with and without prior stroke. Renal failure was defined as creatinine clearance under 45 mL/min or end-stage renal diseases in this scheme. The developed risk stratification scheme performed slightly better than older $CHADS_2$ and $CHA_2DS_2VASc$ stratification schemes (Singer et al. 2013b). The first biomarker-based risk stratification was introduced in 2016. Prior stroke/transient, age and cardiac biomarkers (N-terminal fragment B-type natriuretic peptide and cardiac troponin high-sensitivity) were included in the ABC (Age, Biomarkers, Clinical history) stroke risk score (Hijazi et al. 2016a). Like the ATRIA score, it predicted thromboembolic complications more accurately than the $CHA_2DS_2VASc$ score (C-statistic of 0.68 for ABC stroke vs. C-statistic of 0.62 for $CHA_2DS_2VASc$, $p < 0.001$).

Even though new risk stratifications have perceived at least marginal benefits over $CHA_2DS_2VASc$ score, these schemes are quite complex, which limits their use in everyday clinical practice. Therefore, the major guidelines recommend $CHA_2DS_2VASc$ score for clinical use (Kirchhof et al. 2016, January et al. 2014). For the first time, it was

incorporated in the ESC guidelines in the same year it was introduced (Camm et al. 2010). Its strength is that it identifies patients with a truly low thromboembolic risk who do not benefit from anticoagulation (Larsen et al. 2012). It also covers the most common clinical risk factors confronted in clinical practice. The risk of thromboembolism ranges from 0%/year in patients with AF and a $CHA_2DS_2VASc$ score of 0 to 15.2%/year with a $CHA_2DS_2VASc$ score of 9 (Lip et al. 2010a).

### *2.3.3 Anticoagulation therapy*

Stroke prevention is of paramount importance in the treatment of AF, and most patients benefit from anticoagulation (Chao et al. 2015). Stroke risk often exceeds the risk of major bleeding events with oral anticoagulation, even in elderly patients (Donzé et al. 2012), and the majority of thromboembolic complications can be prevented by well-executed oral anticoagulation therapy (Hart et al. 2007). Bleeding risk with acetylsalicylic acid (ASA) is equal to that of oral anticoagulants (Mant et al. 2007), but it does not prevent strokes in AF patients as effectively (Mant et al. 2007). Hence, new ESC guidelines do not recommend ASA monotherapy for stroke prevention in patients with AF (Kirchhof et al. 2016). A previous version of these guidelines considered ASA for patients who refuse to use oral anticoagulants (Camm et al. 2010). The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines published in 2014 see ASA monotherapy as an alternative to omitting anticoagulation therapy for patients with a $CHA_2DS_2VASc$ score of 1. According to these guidelines, oral anticoagulants may also be considered for these patients (January et al. 2014).

Warfarin and other vitamin K antagonists have been the mainstay of stroke prevention for decades. Warfarin is still the most commonly used anticoagulant in Finland. It works by blocking the vitamin K–dependent synthesis of clotting factors II, VII, IX and X (Zivelin et al. 1993). It takes 5–7 days to achieve the full antithrombotic effect of warfarin (Crowther et al. 1999), and in the beginning, it may even promote clot formation temporarily (Azoulay et al. 2014) since it also prevents regulatory factors protein C and protein S (Weiss et al. 1987, Harrison et al. 1997). Since warfarin achieves its anticoagulation effect by interfering with the vitamin K cycle, dietary sources of vitamin K lower international normalized ratio (INR) levels. Therefore, vitamin K antagonists may require dietary attention (O'Reilly et al. 2008). Warfarin is metabolized by the CYP enzyme 2C9 in the liver, which means that it interacts with many commonly used drugs (Herman et al. 2005). Despite the narrow therapeutic window, effects of diet and multiple drug interactions, well-executed vitamin K antagonist therapy is effective in stroke prevention in AF patients (Lehto et al. 2017).

The effect of the vitamin K antagonist is measured by INR. The therapeutic window is quite narrow, and INR should be 2.0–3.0 in patients with AF (Hirsh et al. 1998). The

risk of stroke increases with an INR below 2.0 (Hylek et al. 1996), whereas the risk of major bleeds increases with INR levels over 4.0 (Hylek et al. 1994). Consequently, warfarin therapy demands frequent INR monitoring and multiple contacts to healthcare professionals when the dose is adjusted. The quality of warfarin treatment is assessed by the time in therapeutic range (TTR). Connolly and colleagues suggest a minimum TTR target of 60% to 65% in their study, since below this target there appears to be little benefit of vitamin K antagonists over antiplatelet therapy (ASA plus clopidogrel) (Connolly et al. 2008). In trials comparing warfarin to non-vitamin K oral anticoagulants, the mean TTRs ranged between 55% and 65% (Patel et al. 2011, Giugliano et al. 2013, Granger et al. 2011, Connolly et al. 2009). Findings in the recently published FinWAF study suggest that the target TTR should exceed 80% since the quality of warfarin therapy is strongly associated with the risk of stroke and prognosis of AF patients (Lehto et al. 2017).

The efficacy of warfarin for stroke prevention was demonstrated in five randomized controlled trials published before the end of 1993 (Stroke Prevention in Atrial Fibrillation Investigators 1991, Ezekowitz et al. 1992, Petersen et al. 1989, Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990, EAFT 1993). The risk of thromboembolic complications can be reduced with warfarin therapy by 64% compared to the placebo (Hart et al. 2007). It is also the only available option for patients with mechanical heart valves or valvular AF, i.e., rheumatic mitral valve disease (Eikelboom et al. 2013).

There are alternative oral anticoagulants nowadays for stroke prevention in patients with non-valvulae AF. These are called non-vitamin K antagonist oral anticoagulants (NOACs). NOACs include dabigatran, apixaban, rivaroxaban and edoxaban. The non-inferiority on stroke prevention of all these drugs compared to warfarin has been proven in large randomized clinical trials (Patel et al. 2011, Giugliano et al. 2013, Granger et al. 2011, Connolly et al. 2009). They all have rapid onset and offset action with time to peak levels ranging from 1–2 hours to 2–4 hours and a half-life of 5–17 hours. NOACs do not require regular anticoagulation monitoring. However, these drugs are not suitable for patients with rheumatic mitral valve disease and mechanical prosthetic heart valves (Eikelboom et al. 2013). Their use is also restricted in patients with severe and end-stage renal failure. The use of NOACs has not been studied in patients with severe chronic kidney disease (creatinine clearance < 30 mL/min) (Patel et al. 2011, Giugliano et al. 2013, Granger et al. 2011, Connolly et al. 2009).

Dabigatran is a direct thrombin inhibitor, and it was the first NOAC compared to warfarin (Connolly et al. 2009). It is also the only NOAC with a specific antidote in clinical use (Pollack et al. 2015). Dabigatran may cause dyspepsia, and the higher dose of dabigatran increases gastrointestinal bleeding by 50% compared to warfarin

(Connolly et al. 2009). A real-world study of 134 414 patients confirmed the benefit of dabigatran over warfarin (Graham et al. 2015). Apixaban, rivaroxaban and edoxaban are Xa inhibitors. Apixaban is the only NOAC with efficacy and safety compared to both warfarin and ASA (Granger et al. 2011, Connolly et al. 2011). Of note, the risk of major hemorrhages was similar in apixaban and ASA (Connolly et al. 2011). Contrary to other NOACs, rivaroxaban and edoxaban are administered once daily (Patel et al. 2011, Giugliano et al. 2013).

After the publication of ARISTOTLE, RE-LY, ROCKET-AF and ENGAGE AF-TIMI 48 trials, Ruff and colleagues performed a meta-analysis comparing NOACs to warfarin. Overall, NOACs reduced thromboembolism by 19%, and the risk of intracranial bleeds was halved (Ruff et al. 2014). Notably, the mean TTR for patients using warfarin in all of these original studies was less than 65%. The ESC position paper recommends that TTR be above 70% when vitamin K antagonists are used in AF patients with risk factors for stroke (De Caterina et al. 2012). .

### *2.3.4 Risk of bleeding*

Anticoagulation therapy exposes patients to an increased risk of bleedings (Chang et al. 2017). However, the majority of patients with AF benefit from anticoagulation, and high bleeding risk is seldom reason to omit anticoagulation therapy (Friberg et al. 2012c). However, it is important to be aware of the potentially high risk for major hemorrhagic complications and the net benefit of prescribing antithrombotic therapy.

According to large, randomized, multicenter studies comparing NOACs with warfarin, the annual risk of major bleedings ranges between 1.6% and 3.6% with NOACs, and between 3.1% and 3.4% with warfarin (Patel et al. 2011, Granger et al. 2011, Connolly et al. 2009). The annual rate of intracranial hemorrhages has been reported to be 0.2–0.5% with NOACs and 0.7–0.8% with warfarin (Patel et al. 2011, Granger et al. 2011, Connolly et al. 2009). The incidence of fatal bleeds during NOAC treatment ranges from 0.2% to 0.4% per year (Granger et al. 2011, Patel et al. 2011). García-Fernández and colleagues (2016) have also assessed bleeding risk related to cardioversion of AF in patients with oral anticoagulation. The annual incidence of major bleedings was 1.9% and only two episodes occurred within 30 days after the procedure. The annual rate of intracranial hemorrhages was as low as 0.4% (García-Fernández et al. 2016).

As in stroke risk, bleeding risk is not homogenous among patients. Major guidelines encourage the use of bleeding risk scores in patients with AF on oral anticoagulation (Kirchhof et al. 2016, January et al. 2014). The aim is to draw attention to revisable bleeding risk factors rather than omit anticoagulation therapy (Kirchhof et al. 2016). Since risk factors for bleeding are mostly the same as those predicting stroke, patients

with high stroke are often at increased risk for thromboembolism (Kirchhof et al. 2016). However, the net clinical benefit of anticoagulation is even greater in these patients, whilst the risk of bleeding is high (Olesen et al. 2011).

The HAS-BLED score was introduced in 2010 (Pisters el al. 2010). Bleeding risk factors included in the scheme are hypertension, abnormal renal/liver function, previous stroke, previous bleeding, labile INR, age above 65 and use of drugs/alcohol. Each clinical characteristic awards 1 point. The overall major bleeding rate was 1.5% and the risk ranged from 1.13 to 12.5 per 100 patient-years according to the HAS-BLED score. Other bleeding risk stratification schemes have also been introduced: $HEMOR_2RHAGES$ in 2006 (Gage et al. 2006), ATRIA in 2011 (Fang et al. 2011), ORBIT in 2015 (O'Brien et al. 2015) and the ABC-bleeding score in 2016 (Hijazi et al. 2016b). The predictive performance of $HEMOR_2RHAGES$, ATRIA and HAS-BLED were compared in patients with AF using anticoagulation. The analysis showed the superiority of HAS-BLED compared to other bleeding risk estimation tools. However, the predictive value of all these bleeding risk stratification schemes was only modest (Apostolakis et al. 2012).

## 2.4 Cardioversion of AF

### *2.4.1 Electrical cardioversion*

Lown and colleagues introduced electrical cardioversion in 1965 and since then it has been the most effective way of terminating AF (Lown et al. 1965); it can be used in the conversion of acute AF episodes, as well as in elective procedures. The success rates are as high as 90–95% in the conversion of acute AF (Michael et al. 1999, Cristoni et al. 2011). Pretreatment with antiarrhythmic medication can even improve the efficacy of electrical cardioversion (Singh et al. 2009). Nowadays, electrical cardioversion is common clinical procedure and is considered reasonably safe if performed during effective anticoagulation (Kirchhof et al. 2016).

Direct current electrical shock is delivered and synchronized to the QRS complex. Paddles or pads are positioned in anterior-lateral or anterior-posterior configurations. Studies suggest that the anterior-posterior electrode position is more successful (Kirchhof et al. 2002, Alp et al. 2000). The initial energy chosen depends on the defibrillator and ranges from 70 J to 200 J. A monophasic defibrillator requires higher energies. The energy is increased stepwise to a maximum of 200 J in biphasic and to 360 J in monophasic defibrillators. An alternative strategy is to begin with higher energies to reduce the number of shocks and consequently the total energy delivered. The superiority of biphasic defibrillators over monophasic waveforms has been demonstrated (Mittal et al. 2000), and these defibrillators are now the industry standard (Kirchhof et al. 2016). Biphasic defibrillators replaced monophasic waveforms in 2004.

Electrical cardioversion is performed under general anesthesia with intravenous propofol or midazolam (Kirchhof et al. 2016). Because of sedation, it requires anesthesiological assistance. Thus, the procedure requires six hours of fasting for the patient. Electrocardiogram, blood pressure and oxygen saturation should be monitored continuously (Furniss et al. 2015).

### *2.4.2 Pharmacological cardioversion*

Pharmacological cardioversion represents approximately 25% of all cardioversion attempts (Crijns et al. 2014). It does not require anesthesia or fasting. However, the procedure is less effective than electrical cardioversion (Cristoni et al. 2011). The success rate is approximately 50% in patients with acute AF (Reisinger et al. 2004, Dankner et al. 2009), and the efficacy of the procedure deteriorates when AF persists. Pharmacological cardioversion also poses a risk of pro-arrhythmia (Reisinger et al. 2004, Camm et al. 2011).

Flecainide, propafenone, ibutilide, vernakalant and amiodarone are used in the pharmacological cardioversion of AF (Kirchhof et al. 2016). To perform pharmacological cardioversion, these drugs are administered intravenously. During the procedure, electrocardiogram should be monitored continuously. Flecainide and propafenone can also be administered orally. Hence, these drugs can be self-administered by patients outside of the hospital setting. This approach is called *pill-in-the-pocket* therapy. In selected patients with symptomatic recurrent AF, it is proven to be safe and results in a reduction of emergency room visits (Alboni et al. 2004).

