UNIVERSITY OF TURKU

SAFETY AND EFFICACY OF ELECTIVE CARDIOVERSION IN ATRIAL FIBRILLATION

the FinCV Studies

Tapio Hellman

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To my family

ABSTRACT

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SAFETY AND EFFICACY OF ELECTIVE CARDIOVERSION IN ATRIAL FIBRILLATION – THE FINCV STUDIES

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Background: Major gaps exist in the evidence for predicting optimal patient outcomes of cardioversion (CV) in atrial fibrillation (AF). The aim of this dissertation was to assess the safety and efficacy of elective CV in AF.

Methods: The Finnish Cardioversion study programme (FinCV) investigates the occurrence of stroke and procedural efficacy in AF patients undergoing CV. Studies included patients undergoing acute CV (FinCV), elective CV in vitamin K antagonist treated patients (FinCV2) and non-vitamin K antagonist treated patients (Fin-CV3). The patients' data were retrospectively collected during the 2003–2016 timeframe from nine Finnish hospitals. Altogether, the FinCV studies comprised 5441 patients and 10852 CVs, of which the FinCV2 study encompassed 1342 patients with 1998 elective CVs.

Results: Elective CV was unsuccessful or AF recurred within the 30-day follow-up after an initially successful CV in 42.6% (FinCV2). Altogether, 6 (0.4%) cerebral thromboembolisms were detected within follow-up and patients with low (2.0–2.4) therapeutic internationalized normalized ratios (INRs) at the time of elective CV had a higher risk for thromboembolic events than patients with high (≥2.5) therapeutic INRs (0.9% vs. 0.1%, p=0.03) (FinCV2). In the combined registry of the FinCV studies the primary composite end-point was designated as an occurrence of death, thromboembolism, unsuccessful CV, recurrence of AF or acute arrhythmic complication within follow-up. The composite adverse outcome was observed after 1669 (38.4%) CVs and patients with AF episodes lasting 24–48 hours had the lowest risk of adverse outcomes.

Conclusions: The intensity of anticoagulation in elective CV of AF is associated with the risk of postprocedural thromboembolisms. Nevertheless, CV in AF has relatively few safety issues, although more room exists for improvement in efficacy outcomes of CV in contemporary medicine

Keywords: Atrial fibrillation, cardioversion, thromboembolism, success rate, recurrence

TIIVISTELMÄ

LL Tapio Hellman

ETEISVÄRINÄN ELEKTIIVISEN KARDIOVERSION TURVALLISUUS JA TEHOKKUUS – FINCV-TUTKIMUKSET

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja kardiovaskulaarilääketiede, Turun kliininen tohtoriohjelma; Sydänkeskus, Turun Yliopistollinen Keskussairaala, Turku, Suomi.

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Tausta: Vaikka rytminsiirto on keskeisin toimenpide eteisvärinän palauttamisessa sinusrytmiin, tehokkaan rytminsiirron ennustetekijöistä on vain vähän tietoa. Tämä väitöskirja selvittää eteisvärinän elektiivisen kardioversion turvallisuuden ja tehokkuuden ennustetekijöitä.

Menetelmät: FinCV-tutkimukset ovat osa retrospektiivistä rekisteritutkimusohjelmaa, jossa selvitetään eteisvärinän kardioversioon liittyvää aivoinfarkti- ja verenvuotoriskiä. Potilasaineisto kerättiin vuosien 2003 – 2016 aikana yhdeksästä suomalaisestsa sairaalasta. Tutkimukset sisältävät yhteensä 5441 potilasta ja 10852 kardioversiota, joista FinCV2-tutkimukseen kuuluu 1342 potilasta ja 1998 elektiivistä kardioversiota.

Tulokset: FinCV-tutkimuksien yhdistelmäaineistossa ensisijainen yhdistelmäpäätetapahtuma, johon sisältyi rytminsiirron epäonnistuminen, eteisvärinän uusiutuminen tai akuutti rytmihäiriökomplikaatio, verenkiertohäiriön ilmaantuminen tai kuolema 30 päivän seuranta-ajan sisällä, ilmeni 1669 (38.4 %) rytminsiirrossa. Potilailla, joiden eteisvärinäkohtauksen kesto oli 24 – 48 tuntia, oli kaikkein vähiten haittatapahtumia. Toisaalta elektiivinen rytminsiirto epäonnistui tai eteisvärinä uusiutui 30 päivän seuranta-ajan kuluessa 42.6 % toimenpiteistä. Aivoverenkiertohäiriöitä todettiin vähän 0.4 % FinCV2-tutkimusaineistossa 30 päivän seuranta-ajan kuluessa ja niillä potilailla, joilla rytminsiirtohetkellä INR-arvo oli 2.0 – 2.4, oli korkeampi aivoverenkiertohäiriöriski kuin potilailla, joiden INR-arvo oli $\geq$ 2.5 rytminsiirtohetkellä (5/529 (0.9 %) vs. 1/895 (0.1 %), p = 0.03).

Päätelmät: Rytminsiirto on keskimäärin turvallinen toimenpide, mutta siihen liittyy suuri rytmihäiriön uusimisen riski jo kuukauden sisällä toimenpiteestä. Antikoagulaatiohoidon korkeampi hoitotaso on yhteydessä eteisvärinän elektiivisen rytminsiirron pienempään aivoverenkiertohäiriöriskiin.

Avainsanat: Eteisvärinä, kardioversio, tromboembolinen verenkiertohäiriö, kardioversion onnistuminen, eteisvärinän uusiutuminen

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ABBREVIATIONS

AF	Atrial fibrillation
CV	Cardioversion
OAC	Oral anticoagulation
ECG	Electrocardiogram
ESC	European Society of Cardiology
OR	Odds ratio
CI	Confidence interval
RR	Risk ratio
EF	Ejection fraction
VKA	Vitamin-K antagonist
INR	Internationalized normalized ratio
TTR	Time in therapeutic range
RCT	Randomized controlled trial
NOAC	Non-vitamin K antagonist oral anticoagulant
ICH	Intracranial hemorrhage
TIA	Transient ischemic attack
$CHADS_2$	Congestive heart failure, hypertension, age 75 years or older, diabetes and prior stroke or transient ischemic attack or thromboembolism (doubled)
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age 75 years or older (doubled), diabetes and prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65–74 years, sex category female
LAA	Left atrial appendage
HAS-BLED	Hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, elderly (>65 years), drugs or alcohol use
$HEMOR_2RHAGES$	Hepatic or renal disease, ethanol abuse, malignancy, older age (> 75 years), rebleeding, reduced platelet count or function, hypertension, anemia, genetic factors, excessive fall risk, stroke
FDA	Food and Drug Administration
bpm	Beats per minute
HR	Hazard ratio

AVN	Atrioventricular node
AA	Antiarrhythmic agent
ACEi	Angiotensin converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
AFCA	Atrial fibrillation catheter ablation
VF	Ventricular fibrillation
AC	Alternating current
DC	Direct current
TOE	Transesophageal echocardiography
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} revision
NCSP	Nordic Classification of Surgical Procedures
J	Joule
LMWH	Low molecular weight heparin
eGFR	Estimated glomerular filtration rate
MDRD	Modification of Diet in Renal Disease
SD	Standard deviation
IQR	Inter-quartile range
PINRR	Percentage of INR measurements in therapeutic range

LIST OF ORIGINAL PUBLICATIONS

I. Hellman T, Kiviniemi T, Vasankari T, Nuotio I, Biancari F, Bah A, Hartikainen J, Mäkäräinen M, Airaksinen KE. Prediction of ineffective elective cardioversion of atrial fibrillation: a retrospective multi-center patient cohort study. BMC Cardiovasc Disord. 2017 Jan 18; 17(1): 33. doi: 10.1186/s12872-017-0470-0.

II. Hellman T, Kiviniemi T, Nuotio I, Vasankari T, Hartikainen J, Lip GYH, Airaksinen KE. Intensity of anticoagulation and risk of thromboembolism after elective cardioversion of atrial fibrillation. Thromb Res. 2017 Aug; 156: 163-167. doi: 10.1016/j.thromres.2017.06.026.

III. Hellman T, Kiviniemi T, Nuotio I, Biancari F, Vasankari T, Hartikainen J, Lehto M, Airaksinen KE. Optimal timing for cardioversion in patients with atrial fibrillation. Clin Cardiol. 2018 Jul; 41(7): 966-971. doi: 10.1002/clc.22986.

1 INTRODUCTION

Atrial fibrillation (AF), the most common arrhythmia in clinical cardiology, is associated with significant mortality and morbidity (Andersson et al., 2013). Electrical cardioversion (CV) is the most important procedure for converting AF into sinus rhythm and has been in clinical use for over 50 years (Lown, 1967). CV can be performed in an acute setting for short-lasting AF episodes in symptomatic patients as well as for longer-lasting episodes in more stable patients in an elective setting. The utilization or aversion of CV divides the management of AF into two prognostically comparable treatment strategies – rate control and rhythm control. Thus, CV serves as one of the fundamental elements in the management of symptomatic AF along with anticoagulation and stroke prevention.

The consideration of CV in AF patients must include the risk assessment of procedural failure and recurrence of AF (the efficacy of CV) as well as stroke and acute arrhythmic complications (the safety of CV). CV of AF is highly effective in contemporary practice, but sinus rhythm maintenance has been a difficult clinical issue for decades. The predictors of AF recurrence after successful CV have been inconsistent, and almost all attempts to formulate clinical risk scores for prediction of sinus rhythm maintenance have failed (Disertori et al., 2010). Therefore, a clinically reasonable approach to efficacy outcome assessment of CV in AF is needed.