### *2.4.3 Elective versus acute cardioversion, and the risk of thromboembolism*

Cardioversions of AF are divided into acute and elective procedures. Immediate cardioversion of AF is possible when the duration of arrhythmia is definitely less than 48 hours. This limit of 48 hours of AF onset was introduced in 1995 by clinical practice guidelines (Fuster et al. 2006).

Historically, the risk of thromboembolism after cardioversion is reported to be as high as 7% when cardioversion was performed without anticoagulation (Bjerkelund et al. 1969, Arnold et al.1992). Thus, before elective cardioversion, the patient requires therapeutic oral anticoagulation for at least three weeks. Exclusion of cardiac thrombus with transesophageal echocardiography can be seen as an alternative to effective oral anticoagulation preceding cardioversion. The anticoagulation treatment should be continued for at least four weeks after cardioversion in all patients (Kirchhof et al. 2016). The recommendation of anticoagulation is largely based on observational studies (Moreyra et al. 1995, Jaber et al. 2000). Effective anticoagulation lowers the risk of

thromboembolism to approximately 0.5% (Nagarakanti et al. 2011, Flaker et al. 2014, Cappato et al. 2014).

Earlier, acute cardioversion of recent-onset AF was considered safe without any anticoagulation treatment. The incidence of thromboembolic complications has ranged from 0% to 0.9% in studies exploring this topic (Weigner et al. 1997, Gallagher et al. 2002, Burton et al. 2004, Stiell et al. 2010, Xavier Scheuermeyer et al. 2010, Michael et al. 1999). In 2010, ESC practice guidelines recommended that these procedures be performed under the cover of heparins, and in patients with risk factors for stroke, oral anticoagulation should be started after cardioversion (Camm et al. 2010). Even though the evidence behind this recommendation was scarce (Hughes et al. 2008, Hart et al. 2007, Singer et al. 2008a), as stated before, there are no prospective studies on this topic.

The increased risk of stroke related to cardioversion of AF is believed to be caused by two mechanisms. AF can cause thrombus formation in the left atrial appendage, which may dislodge after cardioversion (Goldman 1960), or the cardioversion can result in atrial stunning (Khan et al. 2003). Stunning is a period when mechanical contractibility is still impaired, but electrical activity is normal, resulting in blood stasis or at least diminished blood flow in the atria, predisposing the patient to thrombus formation (Khan 2003). The hypercoagulable state during AF may be yet another mechanism increasing the risk of thromboembolism related to cardioversion (Oltrona et al. 1997). Later, other potential mechanisms such as endothelial dysfunction and inflammation have been proposed to account for the increased thromboembolic risk (Procter et al. 2015).

The degree of atrial stunning has been reported to be associated with atrial size (Mattioli et al. 1996), structural heart disease (Mattioli et al. 1996) and duration of preceding AF (Shapiro et al. 1988, Manning et al. 1994). Even though the duration of AF increases the risk of stunning, it does also occur after cardioversion of acute AF (Ammar et al. 2015). Atrial stunning has not been reported after an unsuccessful procedure (Falcone et al. 1996). However, spontaneous conversion of AF also results in stunning (Grimm et al. 1995, Louie et al. 1998), which may explain the occurrence of stroke after an unsuccessful cardioversion procedure.

The long duration of AF increases the risk of thrombus formation in the left atrium (Wysokinski et al. 2010). However, Stoddard et al. (1995) found that 14% of patients have thrombi in the left atrial appendage within 72 hours after the onset of AF. Kleemann et al. (2009) revealed thrombi in 4% of non-anticoagulated patients whose AF duration was less than 48 hours. It is also shown that increased platelet activation and thrombin generation is seen within the first 15 minutes of AF, especially in the left atrium (Lim et al. 2013). These findings suggest that inherent risk of thromboembolism is not isolated to cardioversion of AF with a duration more than 48 hours. However, according to

current knowledge, cardioversion of acute AF can be done safely without prolonged pretreatment with oral anticoagulation (January et al. 2014, Kirchhof et al. 2016).

### *2.4.4 Success of cardioversion and other adverse events*

#### *2.4.4.1 Success of cardioversion*

The success rate has been reported to range from 66% to 98% in electrical cardioversion (Kuppahally et al. 2009, Toso et al. 2012). The rate is higher in patients undergoing cardioversion for recent-onset AF and markedly lower in pharmacological cardioversion (Pisters et al. 2012b), and the efficacy of the procedure declines when AF persists. The success rate is approximately 50% in the pharmacological cardioversion of acute AF (Reisinger et al. 2004, Dankner et al. 2009).

Long duration of AF (Kuppahally et al. 2009, Pisters et al. 2012a, Fumagalli et al. 2002, Frick et al. 2001, Mittal et al. 2000, Botto et al. 1999, Mathew et al. 1999, Van Gelder et al. 1991) and obesity (Frick et al. 2001, Blich et al. 2006, Kirchhof et al. 2002) have been most consistently associated with unsuccessful cardioversion. Other predictors for successful cardioversion reported are the use of biphasic wave form (Mittal et al. 2000, Pisters et al. 2012b), the absence of COPD (Pisters et al. 2012a), pretreatment with antiarrhythmic drugs (Kuppahally et al. 2009), absence of left atrium enlargement (Toso et al. 2012), anteroposterior defibrillator position (Botto et al. 1999, Kirchhof et al. 2002), young age (Van Gelder et al. 1991) and no history of hypertension (Blich et al. 2006). Whilst numerous predictors for successful elective electrical cardioversion have been identified, only few studies have dealt with recent-onset AF (Jaakkola et al. 2017, Xavier Scheuermeyer et al. 2010, Burton et al. 2004, Bellone et al. 2012).

#### *2.4.4.2 Arrhythmic complications following cardioversion*

The cardioversion of AF carries a potential risk for arrhythmic complications. Pharmacological cardioversion can lead to pro-arrhythmias such as polymorphic ventricular tachycardia or torsades de pointes (Reisinger et al. 2004, Stambler et al. 1996), whereas the shock-related arrhythmias after electrical cardioversion are generally bradyarrhythmias, and tachyarrhythmic ventricular complications are rare (Morani et al. 2009). Bradyarrhythmic complications mainly denote sinus bradycardia or sinus arrest. However, in studies shedding light on this matter, the criteria for bradycardia has been variable. Ventricular fibrillation is mainly caused by delivering shock during ventricular repolarization (Gallagher et al. 2008). The previously reported risk of arrhythmic complications has been nearly nonexistent (0–0.3%) in electrical cardioversion of recent-onset AF (Xavier Scheuermeyer et al. 2010, Michael et al. 1999, Burton et al. 2004). The risk of these complications is more pronounced after longer lasting episodes

of AF, with a rate up to 1.5% (Morani et al. 2009, Gallagher et al. 2008, Pisters et al. 2012b, Botkin et al. 2003). A thorough search of the relevant literature yielded no previous large-scale studies focusing on arrhythmic complications after electrical cardioversion of acute AF.

*2.4.4.3 Recurrence of atrial fibrillation after cardioversion*

Recurrence of AF after cardioversion is a common and undesirable event. The recurrence rate of AF has been reported to be as high as 77% after cardioversion of persistent AF at the one-year follow-up (Osmanagic et al. 2015). Considering that AF episodes can be asymptomatic, the frequency of AF can be even higher. However, the rate is lower in patients suffering shorter episodes of AF (Dittrich et al. 1989, Van Gelder et al. 1991). AF remodels atrial substrate, resulting in a larger left atrium (Lu et al. 2008, Wijffels et al. 1995). This exposes patients to the recurrence of AF (Bollmann et al. 2003, Olshansky et al. 2005, Marchese et al. 2011) and lowers the probability of successful cardioversion. In addition to the large left atrium and duration of AF, other risk factors associated with the recurrence of AF have been demonstrated. The AFFIRM trial found that the absence of coronary artery disease and the length of P waves were risk factors for AF recurrence (Raitt et al. 2006). A systematic review by Lafuente-Lafuente and colleagues demonstrated the benefit of antiarrhythmic drugs (Lafuente-Lafuente et al. 2006). Identification of possible predictors for the recurrence of AF would be useful since the high probability of AF recurrence challenges the benefit of rhythm control therapy. The recurrence of AF exposes the patients to repeated cardioversions and consequently to the increased risk of thromboembolism related to cardioversion.

# 3. AIMS OF THE STUDY

The objective of the present work was to provide new information on the cardioversion of recent-onset (duration < 48 hours) AF. The focus was on the safety and efficacy of cardioversion in patients with and without anticoagulation. The specific aims of the study were:

1. To examine the incidence and identify possible predictors of immediate arrhythmic complications and their clinical consequences after electrical cardioversion (I).

2. To investigate the success of electrical cardioversion, the rate of AF recurrence after the procedure and possible predictors of unsuccessful cardioversion and AF recurrence (IV).

3. To determine the incidence and identify possible predictors of thromboembolic complications after cardioversion of recent-onset AF (II, III).

4. To assess the efficacy of anticoagulation in the prevention of thromboembolic complications and the feasibility of the $CHA_2DS_2VASc$ score in the prediction of thromboembolic complications in patients undergoing cardioversion of recent-onset AF (V).

# 4. MATERIALS AND METHODS

## 4.1 Study design and patient identification

The FinCV study is a multicenter, observational, retrospective study of patients undergoing cardioversion of acute (< 48 hours) AF. Its purpose is to investigate the complications of cardioversion of acute AF. Patients were treated in the emergency departments of two university hospitals from 2003 to 2010 and one central hospital in 2010: Turku University Hospital, Kuopio University Hospital and Satakunta Central Hospital, respectively. Study protocol was approved by the Ethics Committees of the Hospital District of Southwest Finland and the National Institutes for Health and Welfare. No informed consent was required due to the retrospective nature of the study. The study complies with the Declaration of Helsinki. Patients with a primary diagnosis of AF (ICD code I48) were identified from the institutional discharge registers of these study centers. After identification of the patient, the emergency clinic admission records and databases were reviewed. Patients were eligible and included in the study if they were 18 years of age or older, if they were living in the catchment area of the study center and if cardioversion was performed within 48 hours of AF onset. All study centers are the only referral hospitals responsible for the acute care of patients with cardiac and stroke events in their catchment area, and thus patients living outside the catchment area were excluded to ensure adequate follow-up data after the cardioversion. If the duration of AF was more than 48 hours or uncertain, the episodes were excluded from the study.

## 4.2 Data collection and study population

Standardized data collection protocol was used to review all case records for information on baseline characteristics and medication of patients, management of the patients during the index cardioversion and follow-up data during 30 days after cardioversion. After completion of the manual registration of data, a computer-based cross-checking of strokes was performed from the discharge register data of the included patients to ensure the complete coverage of all thromboembolic events.

We identified 3134 patients who underwent 7660 cardioversions for acute AF. Of those procedures, 7237 were successful. The majority of cardioversions were electrical (90.2%); 5362 cardioversions were performed without oral anticoagulation or peri-procedural heparin therapy and of those procedures, 5116 were successful. In anticoagulated patients, cardioversions were performed during long-term warfarin treatment (98%) or under cover of parenteral anticoagulants.

In paper II, the risk of definite thromboembolic complications is evaluated after 5116 successful cardioversions in 2481 patients without anticoagulation. In paper III, these

procedures are divided into three groups based on time to cardioversion (< 12 hours, 12–24 hours, 24–48 hours) to assess the impact of delay of cardioversion to thromboembolic complications. Papers I and IV focus on 2868 patients who underwent 6906 electrical cardioversions. The aim is to evaluate the risk of arrhythmic complications and to determine rate and risk factors for unsuccessful electrical cardioversion and AF recurrence. In paper V, cardioversions are divided into 4 groups according to $CHA_2DS_2VASc$ scores: $\leq 1$, 2, 3 to 4, and $\geq 5$. The thromboembolic risk in anticoagulated and non-anticoagulated patients is compared in these groups. The predictive value of the $CHADS_2$ score is also evaluated. Finally, we assess whether the $CHA_2DS_2VASc$ score also predicts other adverse events.

Diagnosis of AF was confirmed by 12-lead electrocardiography. An electrocardiogram was also recorded after the procedure. The duration of the AF episode was determined from the symptom onset and exact time of cardioversion. Cardioversions were performed according to contemporary guidelines. Electrical cardioversions were performed under general anesthesia with propofol, midazolam, or ethomidate. In hemodynamically stable patients, six-hour fasting was required before anesthesia. Paddles or pads were placed in an anteroposterior or anterolateral configuration according to the physician's preference. After 2004, biphasic defibrillators were mainly used.

## 4.3 Outcome definitions

Cardioversion was considered successful if sinus rhythm was obtained and the patient was discharged from the cardioversion unit in this rhythm. Definite thromboembolic complication was defined as a stroke or systemic embolism within 30 days after cardioversion was clinically documented and conformed by imaging, surgery or autopsy. TIAs were classified as probable embolic events. Hemorrhages were defined according to the Thrombolysis In Myocardial Infarction criteria (Rao et al. 1988) within 30 days after cadioversion. Bradycardia after cardioversion was defined as having a heart rate under 40 beats per minute. Asystole was defined as cardiac arrest lasting more than five seconds. Clinical recurrence of AF was evaluated from patient records within 30 days after the procedure. The case records of all patients with bradyarrhythmias were reviewed for pacemaker implantation after the cardioversion. The length of the follow-up period from bradyarrhythmic complication to possible pacemaker implantation was not predefined.

## 4.4 Statistical analysis

Statistical analyses were performed using SPSS software (version 17.0 SPSS Inc., Chicago, version 20.0, IBM Corp., Armonk, NY, and version 22.0 IBM Corp., Armonk,

NY) and SAS software (versions 9.2 and 9.3, SAS Institute Inc., Cary, NC). Continuous variables are presented as the mean ± standard deviation or median (interquartile range) and analyzed with Student's t test, the Wilcoxon nonparametric test, Mann-Whitney U test, and Kruskal-Wallis test, as appropriate. Categorical variables are expressed in absolute numbers and percentages and analyzed with the chi-square test, Fisher's exact test, and Cochran-Armitage test for trend, as appropriate. Multivariable logistic regression analysis with the repeated measure option (the GENMOD procedure) was used to identify independent predictors for primary and secondary outcomes in the papers (definite thromboembolic complications, bradyarrhythmias, unsuccessful cardioversion and recurrence of AF). The GENMOD procedure was chosen because repeated cardioversions were included in the analyses. This test was also used in univariate analyses in papers I and II. Only variables with a 2-sided p value of $< 0.05$ in the univariate analyses were included in the multivariable analyses.

In papers II and V, the ROC (receiver-operating characteristic) curve analysis was used to assess the ability of risk-scoring methods in predicting definite thromboembolic complications. In paper V, only the first cardioversion was included in the analysis, and the difference between the area under the ROC curves of $CHA_2DS_2VASc$ and $CHADS_2$ scores was evaluated by DeLong's method (DeLong et al. 1988). In paper II, classification tree analysis was employed to classify the risk of thromboembolism according to independent predictors identified by the GENMOD procedure. The chi-square automatic interaction detection method was chosen, along with its best model on the basis of obtained predicted probabilities. Validation of the classification tree procedure was assessed by cross-validation through 25 folds. The minimum number of patients for the parent node was set to 50, and the minimum for the child node was 10. The maximum classification tree depth was 5. The minimum change in improvement was set at a significance level of 0.05.

# 5. RESULTS

## 5.1 Failure of electrical cardioversion, early recurrence of AF, and arrhythmic complications after cardioversion (I, IV)

Papers I and IV dealt with 2868 patients undergoing 6906 electrical cardioversions. At the time of cardioversion, the mean age of patients was 62.4 ± 12.3 years. A total of 2436 (35.3%) cardioversions were performed on female patients. The success rate of cardioversion was 94.2%. Baseline clinical characteristics are shown in Table 2 according to the success of cardioversion.

**Table 2.** Baseline characteristics according to success of electrical cardioversion. Modified from paper IV.

| | **Successful ECV (n=6508)** | **Unsuccessful ECV (n=398)** | **p value** |
|---|---|---|---|
| **Age** | 62.2 ± 12.4 | 65.5 ± 10.3 | < 0.001 |
| **Female** | 2,264 (34.8) | 172 (43.2) | < 0.001 |
| **Heart failure** | 363 (5.6) | 26 (6.5) | 0.4 |
| **Diabetes** | 639 (9.8) | 44 (11.1) | 0.4 |
| **AAD therapy** | 1322 (20.3) | 132 (33.2) | < 0.001 |
| **Beta-blockers** | 4984 (76.6) | 335 (84.2) | < 0.001 |
| **Duration of AF < 12 hours** | 2900 (44.6) | 230 (57.8) | < 0.001 |
| **AF episodes within 30 days before index ECV** | 1110 (17.1) | 97 (24.4) | < 0.001 |

ADD=antiarrhythmic drug; AF=atrial fibrillation; ECV=electrical cardioversion.
Values are mean ± SD or n (%).

A total of 398 electrical cardioversions were unsuccessful. Of those unsuccessful procedures, 26% were later cardioverted successfully. In multivariable analysis, antiarrhythmic drug therapy (odds ratio [OR]: 1.97; 95% confidence interval [CI]: 1.52–2.55, p < 0.001), implanted pacemaker (OR: 2.12; 95% CI: 1.42–3.14, p < 0.001), previous episodes of AF within 30 days before cardioversion (OR: 1.46; 95% CI: 1.13–1.89, p = 0.004), beta-blockers (OR: 1.37; 95% CI: 1.02–1.84, p = 0.04), age (per year) (OR: 1.03; 95% CI: 1.02–1.04, p < 0.001) and duration of AF < 12 hours (OR: 1.81; 95% CI: 1.48–2.21, p < 0.001) were independent predictors of unsuccessful cardioversion. Short-duration AF also remained an independent predictor of

unsuccessful cardioversion in subgroup analysis of patients with cardioversion of the first AF episode and patients receiving antiarrhythmic drugs.

The rate of clinical AF recurrence was 17.3% within 30 days after successful electrical cardioversion. The mean time to recurrence was 12.6 ± 9 days. Vascular disease (OR: 1.54; 95% CI: 1.27–1.85, p < 0.001), heart failure (OR: 1.54; 95% CI: 1.10–2.17, p = 0.01), diabetes (OR: 1.36; 95% CI: 1.07–1.72, p = 0.01), renal failure (OR 1.65; 95% CI: 1.09–2.50, p = 0.02), female gender (OR: 1.23; 95% CI: 1.03–1.48, p = 0.02), previous AF episodes (OR: 2.50; 95% CI: 2.02–3.10, p < 0.001), first AF episode (OR: 0.77; 95% CI: 0.62–0.97, p = 0.02), antiarrhythmic drug therapy (OR: 1.51; 95% CI: 1.23–1.86, p < 0.001), increasing number of cardioversions during the study period (OR: 1.07; 95% CI: 1.05–1.09, p < 0.001) and beta-blockers (OR: 1.23; 95% CI: 1.01–1.51, p = 0.04) were independent predictors for recurrence after multivariable analysis.

Bradycardia (< 40 bpm) or asystole or both occurred after 63 (0.9%) electrical cardioversions in 54 patients. Bradycardia alone was seen after 12 (0.2%) procedures. Fifty-one cardioversions (0.7%) resulted in asystole. Of those cases, nine were followed by bradycardia: seven patients needed short resuscitation and two needed extrinsic pacing. Age (per year) (OR: 1.1; 95% CI: 1.05–1.0, p < 0.001), female gender (OR: 2.5; 95% CI: 1.4–4.8, p = 0.004) and unsuccessful cardioversion (OR: 2.2; 95% CI: 1.1–4.6, p = 0.03) were independent predictors of bradyarrhythmias after multivariable analysis. The use of digoxin (9.5% vs. 7.0%, p = 0.45) or β-blockers (74.6% vs.76.3%, p = 0.75) did not differ significantly between patients with and without bradyarrhythmias. The ventricular rate during AF did not differ significantly between patients with and without complications (111 ± 22 vs. 109 ± 26, p = 0.46).

A permanent pacemaker was implanted in 24 patients with bradyarrhythmia. Median time after cardioversion was 66 days. In eight patients, the pacemaker was implanted within a week. For the majority of patients, the indication for implantation was sinus node dysfunction, which was revealed in the cardioversion. Unsuccessful cardioversion (OR: 6.2; 95% CI: 1.1–33.6, p = 0.045) predicted pacemaker implantation in patients who suffered bradyarrhythmia.

## 5.2 Risk of thromboembolism after cardioversion of acute AF (II)

Of 5362 cardioversions in acute AF without oral anticoagulation or peri-procedural heparin therapy, 5116 were successful in 2481 patients. At the time of cardioversion, the mean age of patients was 61.0 ± 12.4 years. Of those successful cardioversions in non-anticoagulated patients, there were 4488 (87.7%) electrical cardioversions, and 1638 (32.0%) procedures were performed on female patients. Table 3 shows baseline characteristics according to the incidence of definite thromboembolic complications.

**Table 3.** Baseline characteristics of patients at the time of 5116 cardioversions according to incidence of definite thromboembolic complications. Modified from paper II.

| | **No thromboembolic complications (n=5078)** | **Thromboembolic complications (n=38)** | **p value** |
|---|---|---|---|
| **Age (yrs)** | 60.9 ± 12.4 | 69.9 ± 9.3 | < 0.001 |
| **Female** | 1616 (31.8) | 22 (57.9) | 0.001 |
| **Hypertension** | 2305 (45.4) | 19 (50.0) | 0.6 |
| **Diabetes** | 401 (7.9) | 8 (21.1) | 0.01 |
| **Vascular disease** | 1128 (22.2) | 17 (44.7) | 0.001 |
| **Heart failure** | 178 (3.5) | 6 (15.8) | 0.002 |
| **Previous thromboembolism** | 288 (5.7) | 3 (7.9) | 0.5 |
| **$CHA_2DS_2VASc$ score** | 1 (0–3) | 3 (1–4) | < 0.001 |

Values are mean ± SD, n (%) or median (interquartile range).

Definite thromboembolic complications occurred after 38 successful cardioversions in 38 patients (0.7%, 95% CI: 0.5–1.0). Of those embolic complications, 31 were strokes and one patient had simultaneous stroke and systemic embolism. In addition, four patients experienced a TIA after successful cardioversion. For the incidence of definite thromboembolic complications, the median time was 2 days (range 1–27 days, mean 4.6) (Figure 1). No embolic complications occurred in non-anticoagulated patients after 246 failed cardioversions.

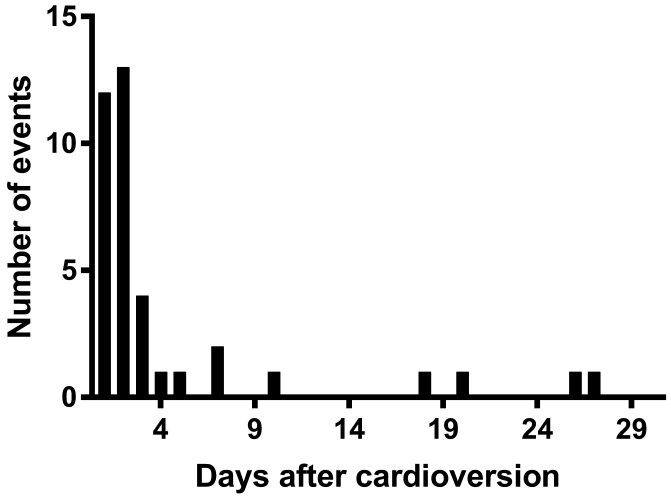


**Figure 1.** Number of definite thromboembolic events according to time from cardioversion.

Multivariable analysis identified age (per year) (OR: 1.05; 95% CI: 1.02–1.08, p < 0.001), the female sex (OR: 2.1; 95% CI: 1.1–4.0, p = 0.03), heart failure (OR: 2.9; 95% CI: 1.1–7.2, p = 0.03) and diabetes (OR: 2.3; 95% CI: 1.1–4.9, p = 0.03) as independent predictors for definite thromboembolic complications after cardioversion in non-anticoagulated patients.

After multivariable analysis, chi-square automatic interaction detection analysis was performed to evaluate the risk of thromboembolic complication in relation to the accumulation of these risk factors. This analysis showed that heart failure, diabetes and age > 60 years were predictive of postprocedural definite thromboembolism (area under the ROC curve: 0.68, 95% CI: 0.60–0.76). On the basis of a ROC curve analysis and the results of a classification tree analysis, a cutoff of 60 years was chosen. The analysis detected that in patients with heart failure and diabetes, the risk of thromboembolic complications was 9.8%, whereas in patients without heart failure and those under age 60, this risk was only 0.2%.

## 5.3 Time to cardioversion for acute AF and thromboembolic complications (III)

Of 5116 successful cardioversions performed without anticoagulation, 2440 were performed after AF episodes with a duration less than 12 hours, 1840 after AF lasting 12 to 24 hours, and 836 procedures after episodes lasting 24 to less than 48 hours. Table 4 shows the baseline characteristics of cardioversions according to duration of AF.

**Table 4.** Clinical characteristics of 5116 successful cardioversions according to time to cardioversion. Modified from paper III.

| | **< 12 hours (n=2440)** | **12–24 hours (n=1840)** | **24–48 hours (n=836)** | **p value** |
|---|---|---|---|---|
| **Age** | 61.0 (12.2) | 60.6 (12.7) | 61.7 (12.5) | 0.04 |
| **Female gender** | 851 (34.9) | 551 (30.0) | 236 (28.2) | < 0.001 |
| **Hypertension** | 1117 (45.8) | 833 (45.3) | 374 (44.7) | 0.86 |
| **Diabetes** | 207 (8.5) | 129 (7.0) | 73 (8.7) | 0.15 |
| **Vascular disease** | 555 (22.8) | 407 (22.2) | 183 (21.9) | 0.83 |
| **Heart failure** | 78 (3.2) | 63 (3.4) | 43 (5.1) | 0.03 |
| **History of thromboembolism** | 142 (5.8) | 106 (5.8) | 43 (5.1) | 0.76 |

Values are mean ± SD or n (%).

During the study period, 38 definite thromboembolic complications occurred (0.7%; 95% CI: 0.5%–1.0%). The rate of these thromboembolic complications increased from 0.3% in cardioversions performed within 12 hours after onset of the episode to 1.1% in those performed after episodes lasting more than 24 hours. Figure 2 shows the incidence of definite thromboembolic complications according to the subgroup of patients.