Stroke prevention in AF improves patient outcomes and oral anticoagulation (OAC) serves as the basis of protection from thromboembolisms. With appropriate OAC treatment the stroke risk in AF patients can be minimized (Hart et al., 2007). However, patients undergoing elective CV are exposed to an extra risk of stroke and have higher rates of thromboembolisms during the postprocedural month than do AF patients in general (Hansen et al., 2015). Nonetheless, the OAC regime is similar in both settings, and an unmet need exists to reduce the postprocedural risk of stroke in AF patients undergoing elective CV.

The risk profiles of efficacy and safety outcomes of CV in AF patients have been examined in numerous studies, and surprisingly little coherence exists in prediction of each outcome. However, AF episodes of short duration have been repeatedly associated with lower rate of procedural failure, and evidence exists that prompt CV may also lower the risk of postprocedural stroke (Van Gelder et al., 1991; Kuppahally et al., 2009; Nuotio et al., 2014). Currently, the optimal timing of CV in AF while taking all efficacy and safety outcomes into account is unclear.

The FinCV studies are a set of observational, retrospective cohort studies investigating the risk of thromboembolisms and bleeds in AF patients undergoing CV. Together, the three FinCV studies include over 10000 CVs in over 5000 patients. These studies offer

contemporary patient data to evaluate the efficacy and safety outcomes of CV in AF and, thus, provide clinically applicable and relevant knowledge to further improve our patient care.

2 REVIEW OF LITERATURE

2.1 Atrial fibrillation in clinical medicine

2.1.1 Epidemiology and economical aspects

AF is the most common supraventricular arrhythmia of the heart and is characterized by a fast and irregular beating of the atria. AF was first documented and characterized with electrocardiogram (ECG) by Sir Thomas Lewis in the early 20th century and has since been the focus of extensive and incremental research with over 19000 publications by 2007 (Lewis, 1920; Prystowsky, 2008).

AF is an increasingly prevalent disease; its prevalence was 0.95% in the general population, as reported in an American study published in 2001. It was estimated that 2.3 million U.S. adults have AF with the highest prevalence of 9.0% being among persons aged 80 years or older. It was also projected that the population affected by AF will double by 2050 (Go et al., 2001). Another American study published in 2006 estimated that the prevalence of AF will exceed 10 million by 2050 (Miyasaka et al., 2006). A similar pattern could be seen in a more recent European study that estimated that 8.8 million persons were affected by AF in the European Union in 2010 and that the number of patients will double by 2060 (Krijthe et al., 2013/B). The high incidence rate of AF was well described in the Rotterdam study. A total of 6432 persons aged 55 years or older were followed up for a mean 6.9 years. The incidence rate rose from 1.1/1000 person-years in persons aged 55-59 years to 20.7/1000 person-years in persons aged 80-84 years. It was estimated that the total life-time risk in middle-aged persons for developing AF was 23.8% in men and 22.2% in women (Heeringa et al., 2006). The increasing number of AF patients in developed countries is attributed to aging of the population, increasing occurrence of the predisposing conditions and improved AF detection (Schnabel et al., 2015).

AF incidence is strongly associated with advancing age and male sex. The incidence of AF doubled with each decade in the 38-year-long follow up of the Framingham Heart study. Hypertension and diabetes were significant independent predictors of AF, whereas heart failure and valvular heart disease were associated with AF after adjusting for other cardiac conditions (Kannel et al., 1998). The Cardiovascular Health Study made similar findings that identified history of valvular disease, advanced age, coronary artery disease, hypertension, diabetes and height as AF predictors (Psaty et al. 1997). Enlargement of the left atrium was identified as an echocardiographic predictor of AF in both studies.

The growing prevalence of AF in the population is likely to lead to increased healthcare costs. Two French studies in the early 2000s analyzed the total healthcare cost associated with AF. Both studies estimated that the total healthcare cost for one patient was 3000 euros per year, and the most significant drivers for increasing the expenses were hospitalizations and congestive heart failure (Moeremans et al., 2000; Le Heuzey et al., 2004). Thus, the massive healthcare burden of the already sizeable and still growing AF population is going to reach an annual cost of tens of billions of euros in Europe in the next decades. Better optimization of AF management in patients is, therefore, acutely warranted.

2.1.2 Clinical presentation of atrial fibrillation

AF is divided roughly into two separate types in clinical medicine: paroxysmal and chronic AF. The former denotes a disease with a predominant sinus rhythm disrupted by episodes of AF, whereas the latter stands for a dominant and permanent AF rhythm. Typically, AF begins paroxysmally and in time progresses through increasingly frequent AF episode relapses to permanent AF. The European Society of Cardiology (ESC) categorizes AF more specifically into five different disease patterns according to its symptomatic duration (Kirchhof et al., 2016):

- First diagnosed AF – first ever episode of AF with no prior AF history.
- Paroxysmal AF – episodic AF with episodes lasting up to 7 days
- Persistent AF – episodic AF with episodes lasting over 7 days
- Long-standing persistent AF – episode of AF lasting up to 1 year
- Permanent AF – Chronic AF with no aspirations toward sinus rhythm

While certain diseases increase the risk of AF, the predisposing conditions may not be immediately responsible for the onset of the index AF episode. Several known triggers for AF are common by themselves and increase the incidence of AF all the more. For instance, alcohol abuse, increased vagal tone, dehydration, congestive heart failure, hyperthyroidism and hypokalemia are known conditions that may promptly initiate AF in a patient (Auer et al., 2001; Mandyam et al., 2012; Krijthe et al., 2013/A; Sibley et al., 2015; Johansson et al., 2017).

AF can cause a wide array of symptoms, ranging from mild discomfort to acute chest pain, breathing difficulties and cardiovascular collapse. AF may cause unspecific dizzi-

ness, weakness and confusion in elderly patients. However, the most problematic feature attributed to AF is the high frequency of symptomless disease presentation, e.g., silent AF. Patients afflicted with silent AF are unknowingly exposed to increased risk of mortality and morbidity (Kirchhof et al., 2016).

In a subanalysis of the AFFIRM study, 481 asymptomatic AF patients' outcomes were compared with symptomatic patients' outcomes; the rate of mortality and major cardiovascular events was similar after adjusting for baseline differences (Flaker et al., 2005). In 2005 a small trial followed up 48 AF patients with prior DDDR pacemaker implantations for 12 months and recorded all atrial activity to correlate between clinical AF and symptoms. Over 90% of the atrial tachyarrhythmias, most of which were AF, that the pacemakers recorded were symptomless, whereas patients reported symptoms during only 6% of the confirmed AF episodes (Strickberger et al., 2005). A notable finding in the much larger PAFAC study (848 patients) comparing the sinus rhythm-sustaining effect of sotalol and quinidine plus verapamil and placebo in cardioverted patients was that 70% of all AF recurrences were completely asymptomatic (Fetsch et al., 2004). Thus, silent AF is a significant, common and economically demanding clinical problem in contemporary healthcare.

2.1.3 Screening for atrial fibrillation

Should patients be screened for AF? Some evidence exits that screening for undiagnosed AF could be effective in selected patient groups. The SAFE study evaluated the cost effectiveness of systematic screening versus common practice in patients aged 65 years or older; the results suggested that only opportunistic screening might be cost-effective (Hobbs et al., 2005). It is even more reasonable to screen for silent AF after thromboembolic events (Levin et al., 2015). The recently updated ESC guidelines for AF, apropos, recommend opportunistic screening for AF in elderly patients and that a more rigorous effort be directed towards detecting AF in patients with thromboembolic events. Systematic screening is generally not recommended (Kirchhof et al., 2016).

2.1.4 Impact on mortality and morbidity

AF increases the risk of early death. The Framingham Heart study released an article, after following up 5209 patients for 40 years, that tied AF to increased mortality (OR

1.5, CI95% 1.2–1.8) and (OR 1.9, CI95% 1.5–2.2) in men and women, respectively (Benjamin et al., 1998). More evidence was offered in the same year regarding the association between mortality and AF when Wolf et al. published the results of a large three-year follow-up study assessing the mortality rate in cardiovascular disease patients with and without AF. Patients with AF had approximately a 20% higher risk of death during each of the study years (Wolf et al., 1998). These results have been replicated many times since. A recent Swedish registry trial compared the risk of all-cause mortality in 272 186 patients with in-hospital diagnosis of AF with 544 344 AF-free controls. The risk for all-cause mortality in AF patients after adjusting for coexisting conditions was 2.15, 1.72, and 1.44 in women and 1.76, 1.36, and 1.24 in men in age groups ≤65, 65–74, and 75–85 years, respectively (Andersson et al., 2013). It appears, concordantly, that women afflicted with AF have worse outcomes than men, although the condition is more common in men. The risk scores associated with management of AF discussed later reflect this finding.

2.1.4.1 Association between stroke and atrial fibrillation

The most disastrous outcome for an AF patient is a stroke leading, with high probability, to permanent disability and early death. The blood flow in the fibrillating atria becomes more static in AF and may lead to thrombus formation, especially in the left atrial appendage. The dislodgement of the thrombus from the left atrium, due to, for example, termination of AF and return of sinus rhythm, may cause the blood clot to enter cerebrovascular circulation and cause an ischemic stroke by embolization. The blood clot may reach the limbs or viscera in much rarer cases, causing peripheral ischemia, a condition called systemic embolization. The Framingham Heart study also yielded foundational data in the field of stroke risk assessment in relation to AF. *Stroke Journal* published an article in 1991 by Wolf et al. addressing AF as a risk factor for stroke. The analysis of the data of 5070 patients after 34 years of follow up established AF as an independent risk factor for stroke with 4.8-fold risk in comparison to patients without AF (Wolf et al., 1991). The rate for stroke or systemic embolism was compared in patients receiving aspirin or warfarin or placebo in the first Stroke Prevention in Atrial Fibrillation Study (SPAF-I). The event rate was as high as 6.3% per year or 0.5% per month in the placebo arm before the study terminated (SPAF investigators, 1991). The stroke risk was highly dependent on the presence of risk factors in a follow-up study focusing on the 568 patients receiving placebo in the SPAF-I study. The stroke risk in the healthiest subcohort was only 1.4% per year, whereas the stroke rate was 17.6% per year in patients with several risk factors, which will be discussed later (SPAF investiga-

tors, 1992). Conversely, at least 10–25% of ischemic strokes are caused by AF even in modern medicine highlighting the magnitude of the issue (Kishore et al., 2014; Sposato et al., 2015). The prevalence of AF appears to be even higher in elderly stroke patients. One registry study reported over 50% prevalence of AF in stroke patients aged over 90 years (Björck et al., 2013).