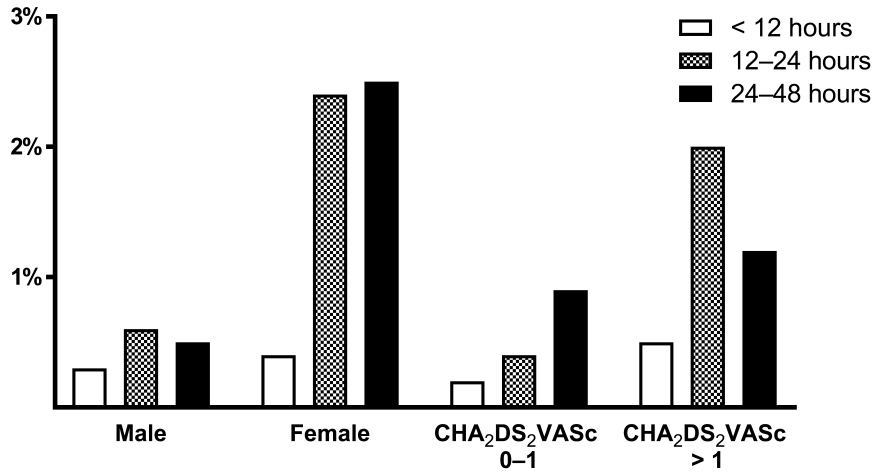


**Figure 2.** Incidence of definite thromboembolic complications in a subgroup of patients according to time delay from symptom onset to cardioversion.

In multivariable analysis, delay to cardioversion longer than 12 hours was an independent predictor for definite thromboembolic complications (OR of 4.0 [95% CI: 1.7–9.1] between episodes lasting 12–24 hours and less than 12 hours [p = 0.001]; OR of 3.3 [95% CI 1.3–8.9] between episodes lasting 24–48 hours and less than 12 hours [p = 0.02]), together with age (per year) (OR: 1.06; 95% CI: 1.03–1.09, p < 0.001), the female sex (OR: 2.1; 95% CI: 1.1–4.3, p = 0.04), heart failure (OR: 3.5; 95% CI: 1.4–8.6, p < 0.001) and diabetes mellitus (OR: 2.7; 95% CI: 1.3–5.8, p = 0.01).

## 5.4 Efficacy of anticoagulation and the usefulness of the $CHA_2DS_2VASc$ score during cardioversion of acute AF (V)

In paper V, the efficacy of anticoagulation was analyzed during 2298 cardioversions with effective anticoagulation and 5362 cardioversions without. In anticoagulated patients, cardioversions were performed during long-term oral anticoagulation (98%) or under cover of heparins. The baseline characteristics are listed in Table 5 according to anticoagulation. Of 7660 cardioversions, 7237 (94.5%) were successful.

**Table 5.** Clinical characteristics of 7660 cardioversions per anticoagulation.

| | No anticoagulation (n=5362) | Anticoagulation (n=2298) | p value |
|---|---|---|---|
| **Age** | 61.2 ± 12.4 | 64.4± 11.8 | < 0.001 |
| **Female gender** | 1740 (32.5) | 1058 (46.0) | < 0.001 |
| **Hypertension** | 2445 (45.6) | 1278 (55.6) | < 0.001 |
| **Heart failure** | 197 (3.7) | 206 (9.0) | < 0.001 |
| **Diabetes mellitus** | 433 (8.1) | 309 (13.4) | < 0.001 |
| **Previous thromboembolism** | 310 (5.8) | 386 (16.8) | < 0.001 |
| **Vascular disease** | 1216 (22.7) | 999 (43.5) | < 0.001 |

Values are mean ± SD or n (%).

A total of 41 (0.5%) definite thromboembolic complications occurred during the study period, and three patients were using anticoagulation therapy during cardioversion. Two patients suffered definite thromboembolism on oral anticoagulation therapy, and their INR values were 2.9 and 3.5 at the time of cardioversion. One patient with peri-procedural heparin therapy suffered stroke after unsuccessful cardioversion. The incidence of definite thromboembolism was significantly lower in anticoagulated patients than in those without anticoagulation (0.1% [3 of 2298] vs 0.7% [38 of 5362],

p = 0.001). The benefit of anticoagulation was statistically significant in patients with a $CHA_2DS_2VASc$ of ≥ 2 (p = 0.001), but not in patients with a CHA2DS2VASc score of 0–1 (p = 0.23) (Figure 3). One anticoagulated patient with an INR value of 5.1 suffered melena three days after cardioversion. No major bleeding complications occurred during the follow-up in non-anticoagulated patients. The only clinically relevant bleeding event was related to surgical embolectomy in non-anticoagulated patients.

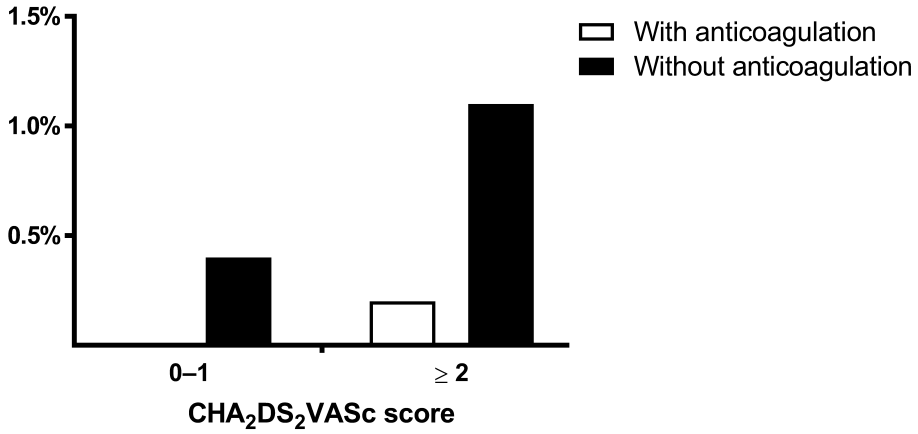


**Figure 3.** The incidence of definite thromboembolic complications (%) following cardioversion of acute AF according to $CHA_2DS_2VASc$ scores and use of anticoagulation.

In non-anticoagulated patients during the first cardioversion, calculated C-statistics of $CHA_2DS_2VASc$ and $CHADS_2$ for definite thromboembolism were 0.72 (95% CI: 0.61–0.83) and 0.66 (95% CI: 0.55–0.78), respectively. The difference was also statistically significant (p = 0.003). An increasing $CHA_2DS_2VASc$ score was associated with a stepwise increase in rates of definite thromboembolic complications in non-anticoagulated patients (p < 0.001 for trend). The risk of thromboembolism was 0.4% in patients with $CHA_2DS_2VASc \leq 1$ compared to the risk of 2.3% patients with $CHA_2DS_2VASc \geq 5$. By multivariate analysis, duration of AF > 12 hours, female sex, diabetes mellitus, age and heart failure were independent predictors of definite thromboembolism.

The $CHA_2DS_2VASc$ score independently increased the risk of unsuccessful cardioversion (OR: 1.09; 95% CI: 1.03–1.16, p = 0.006), recurrence of AF after successful cardioversion (OR: 1.17; 95% CI: 1.12–1.22, p < 0.001) and bradyarrhythmias (OR: 1.44; 95% CI: 1.27–1.62, p < 0.001).

# 6. DISCUSSION

## 6.1 Bradyarrhythmias and their consequences after electrical cardioversion (I)

Paper I shows that electrical cardioversion of acute AF is a safe procedure with respect to immediate arrhythmic complications. These complications were rare (< 1%) and mostly transient bradyarrhythmias, which seldom needed any specific treatment. Female gender, unsuccessful cardioversion and advanced age were found to be predictors for bradycardia and asystole, but use of digoxin, beta-blockers or a slow ventricular rate were not associated with bradyarrhythmias.

Presumably, paper I is the largest study on arrhythmic complications after cardioversion of acute AF, and previous studies on this matter have dealt with elective cardioversion. Previous studies on acute AF have been small and have reported a markedly lower rate of arrhythmias (0–0.3%) (Xavier Scheuermeyer et al. 2010, Burton et al. 2004). Therefore, these studies have not been able to identify any predictors for bradyarrhythmias. The rate of these complications in our study was comparable to studies on elective cardioversion of persistent AF (0.8–1.5%) (Pisters et al. 2012a, Botkin et al. 2003, Siaplaouras et al. 2005, Gallagher et al. 2008, Morani et al. 2009). In line with previous studies, clinically meaningful ventricular arrhythmias were absent. Gallagher and colleagues reported five episodes of ventricular fibrillation after 6398 shocks in their large multicenter study. At least two of these complications, but probably all, were due to ventricular synchronization failure (Gallagher et al. 2008).

Interestingly, bradyarrhythmic complications led to permanent pacemaker implantation in > 40% of patients with these complications. Unsuccessful cardioversion was the only predictor, which triggered the implantation. Sinus node dysfunction is associated with increased risk of AF (Ferrer 1968). Electrical cardioversion results in transient asystole. Thus, it can be considered a surrogate for the assessment of sinus node recovery time during electrophysiological study. Therefore, prolonged asystole can reveal subtle sinus node dysfunction, which was the main indication for a permanent pacemaker in our study.

## 6.2 Failure of electrical cardioversion of acute AF and early clinical recurrence of AF after successful cardioversion (IV)

The high success of cardioversion is within the range reported previously and is in accordance with clinical experience. The rate of early clinical recurrence was lower than expected, but the recurrence rate was high in certain subgroups of patients. Importantly, simple clinical risk factors were identified for both failure of cardioversion and early

recurrence of AF. Based on the results of the study, it is possible to assess the clinical relevance of repeated cardioversions in some patient groups (Jaakkola et al. 2017). Interestingly, heart failure, diabetes, known vascular disease and the female sex, which are risk factors for ischemic stroke, also predicted a recurrence of AF.

Short-duration AF is probably most consistently identified as a predictor of successful cardioversion of AF (Kuppahally et al. 2009, Pisters et al. 2012b, Glover et al. 2008, Fumagalli et al. 2002, Frick et al. 2001, Botto et al. 1999, Mathew et al. 1999, Van Gelder et al. 1991). Hence, it is surprising that very short (< 12 hours) duration was an independent predictor of unsuccessful cardioversion. This risk of electrical cardioversion failure was even more pronounced during the first attacks of AF. However, there are studies suggesting that factors such as autonomic imbalance, which trigger the onset of AF, may persist during the first hours of an AF episode. First of all, it has been shown that induced AF results in a significant increase in sympathetic nervous activity (Wasmund et al. 2003). Moreover, immediate AF recurrence, defined as a recurrence within 60 seconds after restoration of sinus rhythm, is more common when cardioversion is performed within one hour of AF onset compared to cardioversions performed after 24 hours of AF (Oral et al. 2003). This finding is supported by a study in which patients with implantable cardioverter-defibrillators were either randomized to cardioversion by the device as soon as possible or were delayed (1 day later). They found that delayed strategy decreased the rate of AF recurrence (Schwartzman et al. 2005). In light of these evidences, AF duration seems to be inversely related to the likelihood of cardioversion success within the first hours after AF onset.

Factors reflecting high arrhythmic burden, such as previous AF attack and use of antiarrhythmic drugs, predicted both unsuccessful cardioversion and recurrence of AF. Walters and colleagues demonstrated that the burden of paroxysmal AF is associated with progressive left atrial structural remodeling (Walters et al. 2016). Left atrial enlargement is in turn associated with unsuccessful cardioversion (Toso et al. 2012) and recurrence of AF (Bollmann et al. 2003, Olshansky et al. 2005, Marchese et al. 2011). Due to the retrospective nature of our study, patients treated with antiarrhythmic drug therapy probably had higher arrhythmic burden, which justified the use of these drugs. This reasoning explains—at least partly—the inconsistency to earlier studies, which have demonstrated the benefit of antiarrhythmic drugs in relation to successful cardioversion (Crijns et al. 2014) and sinus rhythm maintenance (Lafuente-Lafuente et al. 2006). However, Blecher and coworkers reported reduced success of electrical cardioversion of recent-onset AF when patients were pretreated with antiarrhythmic drugs (Blecher et al. 2012).

## 6.3 Thromboembolic risk of cardioversion of acute AF without adequate anticoagulation (II)

In Finland, it was common practice to perform cardioversion of recent-onset AF without anticoagulation as long as there was a clear history of arrhythmia onset within 48 hours from cardioversion. However, in 2010 this practice was called into question by ESC guidelines, which recommended that acute AF be converted under cover of heparins and followed by long-term oral anticoagulation in high-risk patients (Camm et al. 2010). However, the recommendation was based on a few retrospective small studies with less than 1500 non-anticoagulated patients (Weigner et al. 1997, Michael et al. 1999, Burton et al. 2004, Gallagher et al. 2002, Stiell et al. 2010, Xavier Scheuermeyer et al. 2010). In these studies, the rate of thromboembolic complications was less than 0.9%, and these complications occurred after spontaneous conversion of AF to sinus rhythm.

In paper II, the risk of thromboembolic complications in non-anticoagulated patients was 0.7% and thus comparable to the risk of elective cardioversion performed with adequate anticoagulation. However, "traditional" risk factors were also found to be predictors of thromboembolic complications after cardioversion of acute AF. In fact, the accumulation of these risk factors increased the risk of thromboembolism in some patients by close to 10%. Reassuringly, the risk of thromboembolism was minimal without these risk factors.

The majority of thromboembolic complications occurred within the first days after cardioversion and no thromboembolic complications occurred after unsuccessful cardioversion in non-anticoagulated patients. These findings support the view that conversion of AF to sinus rhythm is responsible for thromboembolic complications. It is commonly accepted that the left atrial appendage is the origin of thrombus in patients with AF suffering thromboembolic complications. In fact, the left atrial thrombus is found in 4% of non-anticoagulated patients as soon as 48 hours after the onset of AF, and in 14% of patients with an AF duration of under 72 hours (Stoddard et al. 1995, Kleemann et al. 2009). AF results in prothrombotic activation early after the onset of arrhythmia, especially in the left atrial appendage (Lim et al. 2013). Conversion of AF to sinus rhythm is often followed by a period of impaired mechanical contractibility, i.e., atrial "stunning" (Grimm et al. 1993, Leistad et al. 1993), which predisposes the patient to thrombus formation due to increased stasis in the left atrium (Khan 2003). Even though the thrombus is not visualized by transesophageal echocardiography before the cardioversion, there is a clear risk of thromboembolic complication after cardioversion. The results of paper II support the view that transitory stunning of atrial myocardium might also occur after cardioversion of recent-onset AF, which results in an elevated risk of thromboembolism if adequate anticoagulation is not used.

The findings in paper II are in line with current clinical practice guidelines (January et al. 2014, Kirchhof et al. 2016). Cardioversion of acute AF should be performed under cover of anticoagulants followed by oral anticoagulation in patients with conventional risk factors for thromboembolism.

## 6.4 Impact of delay to cardioversion for acute AF on risk of thromboembolic complications (III)

The major finding of the paper was that a cardioversion delay of more than 12 hours was associated with an almost fourfold increase in the risk of thromboembolism compared to cardioversions performed within 12 hours of AF onset.

The limit of 48 hours for cardioversion without prior anticoagulation was recommended by clinical practice guidelines in 1995 (Fuster et al. 2006). These recommendations were based more on common sense than on scientific proof. The first systematic report on the risk of thromboembolic complications related to the cardioversion of AF was published in 1969 by Bjerkelund and Orning. In their study, the rate of thromboembolic events in non-anticoagulated patients was 6.9% (Bjerkelund et al. 1969). Later, in studies including only recent-onset AF, this risk was reported to be less than 1% (Weigner et al. 1997, Gallagher et al. 2002, Burton et al. 2004, Stiell et al. 2010, Xavier Scheuermeyer et al. 2010, Michael et al. 1999). Profound activation of coagulation factors and platelets has been observed within 12 hours of AF (Sohara et al. 1997). Some of these changes are measurable 15 minutes after AF onset (Lim et al. 2013). In light of this evidence, it is not surprising that cardioversion delay might increase the risk of thromboembolism within the first 48 hours of AF.

There were only a few apparent prothrombotic differences between study groups. Even though an increase in the risk of thromboembolism was more pronounced in patients with conventional risk factors for stroke, for patients normally deemed low risk ($CHA_2DS_2VASc$ score 0–1), cardioversion was not without risk: it varied from 0.4% to 0.9% if the duration of an AF episode was longer than 12 hours. The time to cardioversion was the most significant predictor of thromboembolic complications. Therefore, we should be more cautious regarding cardioversion after 12 hours in patients without anticoagulation. Especially, if the AF episode is prolonged in a patient with multiple risk factors for stroke and the restoration of sinus rhythm is seen as a reasonable option, starting them on anticoagulation and postponing cardioversion could be a reasonable option.

## 6.5 The benefit of anticoagulation and the $CHA_2DS_2VASc$ score in patients undergoing cardioversion for acute AF (V)

The major finding was that the $CHA_2DS_2VASc$ score was a significant predictor of thromboembolic complications in cardioversion performed without the protection of anticoagulation. More importantly, effective long-term anticoagulation reduced the risk of thromboembolic complications by 82%. Furthermore, the rate of these complications was low after unsuccessful cardioversion.

As shown before, cardioversion in patients with AF increases the risk of thromboembolic complications. Historically, the rate of these events has been reported to vary from to 3% to 7% in non-anticoagulated patients after cardioversion of AF (Bjerkelund et al. 1969, Arnold et al. 1992). This risk has to decrease to 0.5%–1.6% with the use of anticoagulants for three weeks before and four weeks after elective cardioversion or with transesophageal echocardiogram before cardioversion following adequate anticoagulation (Apostolakis et al. 2013, Gallagher et al. 2002, Stellbrink et al. 2004, Nagarakanti et al. 2011, Piccini et al. 2013b, Flaker et al. 2014, Cappato et al. 2014). In our study, the risk of thromboembolism was comparable (0.7%) in non-anticoagulated patients undergoing cardioversion for recent-onset AF. For comparison, the mean monthly risk of thromboembolic complications is approximately 0.3% depending on stroke risk factors in AF patients, and warfarin decreases this risk by 64% (Hart et al. 2007). This benefit of anticoagulation has been recently confirmed by large multicenter prospective studies, where the risk of thromboembolism is decreased to 0.1%–0.2% per month (Connolly et al. 2009, Patel et al. 2011, Granger et al. 2011). In the FinCV study, the rate of thromboembolic events was only 0.1% in patients using (mainly) long-term oral anticoagulation. In light of this evidence, elective cardioversion predisposes the patient to an increased risk for thromboembolism even with proper anticoagulation therapy. However, cardioversion of recent-onset AF does not increase the risk in anticoagulated patients, and should therefore be performed as soon as possible.

The efficacy of anticoagulation during cardioversion of acute AF has been confirmed by other studies. Garg and colleagues have reported that the risk of thromboembolic complications is almost five times higher in patients without therapeutic anticoagulation at the time of cardioversion (Garg et al. 2016). Data from a Swedish study suggests that electrical cardioversion without prior anticoagulation may not be safe for high-risk patients ($CHA_2DS_2VASc$ score $\geq 2$). The rate of thromboembolism was threefold in patients without anticoagulation compared to those with it (Själander et al. 2016). The importance of anticoagulation during cardioversion is also emphasized by a study that found that the incidence of thromboembolic complications was 4.0 per 100 patient-years in patients with anticoagulation and 10.3 per 100 patient-years in patients without anticoagulation (Hansen et al. 2015). However, contrary to Själander et al. and Garg et

al., where low-risk patients ($CHA_2DS_2VASc$ 0–1) did not suffer any thromboembolic complications, in our study, cardioversion was not without risk even in these patients. Especially if the cardioversion was performed after 12 hours of the episode, the risk varied from 0.4% to 0.9%. Keeping in mind that anticoagulation decreases the risk of thromboembolic complications at the expense of an increased risk of bleedings, the mean monthly rate of major hemorrhages has been reported to be less than 0.3% during long-term oral anticoagulation (Connolly et al. 2009, Patel et al. 2011, Granger et al. 2011). It is clear that this risk is even lower in low-risk patients reflecting concomitant low bleeding scores. Based on our findings, short-term anticoagulation should also be considered for patients with a low $CHA_2DS_2VASc$ score, especially if the delay to cardioversion is more than 12 hours. However, only patients with a $CHA_2DS_2VASc$ score of 2 or more derived statistical benefit from anticoagulation in the FinCV study.

The prediction value of the $CHA_2DS_2VASc$ score for thromboembolism in the FinCV study was as good as in the original validation study of this risk stratification schema. Moreover, the increase of thromboembolic risk with increasing $CHA_2DS_2VASc$ score was as steep as in predicting the long-term risk (Lip et al. 2010b). Conventional risk factors, such as age, the female sex, heart failure and diabetes, were independent predictors of embolic events, but hypertension and vascular disease (also included in the $CHA_2DS_2VASc$ score) were not significantly associated with the risk of thromboembolism after multivariable analysis. This might be due to the fact that these risk factors reflect more atherothrombotic etiology of stroke. In our study, the $CHA_2DS_2VASc$ score was superior to $CHADS_2$ in predicting the risk of thromboembolism, which was mostly driven by female sex.

The rate of bleeding events was surprisingly low in our study. During anticoagulation therapy, only one patient had major bleeding, which manifested as a gastrointestinal bleed. In a post hoc analysis of the ARISTOTLE Trial, one patient receiving warfarin and one patient receiving apixaban suffered major bleeding after cardioversion (Flaker et al. 2014). However, this analysis consisted of only 540 patients. There is no clear explanation for the very low incidence of bleeding events after cardioversion.

The low rate of thromboembolic complications after unsuccessful cardioversion in our study supports the view that conversion of AF is responsible for thromboembolic complications, at least in the short-term. There were only two thromboembolisms (stroke and TIA), which occurred after spontaneous conversion to sinus rhythm after failed cardioversion. The spontaneous conversion to sinus rhythm is not uncommon (Danias et al. 1998, Lindberg et al. 2012), and thus these patients should also be adequately anticoagulated (Weigner et al. 1997).

The $CHA_2DS_2VASc$ score was also a significant predictor of unsuccessful cardioversion, bradyarrhythmic complications and early recurrence of AF. Almost one-third of patients with a high risk of stroke suffered some of these adverse events. Keeping in mind that cardioversion carries an inherent risk for thromboembolic complications, multiple cardioversions will expose patients with high $CHA_2DS_2VASc$ score to an increased risk of stroke if anticoagulation is not adequate. This renders questionable clinical relevance of (repeated) cardioversions in patients with high $CHA_2DS_2VASc$ scores. Therefore, a high $CHA_2DS_2VASc$ score challenges the rationality of rhythm control therapy.

## 6.6 Limitations of the study

The FinCV study has all the inherent limitations of retrospective analysis, even though it is the largest study focusing on the cardioversion of acute AF. The retrospective approach does not allow characterization of the study cohort as accurately as in a well-executed prospective trial. The study is also dependent on recorded comorbidities, treatment and outcomes by treating physicians, who were also responsible for the follow-up. Due to the retrospective nature of the study, the number of minor events might be underestimated because they were not deemed clinically significant by a treating physician. This limitation should be kept in mind in paper I, where the incidence of asystole and bradycardia was assessed from the patient records. The recurrence rate of AF might also be underestimated because of the possibility of asymptomatic episodes of AF. Due to the retrospective nature of the study, there was no possibility to assess the incidence of asymptomatic or minimally symptomatic recurrences of AF that did not result in contact with health care professionals in study centers. An important limitation of the study was that AF onset was based on the onset of symptoms, and it is well-known that symptoms might not be reliable for the accurate marking of AF onset. This fact was especially pronounced in the nighttime. However, the duration of AF was under 48 hours in all cases included in the study according to patient records. In paper II, the multivariate model in the classification and regression tree analysis might be somewhat overfitted, although only a small number of variables were included in the models, and the results were cross-validated 25 times. In paper V, the majority of anticoagulated patients were on long-term oral anticoagulation, thus one should be cautious when assessing the benefit of anticoagulation initiated after admission to the emergency clinic based on the paper's findings. Further studies are needed to confirm whether anticoagulation initiated immediately before cardioversion reduces the risk of thromboembolism as hoped. All these limitations must be weighed against the fact that the retrospective study avoids selection bias and hence may give more realistic insight to real life. One must also keep in mind that at present, it would be unethical to perform cardioversion of acute AF without anticoagulation in the majority of patients.

## 6.7 Future perspectives

The prevalence of AF will most likely increase due to the aging of people in the near future. Undiagnosed AF is still uncommon, especially in the elderly (Davis et al. 2012). The ESC guidelines published in 2016 encourage opportunistic screening for silent AF in older populations (Kirchhof et al. 2016). Taking all this into account, the burden of AF on the modern healthcare system will increase. The demand for more cost-effective treatment strategies is evident. Adequately powered studies are also needed to study the usefulness of technological advantages allowing the patients to screen for AF, for example using smart phones.

AF tends to recur and these recurrences result in multiple visits to the emergency department. Multiple cardioversions pose increased risks of cardioversion-related stroke. Current antiarrhythmic drugs are of limited value in the prevention of AF recurrence. Catheter ablation is proven to be a more powerful tool in achieving rhythm control in certain populations. However, there is currently a gap in the evidence as to whether anticoagulation can be safely terminated after a successful ablation procedure. At this point, the ESC guidelines recommend the continuation of anticoagulation after the procedure (Kirchhof et al. 2016).

In the future, the number of AF patients using NOACs will increase and the use of a vitamin K antagonist will decrease. However, the use of NOACs has not been adequately studied in patients with severe chronic kidney disease (creatinine clearance < 30 mL/min). Studies are clearly needed to shed light on this specific AF group.

The use of the $CHA_2DS_2VASc$ score for stroke prediction in patients with AF is recommended by the majority of guidelines (Kirchhof et al. 2016, January et al. 2014). Paper V also proved the benefit of this risk stratification scheme in patients with recent-onset AF. However, the predictive value of the $CHA_2DS_2VASc$ for thromboembolism is quite modest (Lip et al. 2010b). Therefore, there is a demand for more accurate risk stratification schemes, and biomarker-based risk scores may prove useful in the future.

While paper V showed that anticoagulation reduced the risk of thromboembolism in patients undergoing cardioversion of acute AF, the majority of anticoagulated patients were on long-term oral anticoagulation. The second aspect is that NOACs were not in clinical use during the study period. Thus, prospective studies proving the efficacy of NOACs initiated after admission to the emergency department for cardioversion of recent-onset AF are needed.

# 7. CONCLUSIONS

1. Immediate arrhythmic complications are rare and consist of essentially benign bradyarrhythmias after electrical cardioversion of acute AF. These complications seem to reflect sinus node dysfunction and often result in later implantation of a permanent pacemaker. (I)

2. Electrical cardioversion of acute AF is an effective procedure. Simple clinical risk factors predict both success of cardioversion and early recurrence of AF. (IV)

3. In general, the risk of thromboembolic complications after cardioversion of acute AF is quite low, but it becomes unacceptably high in patients with conventional risk factors for stroke if no effective periprocedural anticoagulation is used. (II)

4. The embolic risk is also time-dependent in the cardioversion of acute AF. A delay in cardioversion of 12 hours or longer from symptom onset is associated with a significant increase in thromboembolic complications. (III)

5. Cardioversion of recent-onset AF does not increase the risk of thromboembolic complications in anticoagulated patients. The $CHA_2DS_2VASc$ score is a significant predictor of these complications in non-anticoagulated patients. (V)

# 8. ACKNOWLEDGMENTS

This work was done at Heart Center, University of Turku and Turku University Hospital; Doctoral Programme in Clinical Research, Finland, during 2012-2017.