2.1.4.2 Heart failure and cognitive impairment

Heart failure is another possible complication of AF. However, heart failure can be caused by several underlying diseases, and many times AF is only one of the contributing factors. AF typically causes dilatation of the left atrium and may induce systolic and/or diastolic heart failure. The Manitoba follow-up study established AF as an independent risk factor for heart failure in men with a risk ratio (RR) of 2.98 (Krahn et al., 1995). Patients first diagnosed with heart failure may also develop AF later. One of the Framingham Heart study analyses focused on the relationship between AF and heart failure. The incidence of heart failure in AF patients was 33 per 1000 person-years, whereas the incidence of AF in heart failure patients was 54 per 1000 person-years. The presence of both diagnoses was associated with worse patient outcomes (Wang et al., 2003). Furthermore, in some cases an acute and rapid AF may cause a subtype of heart failure called tachycardia-induced cardiomyopathy, which is characterized by malfunction and lowered ejection fraction (EF) of the left ventricle in a patient with prolonged fast-paced cardiac arrhythmia. The course of the condition was impressively described in a small trial in which eight patients with long-standing, persistent AF were examined at baseline and stepwise after CV. Normal atrial contraction had resumed by one week and left ventricular EF improved from 36 +/- 13% to 53 +/- 8% within one month after CV (Van Gelder et al., 1993). The condition may be life threatening but usually resolves and reverses with adequate treatment and restoration of sinus rhythm. Heart failure associated with AF is one of the most important and common reasons for hospitalization and increased healthcare costs in AF patients (Le Heuzey et al., 2004). A subanalysis of the ROCKET AF study revealed that 1 in 7 patients were hospitalized at least once within the two-year follow-up and 14% of the hospitalizations were due to heart failure, which made it the most important cardiovascular cause for in-hospital treatment (DeVore et al., 2016).

AF has also been associated with dementia, cognitive decline and increased need of assistance in daily routines in patients without cerebrovascular events. Moreover, a

post-hoc analysis of the ONTARGET and TRANSCEND studies tied AF to an increased risk of being admissioned to a long-term care facility (Marzona et al., 2012).

2.2 Management of atrial fibrillation

2.2.1 Estimation of stroke risk in atrial fibrillation

Overall, 15-48% and 10-34% of ischemic strokes are attributed to atherosclerosis and small-vessel disease, respectively. The cause of the stroke remains unknown in one third of the cases, and 21-37% of ischemic strokes are attributed to cardioembolic sources and AF (Soler et al., 2010). Several studies were conducted in the early 1990s to evaluate the risk of stroke and the protective effect of oral anticoagulation (OAC) in AF. Numerous risk factors for stroke in AF patients were identified; later, a number of risk stratification schemes were formulated out of these data for clinical use to direct OAC management in AF. Such classification schemes were produced by the SPAF investigators, the Atrial Fibrillation Investigators (AFI), the American College of Chest Physicians (ACCP) and the Framingham investigators. Two (AFI and SPAF) were combined out of these formulas to form the $CHADS_2$-score, which stratified the risk factors for stroke as follows: congestive heart failure (one point), hypertension (one point), age 75 years or older (one point), diabetes (one point) and a prior stroke or a transient ischemic attack (TIA) or thromboembolism (two points) with a maximum of six points. In the validation study, $CHADS_2$-score yielded an adjusted stroke rate of 1.9 (CI95% 1.2–3.0) for patients receiving 0 points, whereas patients who received six points had an adjusted stroke rate of 18.2 (CI95% 10.5–27.4) (Cage et al., 2001; Cage et al., 2004). The stratification score fared well in clinical practice and was adopted into the AF management guidelines.

The Euro Heart Survey released an update on the $CHADS_2$-score in 2010 – The Birmingham 2009 scheme (later called the CHA_2DS_2-VASc-score) (Table 1). The $CHADS_2$-score reliably identified the high-risk patients, while the stratification scheme left a rather large group of patients at intermediate risk with more ambiguous management recommendations. The CHA_2DS_2-VASc-score provided more clarity in risk stratification and reduced the size of the patient group with intermediate risk while still promptly identifying patients with high or low stroke risk. The scheme doubled the significance of age 75 years or older in scoring and added vascular disease, age 65–74 years and female sex as new risk points, increasing the maximum score to 9. It should be noted that female sex counted only as a risk factor in the presence of at least one other risk factor (Lip et al., 2010).

2.2.2 Clinical utilization of the CHA_2DS_2-VASc-score

The CHA_2DS_2-VASc stratifies the stroke risk in AF patients into three categories: low risk, intermediate risk and high risk for 0 points, 1 point and 2 or more points, respectively. Patients who receive 0 risk points from the scheme require no OAC or antiplatelet medication, according to the 2016 ESC guidelines for AF. Men who receive two or more points and women who receive three or more points have a high risk for a cardioembolic stroke due to AF and benefit from OAC. It is still unclear whether patients at intermediate risk for stroke (men who receive one point or women who receive two points) should start OAC. The ESC guidelines highlight that OAC should be considered in these patients while taking advancing age, bleeding risk and patient preference into account (Kirchhof et al., 2016).

Table 1 CHA_2DS_2-VASc risk factors and adjusted stroke rate for each score.

Risk Factor	CHA_2DS_2-VASc points	CHA_2DS_2-VASc-score	Adjusted stroke rate /y
Congestive heart failure	**1**	**0**	**0%**
Hypertension	**1**	**1**	**1.3%**
Age ≥75 years	**2**	**2**	**2.2%**
Diabetes	**1**	**3**	**3.2%**
Stroke or TIA or thromboembolism	**2**	**4**	**4.0%**
Vascular disease	**1**	**5**	**6.7%**
Age 65–74 years	**1**	**6**	**9.8%**
Female sex	**1**	**7**	**9.6%**
		8	**6.7%**
Maximum points	**9**	**9**	**15.2%**

Adapted from (Lip et al., 2010).

2.2.3 Prevention of thromboembolisms in atrial fibrillation

2.2.3.1 Warfarin

Stroke prevention is the most important prognostic factor in AF management, and OAC has been the basis of primary and secondary prevention for decades. Warfarin, a vitamin K antagonist (VKA), has been the dominant OAC drug in AF until very recently. It is a derivative of Dicumarol, a natural anticoagulant discovered in spoiled sweet clover in 1940 that was first launched as a rodenticide in 1948. Warfarin has been used as a clinical anticoagulant in humans since the 1950s (Link. 1959). It has a rather narrow therapeutic window and, in modern medicine, the intensity of warfarin anticoagulation has been measured with internationalized normalized ratio (INR) – a blood test measuring prothrombin time. Through extensive research, the optimal INR target range in warfarin medication in AF has been set at 2.0–3.0; values below 2.0 are associated with an increased risk for ischemic stroke, values over 3.0 with a higher rate of bleeds (EAFT study group, 1995; Hylek et al., 2003). The INR values in warfarin management have to remain within the target range of 2.0–3.0 as firmly as possible to achieve a sufficiently protective anticoagulant effect. A parameter called time in therapeutic range (TTR) has been developed to describe the long-term quality of warfarin treatment. The TTR value is constructed by dividing the therapeutic (2.0–3.0) INR values by all INR values measured in a certain timeframe. The ESC recommends maintaining a high (>70%) TTR among AF patients receiving warfarin for acceptable anticoagulation (Kirchhof et al., 2016). Recent data from Finland show that TTR values >80% may be associated with lesser event rates than those below 80% (Lehto et al. 2017).

2.2.3.2 Antiplatelet drugs

Antiplatelet medication, mainly acetylic-salicylic acid or aspirin, has also been used in AF patients for stroke prevention with only moderate success and increased risk for bleeds. Aspirin has consistently been less effective in stroke prevention than OAC in randomized controlled trials (RCT) (Hart et al., 2007). Clopidogrel, a less thoroughly researched antiplatelet drug in the setting of AF stroke prevention with similar efficacy, has been used in place of acetylic-salicylic acid in aspirin-intolerant patients in clinical practice. Furthermore, the ACTIVE study compared the efficacy of dual antiplatelet therapy (aspirin + clopidogrel) with warfarin anticoagulation in stroke prevention in AF and concluded that OAC was superior (Connolly et al., 2006). Thus, the contemporary AF management guidelines no longer recommend the use of antiplatelet agents, and

they are no longer a part of the general regime in stroke prevention of AF patients (Kirchhof et al., 2016).

2.2.3.3 Non-vitamin K antagonist oral anticoagulants

Dabigatran etexilate, a new oral direct thrombin inhibitor, entered the repertoire of OAC drugs in 2009. Three oral direct factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, have been added to the OAC roster in AF management since then. Together, the four new drugs formed a new class of medications called non-vitamin K antagonist oral anticoagulants (NOAC). Each NOAC was able to meet the primary endpoint of non-inferiority when compared to warfarin in stroke prevention in AF in the primary studies, with the exception of apixaban and dabigatran (150mg dose), which were slightly superior in efficacy (Table 2). A beneficial characteristic of NOACs is the stable plasma concentration that does not require INR or other blood test monitoring – a common issue with warfarin therapy. Clinicians no longer needed to worry over sufficiently high TTR values, either. NOACs have also had a better safety profile with lower rates of intracranial hemorrhage (ICH) and lower or similar rates of major bleeds (Table 2), whereas gastrointestinal bleeds have been slightly more common when compared to warfarin, again, with the exception of apixaban (Conolly et al., 2009; Patel et al., 2011; Granger et al., 2011; Giugliano et al., 2013).