I want to express my deepest gratitude to my supervisor, Professor Juhani Airaksinen. I truly admire your knowledge, enthusiasm and expertise in both academic work and clinical practice. Your encouragement, guidance and support have been of utmost important.

I wish to express my gratitude to my supervisor docent Ilpo Nuotio for all the help and guidance you have given to me during this project. Your knowledge about statistics has been of crucial importance for my thesis. I am honored to have worked with you.

I wish to thank research coordinator Tuija Vasankari. You have had always time to discuss and help me with both major and minor things. I admire your positivity and diligence. I am amazed by your talent in organizing research projects.

I owe my gratitude to all my co-authors for their valuable contribution and expertise in the original publications in this thesis. I warmly thank Professor Juha Hartikainen for invaluable contribution to this project. I deeply appreciate all your comments in all of the manuscripts. I express my gratitude to docent Antti Ylitalo for his important contribution in the completion of this study. I warmly thank Marko Nikkinen for excellent cooperation. I am sincerely grateful to Professor Fausto Biancari especially for his exceptional skills in statistics. In addition, Kristiina Lahtonen, Anna Karmi, Linus Törnqvist, Tuukka Airaksinen, Minna Ampio, Kiia Ruuhijärvi, Pauliina Autere, Elina Penttilä, Tiina. Rautiainen, Susanna Rissanen, Marja-Liisa Sutinen and Mari Tuhkalainen are acknowledged for their hard work during data collection. I wish to thank also Esa Aaltonen for creating template for data collection.

I am grateful to the official reviewers of this thesis, docent Harri Hyppölä and docent Johan Lassus, for their time and expertise in reviewing my work. Their comments and thorough review certainly helped me to improve the quality of my thesis.

I wish to thank my friends and colleagues at the Seinäjoki Central Hospital for their positive and supporting attitude.

I have been blessed with many incredible friends from childhood as well as from my time in Turku. I am very fortunate for all the moments I have spent with you in abroads, cottage weekends, golf course and ordinary days in life. I deeply appreciate the support and encouragement you all have given to me. I would like to thank Joel Nuotio for the

help you gave me in the last steps of my project when I needed help with practicalities and Suvi Sippola for the help with English language when I needed it.

I warmly thank my parents Hilkka and Jorma Grönberg for your never-ending support and encouragement. Without you two this all, would have not been possible. I also want to express my gratitude to my dear brother Henri. I admire your intelligence and your companionship has been irreplaceable for me.

Above all, I owe my deepest thanks to Sanni for your enormous understanding, support and love. I cannot appreciate enough all the effort and sacrifice you have made. Thank you for sharing your life with me and making all this possible.

This thesis work was financially supported by the Finnish Foundation for Cardiovascular Research, Research Funds from Specified Government Transfers from the Hospital District of Southwest Finland, the Finnish Cardiac Society, the Finnish Medical Foundation, and the Turku University Hospital Foundation.

Turku, November 2017 Toni Grönberg

# REFERENCES


Abe Y, Fukunami M, Yamada T, Ohmori M, Shimonagata T, Kumagai K, Kim J, Sanada S, Hori M and Hoki N. (1997) Prediction of transition to chronic atrial fibrillation in patients with paroxysmal atrial fibrillation by signal-averaged electrocardiography: a prospective study. *Circulation* 96(8):2612–6.

Agarwal M, Apostolakis S, Lane DA and Lip GYH. (2014) The impact of heart failure and left ventricular dysfunction in predicting stroke, thromboembolism, and mortality in atrial fibrillation patients: a systematic review. *Clinical Therapeutics* 36(9):1135–44.

Agbor-Etang BB and Setaro JF. (2015) Management of hypertension in patients with ischemic heart disease. *Current Cardiology Reports* 17(12):119.

Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R et al. (2004) Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *The New England Journal of Medicine* 351(23):2384–91.

Alp N, Rahman S, Bell J and Shahi M. (2000) Randomised comparison of antero-lateral versus antero-posterior paddle positions for DC cardioversion of persistent atrial fibrillation. *International Journal of Cardiology* 75(2–3):211–6.

Ammar AS, Elsherbiny I, El-Dosouky II, Abd El Salam K, Abd El Hamid M, Khalil W and Ammar M. (2015) Left atrial and left atrial appendage functional recovery after cardioversion in patients with recent atrial fibrillation: serial echocardiographic study. *Cardiology Journal* 22(6):699–707.

Anandasundaram B, Lane DA, Apostolakis S and Lip GY. (2013) The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. *Journal of Thrombosis and Haemostasis* 11(5):975–87.

Apostolakis S, Haeusler KG, Oeff M, Treszl A, Andresen D, Borggrefe M, Lip GY, Meinertz T, Parade U, Samol A et al. (2013) Low stroke risk after elective cardioversion of atrial fibrillation: an analysis of the Flec-SL trial. *International Journal of Cardiology* 168(4):3977–81.

Apostolakis S, Lane DA, Guo Y, Buller H and Lip GY. (2012) Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *Journal of the American College of Cardiology* 60(9):861–7.

Arnold AZ, Mick MJ, Mazurek RP, Loop FD and Trohman RG. (1992) Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. *Journal of the American College of Cardiology* 19(4):851–5.

Azoulay L, Dell'Aniello S, Simon TA, Renoux C and Suissa S. (2014) Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes. *European Heart Journal* 35(28):1881–7.

Beller GA, Smith TW, Abelmann WH, Haber E and Hood WB Jr. (1971) Digitalis intoxication. A prospective clinical study with serum level correlations. *The New England Journal of Medicine* 284(18):989–97.

Bellone A, Etteri M, Vettorello M, Bonetti C, Clerici D, Gini G, Maino C, Mariani M, Natalizi A, Nessi I et al. (2012) Cardioversion of acute atrial fibrillation in

the emergency department: a prospective randomised trial. *Emergency Medicine Journal* 29(3):188–91.

Bjerkelund CJ and Orning OM. (1969) The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. *The American Journal of Cardiology* 23(2):208–16.

Björck S, Palaszewski B, Friberg L and Bergfeldt L. (2013) Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke* 44(11):3103–8.

Blecher GE, Stiell IG, Rowe BH, Lang E, Brison RJ, Perry JJ, Clement CM, Borgundvaag B, Langhan T, Magee K et al. (2012) Use of rate control medication before cardioversion of recent-onset atrial fibrillation or flutter in the emergency department is associated with reduced success rates. *Canadian Journal of Emergency Medicine* 14(3):169–77.

Blich M and Edoute Y. (2006) Electrical cardioversion for persistent or chronic atrial fibrillation: outcome and clinical factors predicting short and long term success rate. *International Journal of Cardiology* 107(3):389–94.

Bollmann A, Husser D, Steinert R, Stridh M, Soernmo L, Olsson SB, Polywka D, Molling J, Geller C and Klein HU. (2003) Echocardiographic and electrocardiographic predictors for atrial fibrillation recurrence following cardioversion. *Journal of Cardiovascular Electrophysiology* 14(10 Suppl):S162–5.

Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, Blewett DR, Rosner B and Kistler JP. (1990) The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *The New England Journal of Medicine* 323(22):1505–11.

Botkin SB, Dhanekula LS and Olshansky B. (2003) Outpatient cardioversion of atrial arrhythmias: efficacy, safety, and costs. *American Heart Journal* 145(2):233–8.

Botto GL, Politi A, Bonini W, Broffoni T, Bonatti R. (1999) External cardioversion of atrial fibrillation: role of paddle position on technical efficacy and energy requirements. *Heart* 82(6):726–30.

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

Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ and Sledge I. (2009) Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation two systematic literature reviews and meta-analyses. *Circulation. Arrhythmia and Electrophysiology* 2:349–61.

Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B and Beatch G. (2011) A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *Journal of the American College of Cardiology* 57:313–321.

Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B et al. (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 12(10):1360–420.

Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P et al. (2014) Rivaroxaban vs. vitamin K

antagonists for cardioversion in atrial fibrillation. *European Heart Journal* 35(47):3346–55.

Cardiac Arrhythmia Suppression Trial (CAST) Investigators. (1989) Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *The New England Journal of Medicine* 321(6):406–12.

Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U and STAF Investigators. (2003) Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *Journal of the American College of Cardiology* 41(10):1690–6.

Chang SH, Chou IJ, Yeh YH, Chiou MJ, Wen MS, Kuo CT, See LC and Kuo CF. (2017) Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA* 318(13):1250–1259.

Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY et al. (2015) Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *Journal of the American College of Cardiology* 65(7):635–42.

Chatterjee S, Sardar P, Lichstein E, Mukherjee D and Aikat S. (2013) Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. *Pacing and Clinical Electrophysiology* 36(1):122–33.

Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ et al. (2014) Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 129(8):837–47.

Chyou JY, Hunter TD, Mollenkopf SA, Turakhia MP and Reynolds MR. (2015) Individual and combined risk factors for incident atrial fibrillation and incident stroke: an analysis of 3 million at-risk US patients. *Journal of the American Heart Association* 4(7).

Colilla S, Crow A, Petkun W, Singer DE, Simon T and Liu X. (2013) Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *The American Journal of Cardiology* 112(8):1142–7.

Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R et al. (2011) Apixaban in patients with atrial fibrillation. *The New England Journal of Medicine* 364(9):806–17.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine* 361(12):1139–51.

Connolly SJ, Joyner CD, Hart RG, Lip GY, O'Donnell M, Hohnloser SH, Hankey GJ, Shestakovska O, Yusuf S and AVERROES Steering Committee and Investigators. (2012) Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurology* 11(3):225–31.

Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S and ACTIVE W Investigators. (2008) Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in

therapeutic range. *Circulation* 118(20):2029–37.

Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS et al. (2012) Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *The New England Journal of Medicine* 367:1587–1595.

Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martín A, Ponikowski P, Rosenqvist M, Sanders P, Scanavacca M et al. (2014) Contemporary real life cardioversion of atrial fibrillation: results from the multinational RHYTHM-AF study. *International Journal of Cardiology* 172(3):588–94.

Cristoni L, Tampieri A, Mucci F, Iannone P, Venturi A, Cavazza M and Lenzi T. (2011) Cardioversion of acute atrial fibrillation in the short observation unit: comparison of a protocol focused on electrical cardioversion with simple antiarrhythmic treatment. *Emergency Medicine Journal* 28(11):932–7.

Crowther MA, Ginsberg JB, Kearon C, Harrison L, Johnson J, Massicotte MP and Hirsh J. (1999) A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Archives of Internal Medicine* 159(1):46–8.

Danias PG, Caulfield TA, Weigner MJ, Silverman DI and Manning WJ. (1998) Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *Journal of the American College of Cardiology* 31(3):588–2.

Dankner R, Shahar A, Novikov I, Agmon U, Ziv A and Hod H. (2009) Treatment of stable atrial fibrillation in the emergency department: a population-based comparison of electrical direct-current versus pharmacological cardioversion or conservative management. *Cardiology* 112(4):270–8.

Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, Harvey M, Strickberger SA, Man KC and Morady F. (1996) Effect of an irregular ventricular rhythm on cardiac output. *The American Journal of Cardiology* 78(12):1433–6.

Davis RC, Hobbs FD, Kenkre JE, Roalfe AK, Iles R, Lip GY and Davies MK. (2012) Prevalence of atrial fibrillation in the general population and in high-risk groups: the ECHOES study. *Europace* 14(11):1553–9.

De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD et al. (2012) New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *Journal of the American College of Cardiology* 59(16):1413–25.

DeLong ER, DeLong DM and Clarke-Pearson DL. (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44(3):837–45.

Donzé J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J and Aujesky D. (2012) Risk of falls and major bleeds in patients on oral anticoagulation therapy. *The American Journal of Medicine* 125(8):773–8.

Dittrich HC1, Erickson JS, Schneiderman T, Blacky AR, Savides T and Nicod PH. (1989) Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. *The American Journal of Cardiology* 63(3):193–7.

Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA and Stevenson LW.

(1998) Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. *Journal of the American College of Cardiology* 32(3):695–703.

Dulli DA, Stanko H and Levine RL. (2003) Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology* 22(2):118–23.

EAFT (European Atrial Fibrillation Trial) Study Group. (1993) Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 342(8882):1255–62.

Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K et al. (2013) Dabigatran versus warfarin in patients with mechanical heart valves. *The New England Journal of Medicine* 369(13):1206–14.

Elkayam U. (1998) Calcium channel blockers in heart failure. *Cardiology* 89 Suppl 1:38–46.

Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ et al. (1992) Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *The New England Journal of Medicine* 327(20):1406–12.

Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N and Singer DE. (2011) A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *Journal of the American College of Cardiology* 58(4):395–401.

Falcone RA, Morady F and Armstrong WF. (1996) Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. *The American Journal of Cardiology* 78(4):435–9.

Ferrer MI. (1968) The sick sinus syndrome in atrial disease. *JAMA* 206(3):645–6.

Fetsch T, Bauer P, Engberding R, Koch HP, Lukl J, Meinertz T, Oeff M, Seipel L, Trappe HJ, Treese N et al. (2004) Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *European Heart Journal* 25(16):1385–94.

Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, Zhu J, Mohan P, Garcia D, Bartunek J et al. (2014) Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *Journal of the American College of Cardiology* 63(11):1082–7.

Friberg L, Benson L, Rosenqvist M and Lip GY. (2012a) Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *British Medical Journal* 344:e3522.

Friberg L, Rosenqvist M, Lindgren A, Terént A, Norrving B and Asplund K. (2014) High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke* 45(9):2599–605.

Friberg L, Rosenqvist M and Lip GY. (2012b) Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal* 33(12):1500–10.

Friberg L, Rosenqvist M and Lip GY. (2012c) Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 125(19):2298–307.