2.2.3.4 Efficacy of oral anticoagulation in stroke prevention

Generally, OAC has reduced the risk of stroke by two thirds and aspirin by one fifth in most studies. In 2007, a meta-analysis comprising twenty-nine trials and 28044 patients was published and analyzed stroke prevention in AF patients using warfarin or aspirin. Warfarin reduced the stroke rate by 64% (CI95% 49–74%) and aspirin by 22% (CI95% 6–35%) when compared to a placebo. Warfarin was more effective than aspirin (RR 39%, CI95% 22–52%) (Hart et al., 2007). Warfarin has lowered the yearly stroke rate to 1.5–2.0% per year or 0.1–0.2% per month (Table 2) in modern stroke prevention. A recent meta-analysis of 12 studies and 77011 patients in 2016 compared NOACs and warfarin in stroke prevention in AF. NOACs were more effective than warfarin in stroke or systemic embolism prevention (OR 0.85, CI95% 0.75–0.98) and also reduced all-cause mortality, the rate of ICH and major bleeds (OR 0.86, CI95% 0.82–0.91), (OR 0.48, CI95% 0.40–0.57) and (OR 0.76, CI95% 0.62–0.93), respectively. Importantly, the studies reporting results from the 30-day follow up after the end of each study when

NOACs were switched to warfarin demonstrated an increased incidence in strokes and major bleeds (OR 2.60, CI95% 1.61–4.18) and (OR 2.19, CI95% 1.42–3.36) during the switching period, respectively (Hicks et al., 2016). No prospective head-to-head studies exist that compare different NOACs in stroke prevention in AF.

Table 2 Rate of stroke or systemic embolism and major bleeds in studies comparing NOACs and warfarin.

	stroke or systemic embolism/ y	stroke or systemic embolism/ m	major bleeds/ y	major bleeds/ m
RE-LY:				
dabigatran 150mg	**1.11%**	**0.09%**	**3.11%**	**0.26%**
dabigatran 110mg	**1.53%**	**0.13%**	**2.71%**	**0.23%**
warfarin	**1.69%**	**0.14%**	**3.36%**	**0.28%**
ROCKET-AF:				
rivaroxaban 20mg	**1.70%**	**0.14%**	**3.60%**	**0.30%**
warfarin	**2.20%**	**0.18%**	**3.40%**	**0.28%**
ARISTOTLE:				
apixaban 5mg	**1.27%**	**0.11%**	**2.13%**	**0.18%**
warfarin	**1.60%**	**0.13%**	**3.09%**	**0.26%**
ENGAGE-AF:				
edoxaban 60mg	**1.18%**	**0.10%**	**2.75%**	**0.23%**
edoxaban 30mg	**1.61%**	**0.13%**	**1.61%**	**0.13%**
warfarin	**1.50%**	**0.13%**	**3.43%**	**0.29%**

Adapted from (Conolly et al., 2009; Patel et al., 2011; Granger et al., 2011; Giugliano et al., 2013)

2.2.3.5 Left atrial appendage occlusion

OAC is the most common choice in stroke prevention in AF, but it is not the only option. Since most (>90%) of the atrial thrombi associated with AF are located in the left atrial appendage (LAA) the mechanical closure of the cavity is an intuitive solution in stroke prevention (Blackshear et al., 1996). Thus, it is not unexpected that LAA occlusion is an old idea, with various surgical techniques having been developed and applied in practice since the 1930s (Blackshear et al., 1996). The LAA occlusion surgery is usually performed during cardiac surgery for other indications in modern medicine; however, evidence for clinical benefit is unclear.

The percutaneous LAA closure device is a newer, less invasive, technique that is applied by using the standard transseptal technique in the catheterization laboratory. The Watchman implant is the most validated and researched device. LAA occlusion resulted in a lower rate of bleeds and cardiovascular deaths in a meta-analysis published in 2015, and the rate of all-cause stroke and systemic embolism was similar when compared to VKAs. LAA occlusion device deployment has been highly successful with a failure rate of only 1.5%. However, complications have not been rare, since the rate for serious adverse events was 7.9%, with a major bleed being the most common complication in a recent registry trial. Nevertheless, LAA occlusion devices offer a viable treatment option in stroke prevention of AF for patients with strong contraindications for OAC (Holmes et al., 2015; Boersma et al., 2016).

2.2.4 Evaluation and management of bleeding in patients with atrial fibrillation

OAC is associated with potentially serious complications, despite its high efficacy in stroke prevention in AF. All antithrombotic medications are associated with an increased risk for bleeds. Bleedings may be innocuous and insignificant or acute and life-threatening. The most feared bleed is ICH. The rate for major bleeds has ranged from 1.60 to 3.60% per year in OAC (Table 2), according to the recent studies comparing NOACs and VKAs in AF

As with stroke risk assessment in AF patients, several risk factors should be considered when evaluating a patient's bleeding risk. Unfortunately, many of the bleeding and stroke risk factors coincide; consequently, patients at high risk for stroke are also the ones at high risk for bleeds. The best-known stratification scheme for bleeding risk evaluation to date – the HAS-BLED-score – was presented when the CHA_2DS_2-VASc-score was introduced. The scheme awards risk points for hypertension (1 point), renal

and/or liver failure (1 point each), prior stroke (1 point), bleeding history (1 point), labile INR (1 point), age over 65 years (1 point) and drugs and/or alcohol abuse (1 point each). The maximum score is 9 points, and the cut-off value for poor risk/benefit ratio and potential refrainment from OAC in AF is 3 or more points (Table 3) (Pisters et al., 2010). Several other risk scores for the prediction of bleeds in AF patients have been introduced, such as the HEMORR$_2$HAGES and ATRIA schemes and, more recently, the ABC and ORBIT schemes. The current ESC guidelines do not recommend one scheme over the other. However, it is underscored that a high-risk score for bleeds should focus on and manage the modifiable risk factors, such as uncontrolled hypertension, medications predisposing to bleeds, labile INRs or alcohol abuse (Kirchhof et al., 2016), and should not automatically lead to withholding OAC. Furthermore, Jaakkola et al. demonstrated in a recent study that only very high HAS-BLED-scores (>4) were associated with a higher risk of intracranial bleeds than of ischemic strokes (Jaakkola et al., 2018).

The occurrence of a bleed during OAC must always be taken seriously. Discontinuation of OAC or medications causing potential anticoagulation-intensifying interactions is the first step in managing moderate to severe bleeding episodes. Trivial bleeds may be managed with a cessation of OAC for a dose or two. More serious bleeds may require fluid resuscitation, blood transfusion or endoscopic management of the bleeding foci, as they are usually located in the upper gastrointestinal tract. Severe bleeds associated with VKAs should be treated with intravenous vitamin K supplementation and/or prothrombin complex concentrate (Kirchhof et al., 2016). One limitation with NOACs has been the lack of a direct antidote. This issue has already been partly resolved since idarucizumab – a dabigatran reversal agent – was introduced in 2015 and has entered clinical use (Pollack et al., 2017). A direct antidote for Xa inhibitors, andexanet alfa, was approved by the Food and Drug Administration (FDA) in May 2018.

Table 3 HAS-BLED risk factors and bleed rate for each score.

Risk factor	HAS-BLED points	HAS-BLED-score	Bleeds per 100 patient years
Uncontrolled hypertension (>160/100mmHg)	**1**	**0**	**1.13**
Abnormal kidney or liver function	**1 or 2**	**1**	**1.02**
Stroke	**1**	**2**	**1.88**
Bleeding	**1**	**3**	**3.74**
Labile INRs	**1**	**4**	**8.70**
Elderly (age >65 years)	**1**	**5**	**12.50**
Drugs or alcohol	**1 or 2**	**6**	**0**
		7	
		8	
Maximum points	**9**	**9**	

Adapted from (Pisters et al., 2010).

2.2.5 Rate control management of atrial fibrillation

When it becomes increasingly difficult to achieve and maintain sinus rhythm in symptomatic AF patients, the treatment strategy is often shifted to rate control management, which accepts AF as the dominant rhythm and aims to hold the heart rate within acceptable limits. Factually, rate control therapy is a reasonable first-line management strategy in many cases with elderly and less symptomatic AF patients. Evidence suggests that <110 beats per minute (bpm) is a sufficient target heart rate for AF patients, with similar safety outcomes compared to a stricter (<80 bpm) regime (Van Gelder et al., 2010). Medication is the key in rate control management of AF as with many other arrhythmias. The choice between rate control agents depends on the clinical setting, although the drugs are largely the same in acute and chronic rate control management of AF. Nevertheless, acute AF with a heart rate over 140 bpm often requires intravenous administration of medicine for prompter response, whereas long term rate control is

mostly managed with oral medication. The rate control drugs are often used in combinations in clinical practice.

2.2.5.1 Rate control medication

Beta-blockers are the most common choice in rate control of acute and chronic AF. They are well tolerated, effective and readily available in oral and intravenous form. Beta-1 adrenergic, receptor-specific beta-blockers are favored over non-specific beta-blockers due to the lower chance of bronchospasms in the respiratory tract. Beta-blockers have been associated with better patient outcomes in heart failure. Interestingly, the association has been questioned in the setting of heart failure coexisting with AF (Kotecha et al., 2014). Another trial by the Swedish Heart Registry, however, suggested that beta-blocker use was associated with reduced mortality in sinus rhythm and AF (hazard ratio (HR) 0.77, $p=0.011$) and (HR 0.71, $p<0.001$), respectively (Li et al., 2015).

Calcium channel blockers, verapamil and diltiazem, are viable options for beta-blockers in rate control management of AF. Both are available in oral and intravenous form and may be used in acute or long-term settings. A significant limitation in the use of calcium channel blockers is that they are contraindicated in heart failure – a typical comorbidity in AF.

Cardiac glycosides or digoxin have been used in rate control of AF for over 100 years (Withering. 1941). The narrow therapeutic window, toxicity, proarrhythmia issues and concerns over association with increased mortality have weakened the position of digoxin in AF management. These associations, however, may have been partly caused by selection bias, since digoxin is typically used in older and sicker patients (Fauchier et al., 2016). The mildly positive inotropic effect of digoxin is also beneficial in acute management of AF, since many patients are hypotensive. Nonetheless, the therapeutic indications for digoxin have narrowed down in the recent decades.

Amiodarone can also be used in rate control of AF in selected cases as a last resort. Acute, drug-refractory AF may be slowed down if not converted to sinus rhythm with an intravenous infusion of amiodarone. However, a significant extra-cardiac, side-effect profile is a difficult issue that limits the long-term use of the drug.

2.2.5.2 His bundle ablation and pacemaker treatment

More invasive measures are sometimes needed when rate control medications fail in AF management. The implantation of a pacemaker may be a sufficient intervention, since some patients start suffering from a low heart rate with a high dosing of rate control medications. A pacemaker by itself is not enough, however, in some instances. Ablation of the bundle of His or atrioventricular node (AVN) isolates the ventricular conduction system from the atrial internodal tracts. His bundle ablation is indicated when the symptoms of AF or progressive tachycardia-induced cardiomyopathy cannot be resolved or managed with rate control medications. The procedure is relatively simple and safe and offers effective relief for patients. AVN ablation and rate control medication were compared in AF in a meta-analysis in 2012. No difference in all-cause mortality, exercise duration or left ventricular EF between the regimes was observed. AVN ablation resulted in an improvement of the left ventricular EF in comparison to the pharmacological approach in selected patients with prior left ventricular dysfunction (Chatterjee et al., 2012).

2.2.6 Rhythm control management of atrial fibrillation

A rhythm control strategy of AF pursues and often maintains sinus rhythm with the help of various antiarrhythmic drugs, catheter ablation procedures and rhythm converting methods. Many patients with a new diagnosis of AF wish to have the arrhythmia converted to sinus rhythm because of debilitating symptoms. The intensity of symptoms attributed to AF ordinarily diminish in time; some patients never experience any symptoms at all, and some patients remain highly symptomatic even after years of AF history. Perhaps to ease the large symptomatic disease burden of numerous AF patients many clinicians have pursued rhythm control management of AF with a prognostic effect in mind in patients with increasingly chronic disease patterns. However, the results have been similar – that is, maintaining sinus rhythm in AF patients does not improve their prognosis – in almost all of the studies comparing the patient outcomes of rate and rhythm control strategies in AF. The AFFIRM study enrolled 4060 AF patients, 70.8% of whom had hypertension and 38.2% of whom had coronary artery disease. The mean age of the patients was 69.7 years. Half of the patients were randomized to the rate control group and the other half to the rhythm control group. After a mean 3.5 years of follow up, the mortality rate was 23.8% and 21.3% (HR 1.15, CI95% 0.99–1.34, p=0.08) in the rhythm control and rate control groups, respectively. More hospitalizations and adverse effects were attributed to antiarrhythmic drugs in the rhythm control group. Overall, rhythm control management of AF did not offer any survival benefit when

compared to rate control strategy but was associated with more drug management issues and healthcare costs due to longer hospital stays (Wyse et al., 2002). Furthermore, the recently presented CABANA-trial was unable to demonstrate prognostic benefit in comparing catheter ablation with antiarrhythmic drug therapy in previously untreated AF patients (Poole et al., 2018). Thus far, only the CASTLE-AF trial, which compared the outcomes of medical therapy and catheter ablation treatment in AF patients with heart failure, has demonstrated a lower all-cause and cardiovascular mortality rate (the procedural treatment arm) in rhythm control management of AF (Marrouche et al., 2017). Nonetheless, the ESC guidelines currently state that the only indication for rhythm management strategy is symptomatic AF (Kirchhof et al., 2016).

2.2.6.1 Antiarrhythmic agents in atrial fibrillation

Antiarrhythmic agents (AA) such as vernakalant, flecainide, propafenone, ibutilide, quinidine, disopyramide, sotalol and amiodarone have been used for pharmacological CV of AF and to maintain sinus rhythm in patients with paroxysmal AF. Electrical CV is the golden standard in rhythm conversion of AF and is discussed in detail below. Pharmacological CV is somewhat less effective than electrical CV but requires no sedation or fasting (Crijns et al., 2014). However, AAs carry the possibility of proarrhythmia and require patient selection to minimize such risks. AAs are the first line option, although catheter ablation techniques have yielded better results in sinus rhythm maintenance (Wynn et al., 2014; Marrouche et al., 2017).

The success rate of pharmacological CV has ranged from 55 to 75% in recent observational trials. Amiodarone and flecainide or propafenone have been the most popular AAs and no differences in procedural success rates exist between the drugs (Hernández-Madrid et al., 2012; Gitt et al., 2013). Electrical CV is used more often in AF patients due to its better safety and efficacy profile, although pharmacological CV has its benefits. Electrical CV also requires shorter hospitalizations (Crijns et al., 2014). Sometimes in refractory cases both methods are used in conjunction when patients are given AAs for a short period of time prior to electrical CV to improve the chances of rhythm conversion.

Vernakalant, one of the more novel AAs, was introduced in 2008 as a rapidly acting drug for pharmacological CV. The drug, unlike the other AAs, is not associated with severe proarrhythmic adverse effects (Roy et al., 2008). The procedural success rate was significantly higher (RR 11.56, CI95% 7.12–18.75) and the rate of adverse effects was similar between the groups in a meta-analysis comparing vernakalant with placebo or amiodarone (Yan H., et al 2013). It has to be noted, however, that the trial comparing

vernakalant and amiodarone worked in disfavor for amiodarone, since the follow-up time was shorter than the typical effective timeframe of amiodarone. The procedural success rate of vernakalant in AF has been numerically comparable to other AAs – approximately 50% (Camm et al., 2011; Camm. 2014). Studies exploring the effect of oral vernakalant in sinus rhythm maintenance in AF patients have been somewhat successful (Torp-Pedersen et al., 2011). However, vernakalant has, so far, been solely clinically used for pharmacological CV, and its utilization has also been restricted by the high expenses.

Amiodarone is the most widely used AA in pharmacological CV of AF (Hernández-Madrid et al., 2012; Gitt et al., 2013; Camm. 2014). Its efficacy and clinical benefits have been well established in both rhythm conversion and sinus rhythm preservation. Amiodarone can also be used in patients with heart failure and in critical care settings (Doyle et al., 2009; Kirchhof et al., 2016). Even in failure of CV, amiodarone has value in rate control of AF. Major limitations in the use of amiodarone are the common and potentially severe cardiac and extra-cardiac adverse effects. Bradycardia and conduction disturbances are common cardiac complications, whereas thyroid, liver, ocular and pulmonary toxicity are potential extra-cardiac issues. Amiodarone pulmonary toxicity is a rare and possibly lethal condition. The discontinuation rate in studies exploring amiodarone have been quite high 13–23% for these reasons (Vorperian et al., 1997; Le Heuzey et al., 2010). Dronedarone is an AA used for rhythm control of AF with similar properties as amiodarone but with a lower rate of adverse effects and procedural effectivity. Amiodarone and dronedarone were compared in 504 patients with AF in the DIONYSOS study. The recurrence rate in 12 months was 42.0% and 63.5% and rate of adverse events 44.5% and 39.3% for amiodarone and dronedarone, respectively (Le Heuzey et al., 2010).

Propafenone and flecainide are effective in pharmacologic rhythm conversion of AF with success rates between 50 and 85%, and they can also be used in recurrence prevention (Khan. 2001; Aliot et al., 2011). Both drugs are also compatible with the "pill-in-the-pocket" approach – an AF rhythm management strategy in which clearly symptomatic patients may try to perform a pharmacological CV at home with a designated single oral dose of either flecainide or propafenone. The treatment regime is effective, but to a lesser extent than in-hospital CV treatment and has a lower healthcare burden compared to standard care (Alboni et al., 2004; Saborido et al., 2010). Flecainide and propafenone are, however, contraindicated in patients with structural heart disease.

Quinidine, disopyramide and sotalol are older and more traditional AAs in AF management. They have been in extensive use previously but lost their significance to more modern drugs, since each has been associated with increased mortality (Lafuente-Lafuente et al., 2015). Sotalol, an unselective beta-blocker, is still used rarely in selected patients in AF.

Overall, AAs have to be used carefully in sinus rhythm maintenance. They effectively reduce AF recurrences by half but, in the long-term, only 33–57% of patients remain in sinus rhythm at one year of follow up (Lafuente-Lafuente et al., 2015). Safety concerns and moderate efficacy have led the ESC to take a less lenient stand on the use of AAs. Shorter periods of AA treatment should be pursued when applicable (Kirchhof et al., 2016). The Flec-SL trial compared a short term, 4-week regime with a longer 6-month regime of flecainide treatment following a successful CV of AF and demonstrated that, while being less effective in recurrence prevention overall, the short-term regime still prevented most relapses of AF (Kirchhof et al., 2012).

2.2.6.2 Non-antiarrhythmic medications and non-pharmacological treatment in prevention of atrial fibrillation

Other medications than AAs have also been tested in primary and secondary prevention of AF. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) have had positive results in AF prevention in patients with heart failure (Vermes et al., 2003; Ducharme et al., 2006). There are similarly favorable results with beta-blockers in patients with AF and heart failure (Kotecha et al., 2014). However, ARBs have not demonstrated such a preventive effect in patients without a significant heart condition (The GISSI-AF Investigators. 2009). Statin therapy, which is usually used in hypercholesterolemia, has also been tested in this setting and showed no effect in AF prevention (Rahimi et al., 2011). Non-pharmacological approaches have also been explored in this setting and weight loss, especially, has demonstrated favorable results in AF prevention (Middeldorp et al., 2018).