Frick M, Frykman V, Jensen-Urstad M, Ostergren J and Rosenqvist M. (2001) Factors predicting success rate and recurrence of atrial fibrillation after first electrical cardioversion in patients with persistent atrial fibrillation. *Clinical Cardiology* 24(3):238–44.

Fumagalli S, Boncinelli L, Bondi E, Caleri V, Gatto S, Di Bari M, Baldereschi G, Valoti P, Masotti G and Marchionni N. (2002) Does advanced age affect the immediate and long-term results of direct-current external cardioversion of atrial fibrillation? *Journal of the American Geriatrics Society* 50(7):1192–7.

Furniss SS and Sneyd JR. (2015) Safe sedation in modern cardiological practice. *Heart* 101(19):1526–30.

Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE et al. (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 8(9):651–745.

Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW and Radford MJ. (2006) Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *American Heart Journal* 151(3):713–9.

Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW and Radford MJ. (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 285(22):2864–70.

Gallagher MM, Hennessy BJ, Edvardsson N, Hart CM, Shannon MS, Obel OA, Al-Saady NM and Camm AJ. (2002) Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. *Journal of the American College of Cardiology* 40 (5):926–33.

Gallagher MM, Yap YG, Padula M, Ward DE, Rowland E and Camm AJ. (2008) Arrhythmic complications of electrical cardioversion: relationship to shock energy. *International Journal of Cardiology* 123(3):307–12.

Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P and McGavigan AD. (2016) The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *European Heart Journal* 37(20):1591–602.

García-Fernández A, Marín F, Roldán V, Galcerá-Jornet E, Martínez-Martínez JG, Valdés M, Sogorb F and Lip GY. (2016) The HAS-BLED score predicts long-term major bleeding and death in anticoagulated non-valvular atrial fibrillation patients undergoing electrical cardioversion. *International Journal of Cardiology* 217:42–8.

Garg A, Khunger M, Seican S, Chung MK and Tchou PJ. (2016) Incidence of thromboembolic complications within 30 days of electrical cardioversion performed within 48 hours of atrial fibrillation onset.

*JACC Clinical Electrophysiology* 2(4): 487–94.

Gheorghiade M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K, Aban IB, Aronow WS, Anker SD et al. (2013) Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *European Heart Journal* 34(20):1489–97.

Gitt AK, Smolka W, Michailov G, Bernhardt A, Pittrow D and Lewalter T. (2013) Types and outcomes of cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF Study. *Clinical Research in Cardiology* 102:713–23.

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J et al. (2013) Edoxaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine* 369(22):2093–104.

Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R et al. (2014) Atrial fibrillation in patients with cryptogenic stroke. *The New England Journal of Medicine* 370(26):2467–77.

Glover BM, Walsh SJ, McCann CJ, Moore MJ, Manoharan G, Dalzell GW, McAllister A, McClements B, McEneaney DJ, Trouton TG et al. (2008) Biphasic energy selection for transthoracic cardioversion of atrial fibrillation. The BEST AF Trial. *Heart* 94(7):884–7.

Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV and Singer DE. (2001) Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 285(18):2370–5.

Goldman MJ. (1960) The management of chronic atrial fibrillation: indications for and method of conversion to sinus rhythm. *Progress in Cardiovascular Diseases* 2:465–479.

Goldstein RE, Boccuzzi SJ, Cruess D and Nattel S. (1991) Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 83(1):52–60.

Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D and Olshansky B. (2015) Arrhythmia-induced cardiomyopathies: mechanisms, recognition, and management. *Journal of the American College of Cardiology* 66(15):1714–28.

Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M et al. (2015) Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 131(2):157–64.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine* 365(11):981–92.

Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE and Klein AL. (1993) Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. *Journal of the American College of Cardiology* 22(5):1359–66.

Grimm RA, Leung DY, Black IW, Stewart WJ, Thomas JD and Klein AL. (1995) Left atrial appendage "stunning" after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. *American Heart Journal* 130(1):174–6.

Hakalahti A, Biancari F, Nielsen JC and Raatikainen MJ. (2015) Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace* 17:370–8.

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

Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, Hansen J, Køber L, Husted S and Torp-Pedersen C. (2015) Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace* 17(1):18–23.

Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K and Hirsh J. (1997) Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Annals of Internal Medicine* 126(2):133–6.

Hart RG, Pearce LA and Aguilar MI. (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine* 146(12):857–67.

Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C et al. (2012) Subclinical atrial fibrillation and the risk of stroke. *The New England Journal of Medicine* 366(2):120–9.

Heijman J, Voigt N, Nattel S and Dobrev D. (2014) Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. *Circulation Research* 114(9):1483–99.

Herman D, Locatelli I, Grabnar I, Peternel P, Stegnar M, Mrhar A, Breskvar K and Dolzan V. (2005) Influence of CYP2C9 polymorphisms, demographic factors and concomitant drug therapy on warfarin metabolism and maintenance dose. *The Pharmacogenomics Journal* 5(3):193–202.

Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA et al. (2016a) The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *European Heart Journal* 37(20):1582–90.

Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD et al. (2016b) The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 387(10035):2302–11.

Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D and Brandt JT. (1998) Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 114(5 Suppl):445S–469S.

Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vítovec J, Aldershvile J et al. (2000) Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 283(10):1295–302.

Hughes M, Lip GY and Guideline Development Group, National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care, National Institute for Health and Clinical Excellence. (2008) Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thrombosis and Haemostasis* 99:295–304.

Hylek EM and Singer DE. (1994) Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Annals of Internal Medicine* 120(11):897–902.

Hylek EM, Skates SJ, Sheehan MA and Singer DE. (1996) An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *The New England Journal of Medicine* 335(8):540–6.

Jaakkola J, Mustonen P, Kiviniemi T, Hartikainen JE, Palomäki A, Hartikainen P, Nuotio I, Ylitalo A and Airaksinen KE. (2016) Stroke as the first manifestation of atrial fibrillation. *PLoS One* 11(12):e0168010.

Jaakkola S, Lip GY, Biancari F, Nuotio I, Hartikainen JE, Ylitalo A and Airaksinen KE. (2017) Predicting unsuccessful electrical cardioversion for acute atrial fibrillation (from the AF-CVS Score). *The American Journal of Cardiology* 119(5):749–52.

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME et al. (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology* 64(21):e1–76.

Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA and Roger VL. (2011) Atrial fibrillation and death after myocardial infarction: a community study. *Circulation* 123(19):2094–100.

Jaber WA, Prior DL, Thamilarasan M, Grimm RA, Thomas JD, Klein AL and Asher CR. (2000) Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: a transesophageal echocardiographic study. *American Heart Journal* 140(1):150–6.

Kannel WB, Wolf PA, Benjamin EJ and Levy D. (1998) Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *The American Journal of Cardiology* 82(8A):2N–9N.

Kerr AJ, Williams MJ and Stewart RA. (2001) Ventricular rate and beat-to-beat variation of stroke volume in atrial fibrillation. *The American Journal of Cardiology* 87(9):1116–9, A9.

Khan IA. (2003) Atrial stunning: basics and clinical considerations. *International Journal of Cardiology* 92(2–3):113–28.

Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I and Cleland JG. (2003) Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *Journal of the American College of Cardiology* 42(11):1944–51.

Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A, Steinbeck G, Treszl A et al. (2012) Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet* 380(9838):238–46.

Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener

HC, Heidbuchel H, Hendriks J et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal* 37(38):2893–962.

Kirchhof P, Eckardt L, Loh P, Weber K, Fischer RJ, Seidl KH, Böcker D, Breithardt G, Haverkamp W and Borggrefe M. (2002) Anterior-posterior versus anterior-lateral electrode positions for external cardioversion of atrial fibrillation: a randomised trial. *Lancet* 360:1275–9.

Kleemann T, Becker T, Strauss M, Schneider S and Seidl K. (2009) Prevalence of left atrial thrombus and dense spontaneous echo contrast in patients with short-term atrial brillation < 48 hours undergoing cardioversion: value of transesophageal echocardiography to guide cardioversion. *Journal of the American Society of Echocardiography* 22:1403–8.

Koike H, Fujino T, Koike M, Shinohara M, Kitahara K, Kinoshita T, Yuzawa H, Suzuki T, Sato H, Fukunaga S et al. (2016) Obesity is associated with the development of interstitial pneumonia under long-term administration of amiodarone in refractory atrial fibrillation patients. *International Heart Journal* 57(1):30–4.

Kuppahally SS, Foster E, Shoor S and Steimle AE. (2009) Short-term and long-term success of electrical cardioversion in atrial fibrillation in managed care system. *International Archives of Medicine* 2:39.

Lafuente-Lafuente C, Mouly S, Longás-Tejero MA, Mahé I and Bergmann JF. (2006) Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Archives of Internal Medicine* 166(7):719–28.

Larsen TB, Lip GY, Skjøth F, Due KM, Overvad K and Hvilsted Rasmussen L. (2012) Added predictive ability of the CHA2DS2VASc risk score for stroke and death in patients with atrial fibrillation: the prospective Danish Diet, Cancer, and Health cohort study. *Circulation. Cardiovascular Quality and Outcomes* 5(3):335–42.

Lee AY, Kutyifa V, Ruwald MH, McNitt S, Polonsky B, Zareba W, Moss AJ and Ruwald AC. (2015) Digoxin therapy and associated clinical outcomes in the MADIT-CRT trial. *Heart Rhythm* 12(9):2010–7. 5(3):335–42.

Lehto M, Niiranen J, Korhonen P, Mehtälä J, Khanfir H, Hoti F, Lassila R and Raatikainen P. (2017) Quality of warfarin therapy and risk of stroke, bleeding, and mortality among patients with atrial fibrillation: results from the nationwide FinWAF Registry. *Pharmacoepidemiology and Drug Safety* 26(6):657–665.

Leistad E, Christensen G and Ilebekk A. (1993) Atrial contractile performance after cessation of atrial fibrillation. *American Journal of Physiology* 264(1 Pt 2):H104–9.

Lim HS, Willoughby SR, Schultz C, Gan C, Alasady M, Lau DH, Leong DP, Brooks AG, Young GD, Kistler PM et al. (2013) Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *Journal of the American College of Cardiology* 61(8):852–60.

Lindberg S, Hansen S and Nielsen T. Spontaneous conversion of first onset atrial fibrillation. *Internal Medicine Journal* 42(11):1195–9.

Linderer T, Chatterjee K, Parmley WW, Sievers RE, Glantz SA and Tyberg JV. (1983) Influence of atrial systole on the Frank-Starling relation and the end-diastolic pressure-diameter relation of the left ventricle. *Circulation* 67(5):1045–53.

Lip GY, Frison L, Halperin JL and Lane DA. (2010a) Identifying patients at high risk for stroke despite anticoagulation: a

comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 41(12):2731–8.

Lip GY, Nieuwlaat R, Pisters R, Lane DA and Crijns HJ. (2010b) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 137(2):263–72.

Louie EK, Liu D, Reynertson SI, Loeb HS, McKiernan TL, Scanlon PJ and Hariman RJ. (1998) "Stunning" of the left atrium after spontaneous conversion of atrial fibrillation to sinus rhythm: demonstration by transesophageal Doppler techniques in a canine model. *Journal of the American College of Cardiology* 32(7):2081–6.

Lown B, Perloth MG, Kaidbey S and Abe T and Harken DW. (1963) "Cardioversion" of atrial fibrillation: a report on the treatment of 65 episodes in 50 patients. *The New England Journal of Medicine* 269:325–331

Lu Z, Scherlag BJ, Lin J, Niu G, Fung KM, Zhao L, Ghias M, Jackman WM, Lazzara R, Jiang H et al. (2008) Atrial fibrillation begets atrial fibrillation: autonomic mechanism for atrial electrical remodeling induced by short-term rapid atrial pacing. *Circulation. Arrhythmia and Electrophysiology* 1(3):184–92.

Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, Munson JT and Douglas PS. (1994) Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. *Journal of the American College of Cardiology* 23(7):1535–40.

Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E and BAFTA investigators; Midland Research Practices Network (MidReC). (2007) Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 370(9586):493–503.

Marchese P, Bursi F, Delle Donne G, Malavasi V, Casali E, Barbieri A, Melandri F and Modena MG. (2011) Indexed left atrial volume predicts the recurrence of non-valvular atrial fibrillation after successful cardioversion. *European Journal of Echocardiography* 12(3):214–21.

Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R and Carolei A. (2005) Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 36(6):1115–9.

Mathew TP, Moore A, McIntyre M, Harbinson MT, Campbell NP, Adgey AA and Dalzell GW. (1999) Randomised comparison of electrode positions for cardioversion of atrial fibrillation. *Heart* 81(6):576–9.

Mattioli AV, Tarabini Castellani E, Vivoli D, Molinari R and Mattioli G. (1996) Restoration of atrial function after atrial fibrillation of different etiological origins. *Cardiology* 87(3):205–11.

McManus DD, Corteville DC, Shlipak MG, Whooley MA and Ix JH. (2009) Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). *The American Journal of Cardiology* 104(11):1551–5.

Michael JA, StiellI G, Agarwal S and Mandavia DP. (1999) Cardioversion of paroxysmal atrial fibrillation in the emergency department. *Annals of Emergency Medicine* 33 (4):379–87.

Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C and Olesen JB. (2012) Female sex as a risk factor for stroke in atrial fibrillation: a nationwide

cohort study. *Journal of Thrombosis and Haemostasis* 10(9):1745–51.

Mittal S, Ayati S, Stein KM, Schwartzman D, Cavlovich D, Tchou PJ, Markowitz SM, Slotwiner DJ, Scheiner MA and Lerman BB. (2000) Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. *Circulation* 101(11):1282–7.