2.2.6.3 Catheter Ablation and surgery in prevention of atrial fibrillation

Haïssaguerre et al. (1998) discovered in 1998 that there are hot foci around the pulmonary veins prone to produce ectopic beats triggering attacks of AF in patients with paroxysmal AF. This finding eventually led to the development of an endovascular technique, AF catheter ablation (AFCA), which is now widely and successfully used in recurrence prevention of AF. There have been different regimes in the atrial targeting of AFCA, although the primary target of the procedure is the isolation of right pulmonary veins from the left atrial myocardium. The isolation is performed by inflicting controlled superficial tissue damage with either radiofrequency or cryoablation technology. Radiofrequency ablation relies on heat generated from medium frequency alternating

current, whereas cryoablation uses extreme cold to damage the target tissue. Multiple procedures are often needed. The ESC generally recommends AFCA as a second-line option for symptomatic AF patients when treatment with AAs have failed (Kirchhof et al., 2016). However, studies investigating AFCA as a first-line treatment for paroxysmal AF have also yielded favorable results (Nielsen et al., 2012).

The efficacy outcomes have been superior for AFCA in studies comparing AFCA and AAs in recurrence prevention of AF. AFCA fared significantly better in AF recurrence prevention compared to AAs in a 2014 meta-analysis (OR 0.32; CI95% 0.20-0.53, $p<0.001$) (Wynn et al., 2014). A meta-analysis described the long-term efficacy of AFCA with one-year AF-free rates of 65.3% and 85.7% and three-year success rates of 56.4% and 79.3% for single-procedure and multiple-procedure ablation, respectively (Ganesan et al., 2013). Furthermore, the CASTLE-AF trial demonstrated superior patient outcomes for AFCA compared with pharmacological therapy in AF patents suffering from heart failure (Marrouche et al., 2017). The rate for complications in AFCA has been approximately 6%, with some being life-threatening. The rate of cardiac complications (e.g., pericardial effusion or acute myocardial infarction) has been a little over 2%, whereas the periprocedural stroke rate has been less than 1%. The incidence of complications has been associated with the experience of the operator (Deshmukh et al., 2013). Thus, more experienced treatment centers yield more consistent results and fewer complications. Some evidence also exists that combining AA treatment and AFCA (hybrid therapy) may be more efficacious than either alone (Calkins et al., 2009).

Over 30 years ago (in 1987), a surgical treatment for AF, the maze procedure, was developed. The ultimate goal of the maze procedure was the permanent eradication of AF in a patient. The maze operation, through controlled tissue damage, creates a labyrinth of iatrogenic conduction pathways in the atrium that prevent the fibrillatory wavelet conduction and development of AF. The initial patient series demonstrated an AF-free rate of 89% in long-term follow up; however, as many as 40% of the patients required pacemaker implantation, and complications were frequent (Cox et al., 1993). In contemporary practice, maze procedure is mostly considered for symptomatic AF patients who are undergoing open heart surgery for another indication, since effective and less risky options are currently available for AF rhythm management (Kirchhof et al., 2016). A thoracoscopic, mini-invasive, surgical ablation is another option for symptomatic AA-resistant AF patients. The FAST trial compared surgical ablation and AFCA in AF patients and suggested that the surgical ablation procedure may be more effective than AFCA. Surgical ablation was also associated with an increased risk for complications. The findings were confirmed by a recent meta-analysis on the subject (Boersma et al., 2012; Phan et al., 2016). Thus, the ESC recommends surgical ablation in symptomatic AF patients in whom standard AFCA has failed (Kirchhof et al., 2016).

2.3 Electrical cardioversion in atrial fibrillation

In electrical CV, the excitatory system of the heart is depolarized with a controlled countershock that allows the most dominant native pacemaker of the heart – the sinus node – resume control. Bernard Lown introduced the term CV in the early 1960s, but the history of CV goes beyond that. A Danish doctor, Peter C. Abildgaard, first performed experiments with animals and electricity in 1775. He was able to render hens lifeless with electrical countershocks and revive their hearts with another shock to the chest (Driscol et al., 1975). Some years later the first attempts at resuscitation of human patients occurred, and English scientist James Curry published a first review article on resuscitation cases in 1792.

Defibrillation of the heart became a topical research subject only much later, at the turn of the 19th and 20th centuries, when wider availability of electric power brought forth an increasing number of accidental deaths involving electrocutions. A John Hopkins University research team was able to terminate ventricular fibrillation (VF) in a dog with a subsequent accidental shock – "the countershock" – in 1933. Alternating current (AC) was determined to be more effective in defibrillation of the heart than direct current (DC) electricity. Cardiothoracic surgeon Claude Beck later successfully performed a defibrillation of VF of a human patient in operating conditions in 1947. The Soviet Union was concurrently conducting research on the defibrillation of the heart. Doctor Naum L. Gurvich, ahead of his time in the 1930s, determined that it was effective and safer to apply DC than AC in defibrillation of the human heart, and in 1939 he had already proposed the idea to use the biphasic waveform. Gurvich designed the first commercial cardiac defibrillator in 1952, and the Soviet Union reported the first cardioversion of AF seven years later. Gurvich first demonstrated in 1967 that the biphasic waveform was superior in efficacy compared to monophasic waveform in electrical CV of AF. However, the biphasic waveform did not see wider use over the next 40 years due to the high popularity of the monophasic waveform technique of his western colleagues (Cakulev et al., 2009).

Bernard Lown is often credited as the father of cardioversion (Lown et al., 1963). From his extensive animal research, Lown concluded that AC shocks posed greater safety concerns than DC shocks, and he introduced the monophasic DC defibrillation of the heart to the west, technology that had existed for almost 30 years outside the Iron Curtain. However, Lown pushed the research further. Heart defibrillation had only concerned VF until the 1960s, and Lown applied the technique more widely to other arrhythmias, as well. He also discovered that the countershock could occasionally produce VF due to the heart's "vulnerable period." This period of time was, in fact, the QT-interval, and Lown developed a synchronized defibrillation technique that timed the shock to be produced over the QRS complex, thus avoiding the vulnerable period. He ultimately called this technique the "cardioversion" and began applying extensively it to

AF patients. CV revolutionized the management of AF patients. Quinidine had been used in AF patients with high, near-toxic doses and not without difficulties. Lown demonstrated over a 90% efficacy in resuming sinus rhythm with CV in the first series of AF patients. He deduced that anteroposterior arrangement of the leads was more effective and required less energy in CV of AF. Lown also recognized one of the most difficult problems with AF patients – maintenance of sinus rhythm. Despite AAs and successive CVs, 50% of patients experienced a recurrence of AF. In many cases this still holds true in contemporary medicine (Lown, 1967).

2.3.1 Electrical cardioversion of atrial fibrillation in clinical practice

CV is the most important tool in rhythm control strategy of AF. Clinically, electrical CV of AF can be divided into two settings: acute and elective. The division is driven by the stroke risk associated with the duration of AF episodes prior to rhythm conversion. CV of an acute episode of AF is defined as a rhythm conversion of an AF episode lasting less than 48 hours. The most recent update on guidelines recommends always starting anticoagulation prior to CV, regardless of the AF episode duration. However, the recommendations do not take a specific stand on the need for postprocedural anticoagulation in patients with acute (<48 hours) AF episodes and overall low (CHA_2DS_2-VASc-score = 0) risk for stroke. The situation is more straight forward when the index AF episode has lasted longer than 48 hours. Anticoagulation is mandatory in this setting for three weeks prior to the elective CV and at least four weeks after the CV, regardless of the individual patient's stroke risk. Since many AF patients are asymptomatic or seek medical help late for their symptoms, elective CV is often the basis of rhythm control strategy of AF. Only four weeks of postprocedural anticoagulation is required after elective CV in low risk patients, whereas high risk (CHA_2DS_2-VASc-score $\geq$2) and often intermediate risk (CHA_2DS_2-VASc-score = 1) patients must continue anticoagulation indefinitely. The atrial thrombus can be excluded by performing a transesophageal echocardiography (TOE) when early CV is pursued in a patient with no prior anticoagulation and an index AF episode lasting longer than 48 hours. If no blood clot is detected, the CV may proceed with the usual anticoagulation regime (Kirchhof et al., 2016).

Patient selection for CV of AF is not simple, although rhythm control strategy is very popular among both clinicians and patients. The rhythm management strategy in AF does not offer prognostic benefit, and the CV procedure is not without additional risk. Keeping in mind that only symptomatic AF is an indication for successive CVs, the probability of successful rhythm conversion and maintenance of sinus rhythm (the efficacy of CV) should be weighed against the periprocedural risk of stroke and acute ar-

rhythmic complications (the safety of CV). The specifics on safety and efficacy outcomes attributed to CV are discussed next.

2.3.2 Predictors for failure of electrical cardioversion in atrial fibrillation

Rhythm conversion of AF has been very effective ever since electrical CV was developed. Lown recognized anterior-posterior electrode positioning as superior to anterior-lateral positioning at an early stage, a finding that was verified later (Lown, 1967; Kirchhof et al., 2002). Additionally, biphasic waveform in electrical CV of AF was eventually compared with Lown's monophasic waveform and found to be superior; most defibrillators have been biphasic since 2000. A meta-analysis published in *Resuscitation* in 2016 concluded that biphasic waveform had a 3.2-fold higher probability of success in CV in AF and a lower requirement of energy and countershocks when compared to monophasic waveform (Inácio et al., 2016). One other option for decreasing the failure rate of CV in AF is the pretreatment with AAs. A substudy of the SAFE-T trial showed the beneficial effect of preprocedural amiodarone or sotalol on the success rate of CV in AF (Singh et al., 2009). Other AAs can also be used in this setting (Kirchhof et al., 2016).

Recently, the failure rate of CV performed in acute AF lasting less than 48 hours has been approximately 10% (Michael et al., 1999; Bellone et al., 2012; Pisters et al., 2012). In the recent FinCV study, 3143 patients with AF lasting less than 48 hours underwent 7660 CVs, 90% of which were electrical. The overall failure rate of CV was only 5.5% (Grönberg et al., 2016). Generally, elective electrical CVs have had numerically higher failure rates than CVs performed for AF lasting less than 48 hours. The failure rate has also been more variable in numerous trials between 5% and 34% (Table 4). However, this phenomenon may partly be explained by the higher degree of inconsistency in the patient cohorts in terms of index AF episode duration, whereas cohorts examining acute AF episodes may vary much less in this sense. Failure rates of acute and elective CV have not been compared in large data sets. The 2012 Euro Heart Survey of a small subset of data exploring electrical CV in AF patients demonstrated that patients with an index AF episode lasting less than 48 hours had lower failure rates in CV when compared to patients with longer lasting episodes (3% vs. 13%, p=0.003) (Pisters et al., 2012).

Bernard Lown's 1967 review already recognized duration of the index AF episode as a factor affecting the failure rate of elective electrical CV (Lown, 1967). This finding has

been replicated many times since then; that is, shorter duration of the index AF episode is associated with a lower rate of failure in CV (Van Gelder et al., 1991; Frick et al., 2001; Fumagalli et al., 2002; Elhendy et al., 2002; Kuppahally et al., 2009). Other predictors for failure of elective electrical CV have been hypertension (Blich et al., 2006); increasing age (Van Gelder et al., 1991); higher body weight or body mass index (Frick et al., 2001; Elhendy et al., 2002; Blich et al., 2006); left ventricular failure (Elhendy et al 2002); greater body surface area (Alegret et al., 2007) and COPD (Pisters et al., 2012) in previous studies.

Table 4 Failure rate of elective electrical CV in AF in previous studies.

First Author	n	Mean Age (y)	Male (%)	Median Duration of AF (mo)	Failure rate (%)
Carlsson et al. (1998)	181	58	70	8	19%
Kuppahally et al. (2009)	370	67	65	NA	34%
Blich et al. (2006)	68	75	38	4	5%
McCarthy et al. (1969)	149	NA	54	NA	17%
Van Gelder et al. (1991)	246	60	56	28	30%
Fumagalli et al. (2002)	250	69	63	NA	9%
Frick et al. (2001)	166	68	67	5	25%
Dittrich et al. (1989)	85	63	74	NA	24%
Sandler (2010)	153	63	78	5	27%
Elhendy et al. (2002)	692	67	66	NA	14%
Alegret et al. (2007)	1355	63	65	NA	13%
Pisters et al. (2012)	712	65	65	1	12%

AF = atrial fibrillation

2.3.3 Predicting recurrence of atrial fibrillation after successful cardioversion

Lown wrote over 50 years ago:

"Though atrial fibrillation can now be readily terminated, maintenance of sinus rhythm continues as the central problem. … Whether cardioversion is to be carried out depends not so much on the ability to terminate the arrhythmia, but rather on the capacity to sustain a long-lasting sinus rhythm." (Lown, 1967)

Disappointingly little progress has been made in the many decades since Lown's review paper in the maintenance of sinus rhythm in AF patients after CV. Only very recently have advances made in the field of AFCA demonstrated improvements in sinus rhythm maintenance. Before the time of ablation techniques, however, the recurrence rate of paroxysmal AF was approximately 50% at one year of follow up, despite advanced AA management in most of the studies (Table 5), and it has also been remarkably difficult to identify the patients who are most likely to experience AF relapses. The predictors for AF recurrence in virtually all of the studies have been very inconsistent (Table 5).

Much effort was made in the 1990s to understand the mechanism behind the frequent relapses of AF and the typical progression to more a permanent disease pattern. Wijffels et al. performed instrumental experiments on goats and suggested that longer maintenance of AF leads to further stability and inducibility of AF – that "AF begets AF" (Wijffels et al., 1995). Research on atrial remodelling has delved into cellular biology of the atria in recent years, and it appears that atrial fibrosis plays a major role in the AF disease process through a multitude of pathways. AF recurrence promoting atrial remodelling may be caused by AF itself as well as other cardiac conditions, increasing age or systemic illnesses. However, the exact relationship between atrial fibrosis and AF remains still poorly understood (Dzeshka et al., 2015).

Table 5 Recurrence of AF after successful electrical CV in previous studies.

First Author	n	Mean Age (y)	Male (%)	Mean Follow-up (mo)	Recurrence rate (%)	Predictors for recurrence
Carlsson et al. (1998)	181	58	70	8	31.1%	high number of prior CVs
Kuppahally et al. (2009)	370	67	65	12	53%	age <65 years, paroxysmal AF, alcohol use
Blich et al. (2006)	68	75	38	37	67%[a]	beta-blocker medication, age <75 years[b]
McCarthy et al. (1969)	149	NA	54	6-36[c]	45%[a]	NA
Van Gelder et al. (1991)	246	60	56	9	58%[a]	Atrial flutter, lower NYHA class, mitral insufficiency[b]
Fumagalli et al. (2002)	250	69	63	34	46%	Underlying heart disease
Frick et al. (2001)	166	68	67	1	63%	AF duration <3 months, beta-blocker or calcium channel blocker medication, small right atrium[b]
Dittrich et al. (1989)	85	63	74	NA	47%[d]	AF duration <3 months, large left atrium[b]
Sandler (2010)	153	63	78	11	80%	NA
Melduni et al. (2015)	3251	69	67	59	43-55%[e]	low left atrial appendage emptying flow velocity
Raitt et al. (2006)	1293	NA	65	12	50%[f]	no coronary artery disease, P-wave >135ms in lead II
Tieleman et al. (1998)	61	61	56	1	57%	Calcium channel blocker medication[b]
Pisters et al. (2012)	712	65	65	12	39%	Paroxysmal AF, short AF history, Ic class or amiodarone use, younger age, smaller left atrium, no COPD[b]
Schmidt et al. (2011)	159	68	60	12	64%	low estimated glomerular filtration rate

[a] At 1 year of follow-up, [b] Predictors for sinus rhythm maintenance, [c] Range of follow-up, [d] At 1 month of follow-up, [e] range of recurrence rate in study groups at 1 year of follow-up,

[f] Rhythm control arm, CV = cardioversion, AF = atrial fibrillation, NYHA = New York Heart Association, COPD = chronic obstructive pulmonary disease.

2.3.4 Risk of stroke and anticoagulation in cardioversion of atrial fibrillation

A significant proportion of strokes in patients with paroxysmal AF occurs after CVs. The Fibstroke study explored 3677 patients and demonstrated that 6.4% of strokes in patients with paroxysmal AF occur after rhythm conversion (Palomäki et al., 2016). Importantly, CV of AF is associated with excess risk of stroke in addition to the general stroke risk assessed with the CHA_2DS_2-VASc-score. This phenomenon is explained by stunning, a temporary dysfunction of the atria, following CV. The atria do not resume their normal contractions right after conversion to sinus rhythm despite normal pacing of the sinus node. This leads to weaker localized blood flow in the atria which, in turn, promotes thrombus formation, and when the normal atrial contractility finally recovers, the thrombus may dislodge into the blood stream (Khan, 2003). Depending on the duration of the preceding AF episode, the duration of atrial stunning ranges from one day to one month (Manning et al., 1994). These approximations serve as the basis for the recommendations regarding the minimum of postprocedural anticoagulation duration (four weeks) after CV in AF. The first days after CV are the most important in stroke prevention, since atrial stunning appears to be strongest right after the procedure, and research has demonstrated that most embolizations occur during the first postprocedural week (Berger et al., 1998; Palomäki et al., 2016). Thus, any patient with paroxysmal AF, regardless of stroke risk, may experience a cerebrovascular embolization after CV due to the mechanism of atrial stunning. This reasoning was confirmed in a large Danish study with 16274 patients undergoing first-ever CV of AF. The incidence of thromboembolism was 2.2% within the 30-day follow up, and patients with no OAC fared worse than anticoagulated patients (HR 2.25, CI95% 1.45–3.53). Importantly, this risk ratio also persisted in nonanticoagulated patients with low or intermediate risk (CHA_2DS_2-VASc = 0-1) and high risk (CHA_2DS_2-VASc $\geq$2) for stroke (HR 2.21, CI95% 0.79–6.77) and (HR 2.40, CI95% 1.46–3.95), respectively (Hansen et al., 2015).

The risk of stroke after CV of AF episodes lasting less than 48 hours has been 0.1–1.1% within 30-days after rhythm conversion in previous studies (Weigner et al., 1997; Airaksinen et al., 2013; Garg et al., 2016; Stiell et al., 2017). Evidence in the 1990s on relatively low stroke risk in conversion of acute AF suggested that no anticoagulation was needed in this setting (Weigner et al., 1997). However, there was echocardiographical data that thrombus formation was active already in short-lasting episodes of AF (Stoddard et al., 1995). More recent research, such as the FinCV study, in a nonantico-

agulated patient cohort with AF episodes lasting less than 48 hours demonstrated that while the overall stroke risk was in line with previous studies (0.7%), patients with selected coexisting conditions undergoing CV were at considerably higher risk (9.8%) for stroke (Airaksinen et al., 2013). Similarly, Garg et al. compared safety outcomes of CV in patients with acute (<48 hours) AF episodes. The anticoagulated patients had lower stroke rate compared to nonanticoagulated patients (0.22% vs. 1.06%, p=0.03). Thus, current guidelines recommend stroke risk assessment with the CHA_2DS_2-VASc-score always prior to CV and starting anticoagulation as soon as possible before CV – even in patients with short-lasting AF episodes.