Morani G, Cicoira M, Pozzani L, Angheben C, Zanotto G and Vassanelli C. (2009) Outpatient electrical cardioversion of atrial fibrillation: 8 years' experience. Analysis of shock-related arrhythmias. *Pacing and Clinical Electrophysiology*. 32(9):1152–8.

Moreyra E, Finkelhor RS and Cebul RD. (1995) Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. *American Heart Journal* 129(1):71–5.

Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A et al. (2011) Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 123(2):131–6.

O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P et al. (2015) The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *European Heart Journal* 36(46):3258–64.

Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P, Sigamani A, Morillo CA et al. (2014) 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* 129(15):1568–76.

Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH et al. (2011) Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. *Thrombosis and Haemostasis* 106(4):739–49.

Olesen JB, Fauchier L, Lane DA, Taillandier S and Lip GY. (2012a) Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 141(1):147–53.

Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH and Torp-Pedersen C. (2012b) Stroke and bleeding in atrial fibrillation with chronic kidney disease. *The New England Journal of Medicine* 367(7):625–35.

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

Olshansky B, Heller EN, Mitchell LB, Chandler M, Slater W, Green M, Brodsky M, Barrell P and Greene HL. (2005) Are transthoracic echocardiographic parameters associated with atrial fibrillation recurrence or stroke? Results from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *Journal of the American College of Cardiology* 45(12):2026–33.

Oltrona L, Broccolino M, Merlini PA, Spinola A, Pezzano A and Mannucci PM. (1997) Activation of the hemostatic mechanism after pharmacological cardioversion of acute nonvalvular atrial fibrillation. *Circulation* 95(8):2003–6.

Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk P and Investigators of the Polish How to Treat Chronic Atrial Fibrillation Study. (2004) Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest* 126(2):476–86.

Oral H, Ozaydin M, Sticherling C, Tada H, Scharf C, Chugh A, Lai SW, Pelosi F Jr, Knight BP, Strickberger SA et al. (2003) Effect of atrial fibrillation duration on probability of immediate recurrence after transthoracic cardioversion. *Journal of Cardiovascular Electrophysiology* 14(2):182–5.

O'Reilly RA and Rytand DA. (1980) "Resistance" to warfarin due to unrecognized vitamin K supplementation. *The New England Journal of Medicine* 303(3):160–1.

Orlando JR, van Herick R, Aronow WS and Olson HG. (1979) Hemodynamics and echocardiograms before and after cardioversion of atrial fibrillation to normal sinus rhythm. *Chest* 76(5):521–6.

Osmanagic A, Möller S, Osmanagic A, Sheta HM, Vinther KH and Egstrup K. (2015) Effect of early direct current cardioversion on the recurrence of atrial fibrillation in patients with persistent atrial fibrillation. *The American Journal of Cardiology* 116(2):225–9.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England Journal of Medicine* 365(10):883–91.

Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB et al. (2001) Effect of carvedilol on survival in severe chronic heart failure. *The New England Journal of Medicine* 344(22):1651–8.

Petersen P, Boysen G, Godtfredsen J, Andersen ED and Andersen B. (1989) Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1(8631):175–9.

Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf R and Kong DF. (2009a) Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *Journal of the American College of Cardiology* 54(12):1089–95.

Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K and Al-Khatib SM. (2009b) Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circulation. Arrhythmia and Electrophysiology* 2:626–33.

Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G et al. (2013a) Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 127(2):224–32.

Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, et al. (2013b) Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the

ROCKET AF trial. *Journal of the American College of Cardiology* 61(19):1998–2006.

Piña PG and Chicos AB. (2017) Early cardioversion in atrial fibrillation: earlier is better, but not always and (maybe) not immediately. *Current Atherosclerosis Reports* 19(1):3.

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ and Lip GY. (2010) A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 138(5):1093–100.

Pisters R, Lane DA, Marin F, Camm AJ and Lip GYH. (2012a) Stroke and thromboembolism in atrial fibrillation. *Circulation Journal* 76:2289–304.

Pisters R, Nieuwlaat R, Prins MH, Le Heuzey JY, Maggioni AP, Camm AJ, Crijns HJ and Euro Heart Survey Investigators. (2012b) Clinical correlates of immediate success and outcome at 1-year follow-up of real-world cardioversion of atrial fibrillation: the Euro Heart Survey. *Europace* 14(5):666–74.

Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW et al. (2015) Idarucizumab for dabigatran reversal. *The New England Journal of Medicine* 373(6):511–20.

Procter NE, Stewart S and Horowitz JD. (2016) New-onset atrial fibrillation and thromboembolic risk: Cardiovascular syzygy? *Heart Rhythm* 13(6):1355–61.

Prystowsky EN, Padanilam BJ and Fogel RI. (2015) Treatment of atrial fibrillation. *JAMA*. 314(3):278–88.

Qin D, Leef G, Alam MB, Rattan R, Munir MB, Patel D, Khattak F, Adelstein E, Jain SK and Saba S. (2016) Comparative effectiveness of antiarrhythmic drugs for rhythm control of atrial fibrillation. *Journal of Cardiology* 67(5):471–6.

Queiroga A, Marshall HJ, Clune M and Gammage MD. (2013) Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. *Heart* 89(9):1035–8.

Raitt MH, Volgman AS, Zoble RG, Charbonneau L, Padder FA, O'Hara GE, Kerr D and AFFIRM Investigators. (2006) Prediction of the recurrence of atrial fibrillation after cardioversion in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *American Heart Journal* 151(2):390–6.

Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson T and Terrin ML. (1988) Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *Journal of the American College of Cardiology* 11(1):1–11.

Reisinger J, Gatterer E, Lang W, Vanicek T, Eisserer G, Bachleitner T, Niemeth C, Aicher F, Grander W, Heinze G et al. (2004) Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *European Heart Journal* 25(15):1318–24.

Renda G, Ricci F and De Caterina R. (2017) Non-vitamin K antagonist oral anticoagulants for cardioversion in atrial fibrillation: an updated meta-analysis. *The American Journal of Medicine* 130(4):457–461.

Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M et al. (2000) Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation

Investigators. *The New England Journal of Medicine* 342(13):913–20.

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

Sakamoto H, Okamoto E, Imataka K, Ieki K and Fujii J. (1995) Prediction of early development of chronic nonrheumatic atrial fibrillation. *Japanese Heart Journal* 36(2):191–9.

Scaglione M, Gallo C, Battaglia A, Sardi D, Gaido L, Anselmino M, Garberoglio L, Giustetto C, Castagno D, Ferraris F et al. (2014) Long-term progression from paroxysmal to permanent atrial fibrillation following transcatheter ablation in a large single-center experience. *Heart Rhythm* 11(5):777–82.

Schwartzman D, Musley S, Koehler J and Warman E. (2005) Impact of atrial fibrillation duration on postcardioversion recurrence. *Heart Rhythm* 2(12):1324–9.

Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP and Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *Journal of the American College of Cardiology* 29(4):709–15.

Shapiro EP, Effron MB, Lima S, Ouyang P, Siu CO and Bush D. (1988) Transient atrial dysfunction after conversion of chronic atrial fibrillation to sinus rhythm. *The American Journal of Cardiology* 62(17):1202–7.

Shapiro W and Klein G. (1968) Alterations in cardiac function immediately following electrical conversion of atrial fibrillation to normal sinus rhythm. *Circulation* 38(6):1074–84.

Siaplaouras S, Buob A, Heisel A, Böhm M and Jung J. (2005) Outpatient electrical cardioversion of atrial fibrillation: efficacy, safety and patients' quality of life. *International Journal of Cardiology* 105(1):26–30.

Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GYH and Manning WJ. (2008a) Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 133(6 Suppl):546S–592S.

Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K and Go AS. (2008b) A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *Chest* 133(6 Suppl):546S–592S.

Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C and Lazzeri D. (1995) Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *The New England Journal of Medicine* 333(2):77–82.

Singh SN, Tang XC, Reda D and Singh BN. (2009) Systematic electrocardioversion for atrial fibrillation and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. *Heart Rhythm* 6(2):152–5.

Själander S, Svensson PJ and Friberg L. (2016) Atrial fibrillation patients with CHA2DS2-VASc >1 benefit from oral anticoagulation prior to cardioversion. *International Journal of Cardiology* 215:360–3.

Sohara H, Amitani S, Kurose M and Miyahara K. (1997) Atrial fibrillation

activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. *Journal of the American College of Cardiology* 29 (1):106–12.

Soyka LF, Wirtz C and Spangenberg RB. (1990) Clinical safety profile of sotalol in patients with arrhythmias. *The American Journal of Cardiology* 65(2):74A–81A; discussion 82A–83A.

Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK and VanderLugt JT. (1996) Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study Investigators. *Circulation* 94(7):1613–21.

Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mügge A, Sehnert W, Schmidt-Lucke C et al. (2004) Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation* 109(8):997–1003.

Stiell IG, Clement CM, Perry JJ, Vaillancourt C, Symington C, Dickinson G, Birnie D and Green MS. (2010) Association of the Ottawa Aggressive Protocol with rapid discharge of emergency department patients with recent-onset atrial fibrillation or flutter. *Canadian Journal of Emergency Medicine* 12 (3):181–91.

Stoddard MF, Dawkins PR, Prince CR and Ammash NM. (1995) Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *Journal of the American College of Cardiology* 25:452–459.

Stroke Prevention in Atrial Fibrillation Investigators. (1991) Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 84(2):527–39.

Stroke Risk in Atrial Fibrillation Working Group. (2007) Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 69:546–554.

Thrall G, Lane D, Carroll D and Lip GY. (2006) Quality of life in patients with atrial fibrillation: a systematic review. *The American Journal of Medicine* 119(5):448.e1–19.

Toso E, Blandino A, Sardi D, Battaglia A, Garberoglio L, Miceli S, Azzaro G, Capello AL and Gaita F. (2012) Electrical cardioversion of persistent atrial fibrillation: acute and long-term results stratified according to arrhythmia duration. *Pacing and Clinical Electrophysiology* 35(9):1126–34.

Turakhia MP, Santangeli P, Winkelmayer WC, Xu X, Ullal AJ, Than CT, Schmitt S, Holmes TH, Frayne SM, Phibbs CS et al. (2014) Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *Journal of the American College of Cardiology* 64(7):660–8.

Van Gelder IC, Crijns HJ, Van Gilst WH, Verwer R and Lie KI. (1991) Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. *The American Journal of Cardiology* 68(1):41–6.

Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH et al. (2010) Lenient versus strict rate control in patients with atrial fibrillation. *The New England Journal of Medicine* 362(15):1363–73.

Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG et al. (2002) A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *The New England Journal of Medicine* 347(23):1834–40.

Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, Crijns HJ and RACE and AFFIRM Investigators. (2006) Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 8(11):935–42.

Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, McMurtry MS, Connolly S, Cox JL et al. (2014) 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Canadian Journal of Cardiology* 30(10):1114–30.

Wagstaff AJ, Overvad TF, Lip GY and Lane DA. (2014) Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *QJM* 107(12):955–67.

Walters TE, Nisbet A, Morris GM, Tan G, Mearns M, Teo E, Lewis N, Ng A, Gould P, Lee G et al. (2016) Progression of atrial remodeling in patients with high-burden atrial fibrillation: implications for early ablative intervention. *Heart Rhythm* 13(2):331–9.

Wasmund SL, Li JM, Page RL, Joglar JA, Kowal RC, Smith ML and Hamdan MH. (2003) Effect of atrial fibrillation and an irregular ventricular response on sympathetic nerve activity in human subjects. *Circulation* 107(15):2011–5.

Weigner MJ, Caulfield TA, Danias PG, Silverman DI and Manning WJ. (1997) Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Annals of Internal Medicine* 126(8):615–20.

Wijffels MC, Kirchhof CJ, Dorland R and Allessie MA. (1995) Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 92(7):1954–68.

Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B et al. (2010) Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 303(4):333–40.

Wolf PA, Dawber TR, Thomas HE Jr and Kannel WB. (1978) Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 28(10):973–7.

Wolf PA, Abbott RD and Kannel WB. (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 22:983–8.

Wolkove N and Baltzan M. (2009) Amiodarone pulmonary toxicity. *Canadian Respiratory Journal* 16(2):43–8.

Wood MA, Brown-Mahoney C, Kay GN and Ellenbogen KA. (2000) Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation* 101(10):1138–44.

Wyse DG. (2008) Therapeutic considerations in applying rate control therapy for atrial fibrillation. *Journal of Cardiovascular Pharmacology* 52(1):11–7.

Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE et al. (2002) A comparison of rate control and rhythm control in patients

with atrial fibrillation. *The New England Journal of Medicine* 347(23):1825–33.

Wysokinski WE, Ammash N, Sobande F, Kalsi H, Hodge D and McBane RD. (2010) Predicting left atrial thrombi in atrial fibrillation. *American Heart Journal* 159(4):665–71.

Xavier Scheuermeyer F, Grafstein E, Stenstrom R, Innes G, Poureslami I and Sighary M. (2010) Thirty-day outcomes of emergency department patients undergoing electrical cardioversion for atrial fibrillation or flutter. *Academic Emergency Medicine* 17(4):408–15, 120(3 Suppl 1):S3–S11.

Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J and Kotecha D. (2015) Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *British Medical Journal* 351:h4451.

Zivelin A, Rao LV and Rapaport SI. (1993) Mechanism of the anticoagulant effect of warfarin as evaluated in rabbits by selective depression of individual procoagulant vitamin K-dependent clotting factors. *The Journal of Clinical Investigation* 92(5):2131–40.

*Annales Universitatis Turkuensis*

Turun yliopisto
University of Turku

Painosalama Oy, Turku, Finland 2017

ISBN 978-951-29-7064-3 (PRINT)
ISBN 978-951-29-7065-0 (PDF)
ISSN 0355-9483 (Print) | ISSN 2343-3213 (Online)