Evidence exists that prompt CV of acute (<48 hours) AF may lead to better patient outcomes. A subanalysis of the FinCV study demonstrated that the delay between diagnosis of acute AF and CV had an effect on the rate of stroke. Patients with time to CV lower than 12 hours had lower stroke rate than patients with time to CV between 24 and 48 hours (0.3% vs. 1.1%, p=0.004) (Nuotio et al., 2014).

While the rate of stroke after CV of acute AF has ranged between 0.7–1.1% in non-anticoagulated patients the risk has been higher for patients undergoing elective CV in AF lasting over 48 hours (Airaksinen et al., 2013; Garg et al., 2016). In the few studies comparing the post-CV outcomes in anticoagulated and non-anticoagulated patients with AF lasting over 48 hours the rate of stroke has been as high as 3–7% (Bjerkelund et al., 1969; Weinberg et al., 1989; Arnold et al., 1992). Modern anticoagulation has substantially lowered this risk (Table 6). Nevertheless, even with proper anticoagulation the risk of stroke during the first postprocedural month remains higher after elective CV than in general management of AF. Also, the rate of major bleeds has been higher after elective CV (compare Tables 2 and 6). The efficacy in stroke prevention after elective CV of AF has been comparable in NOACs and VKAs. However, the time to CV has been shorter with NOACs (Cappato et al., 2014).

Since all AF patients are at risk for stroke despite adequate anticoagulation, especially so in the setting of elective CV, a clinically unmet need still exists to further reduce stroke risk in AF management. The effect of TOE in stroke prevention prior to elective CV in AF patients has been explored in a number of trials. As with NOACs in more

Table 6 Rate of stroke or systemic embolism and major bleeds in studies examining anticoagulants and CV outcomes in patients with AF lasting over 48 hours.

	stroke or systemic embolism (overall)	**stroke or systemic embolism /m**	**major bleeds (overall)**	**major bleeds /m**
ACE:				
LMWH	**0.8%**	**0.4-0.8%**	**0.8%**	**0.4-0.8%**
UFH + VKA	**0.8%**	**0.4-0.8%**	**2.4%**	**1.2-2.4%**
ACUTE:				
TOE + UFH + VKA	**0.8%**	**0.4%**	**0.8%**	**0.4%**
VKA	**0.5%**	**0.3%**	**1.5%**	**0.8%**
Gallagher et al:				
VKA - INR <2.5	**0.9%**	**0.9%**	**0.1%**	**0.1%**
VKA - INR ≥2.5	**0%**	**0%**	**0.1%**	**0.1%**
X-VERT:				
rivaroxaban	**0%**	**0%**	**0.6%**	**0.6%**
VKA	**0.6%**	**0.6%**	**0.8%**	**0.8%**
ENSURE-AF:				
edoxaban	**0.2%**	**0.2%**	**0.3%**	**0.3%**
LMWH + VKA	**0.3%**	**0.3%**	**0.5%**	**0.5%**
RE-LY:				
dabigatran 150mg	**0.3%**	**0.3%**	**0.6%**	**0.6%**
dabigatran 110mg	**0.8%**	**0.8%**	**1.7%**	**1.7%**
VKA	**0.6%**	**0.6%**	**0.6%**	**0.6%**

LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin-K antagonist, TOE = transesophageal echocardiography, INR = international normalized ratio

The follow-up in all trials was 4 weeks except in the ACUTE study the follow-up was 8 weeks.

Adapted from (Klein et al., 2001; Gallagher et al., 2002; Stellbrink et al., 2004; Nagarakanti et al., 2011; Cappato et al., 2014; Goette et al., 2016;)

recent trials, preprocedural TOE has shortened time to CV. However, no benefit in stroke prevention has been detected when TOE guided CV and conventional CV in AF have been compared (Klein et al., 2001; Seidl et al., 2002; Nagarakanti et al., 2011; Cappato et al., 2014). Due to the established noninferiority compared to the proper anticoagulation, TOE guided CV is particularly recommended prior to early CV of an AF episode lasting over 48 hours (Kirchhoff et al., 2016).

Some evidence exists that supports more intensive anticoagulation to counter the extra stroke risk associated with elective CV of AF. Gallagher et al. published an article in 2002 investigating intensity of VKA anticoagulation and stroke risk attributed to CV of AF. Almost 2000 patients with 2639 CVs were enrolled, and over 80% of the CVs were elective. Among the elective CVs, the rate of thromboembolisms was lower after the 779 CVs that were performed with an INR of ≥2.5 compared to the 756 CVs that were performed with an INR of <2.5 (0% vs. 0.9%, p=0.012). This finding has not been replicated in other studies due to the arrival of NOACs. Nonetheless, more intensive anticoagulation in elective CV of AF, along with the minimization of delays between detection of AF and rhythm conversion, offers interesting potential clinical implications in stroke prevention of AF and research.

2.3.5 Acute arrhythmic complications of electrical cardioversion in atrial fibrillation

Most arrhythmic complications attributed to CV of AF are bradyarrhythmias. The rate of VF was less than 2%, and five (0.8%) ventricular tachycardias were detected, in the series of 601 monophasic DC CVs in AF patients in Lown's experimental series investigating the effect of asynchronous counter shock in dogs (Lown. 1967). Ventricular tachyarrhythmias have become an extremely rare complication since the effective omission of the vulnerable period by the synchronous CV, and such arrhythmias are usually attributed to the proarrhythmic effect of AAs. The rate of VF, ventricular tachycardia and Torsades des pointes ventricular tachycardia was 0.4%, 0.8% and 0.1%, respectively, in the 2012 Euro Heart Survey (Pisters et al., 2012).

Conversely, bradyarrhythmic complications are common after CV of AF. This tendency was already noted in the 1960s, and Lown first introduced the term "sick sinus syndrome." The atrioventricular block is another common mechanism for bradycardia after CV of AF. The bradycardic complications usually present themselves in patients as a severe bradycardia with a ventricular rate slower than 30 bpm or an episode of asystole. The situations are managed with atropine, isoprenaline or emergency transthoracic pacing and sometimes require implantation of temporary or permanent pacemakers. The incidence of bradycardia or asystole after CV in AF patients has been 0.7–1.5% in previous studies (Botkin et al., 2003; Gallagher et al., 2008; Morani et al., 2009; Pisters et al., 2012; Grönberg et al., 2013). Predictors for bradyarrhythmic complications after CV of AF have been atrial flutter and prosthetic heart valve (Morani et al., 2009); increasing age, female sex and unsuccessful CV (Grönberg et al., 2013) and low ventricular rate (Shin et al., 2015). However, use of AAs or amount of energy used in CV have not been associated with bradycardic complications. The rate of arrhythmic complications has also been similar in acute vs. elective CVs of AF (Gallagher et al., 2008; Pisters et al., 2012). Implantation of permanent pacemakers has been frequent (38–44% of cases) in bradyarrhythmic complications of CV in AF patients (Grönberg et al., 2013; Shin et al., 2015).

3 AIMS OF THE STUDY

1. To evaluate the rate of and identify the predictors for ineffective elective CV, defined as a failure of CV or a recurrence of AF within 30-days follow up (I).

2. To examine the effect of a more intensive periprocedural VKA anticoagulation on the rate of thromboembolisms after elective CV in AF patients (II).

3. To investigate the optimal timing of CV in AF patients in terms of efficacy and safety outcomes (III).

4 MATERIALS AND METHODS

4.1 Study population of Studies I-II

The FinCV2 study population served as the basis for the study cohorts of Studies I-II. The FinCV2 study ([http://]www.ClinicalTrials.gov, identifier NCT02850679) is a part of the FinCV study program – a retrospective, observational, multi-center trial investigating the rate of and predictors for stroke and bleeds after CV in AF patients. The FinCV2 study focused on AF patients undergoing elective CV in AF episodes lasting over 48 hours. Data were gathered during the 2003–2014 timeframe from Turku University Hospital, Turku City Hospital and Raisio City Hospital and from Kuopio University hospital during the 2013–2015 timeframe. All patients over 18 years of age undergoing elective CV for an AF episode lasting over 48 hours were eligible for the study. Only patients living in the catchment area of the study hospitals were included in the study cohort to secure consistent follow-up data.

A database search was initially performed in the patient records for the ICD-10 code I48 (AF) and the NCSP code TFP20 (CV). The screening resulted in 2373 patients. Next, the patient records of all the screened patients were manually reviewed, and only patients with AF episodes lasting longer than 48 hours undergoing electrical CV were included in the study. Thus, the final study cohort comprised 1342 patients with 1998 elective CVs. All of the FinCV2 study cohort served as the study population for Study I.

The second publication focused on patients with adequate preprocedural warfarin anticoagulation and INR data. The study population of the second publication comprised 1021 patients and 1424 elective CVs (Figure 1) when patients using low molecular weight heparin (LMWH) or NOACs and patients with low preprocedural INRs or incomplete INR data were excluded. In Study II an additional, secondary screening was performed in the patients of the primary study population for all INRs 30 days prior to and after the index CV. The comprehensive INR data were provided by the laboratory services of Turku University Hospital (TYKSLAB) for a subpopulation of 733 patients with 1007 elective CVs. Such additional data were unavailable for study patients treated in Kuopio University Hospital.

All relevant medical background data, including AF history, medications, cardiovascular risk profile and CV characteristics of the patients, were recorded in electronic case report forms during the inclusion process. The time since AF disease was diagnosed was divided into six groups: 31–90 days, 90–180 days, 180 days – 1 year, 1–2 years, 2–5 years and >5 years. The duration of the index AF episode was divided in the same manner into <30 days, 30–60 days, 61–90 days, 91–120 days, 121–180 days and >180 days. The 30-day follow up was explored after the index CV, and all unsuccessful CVs,

recurrences of AF, thromboembolisms, mortality and acute arrhythmic complications were collected.

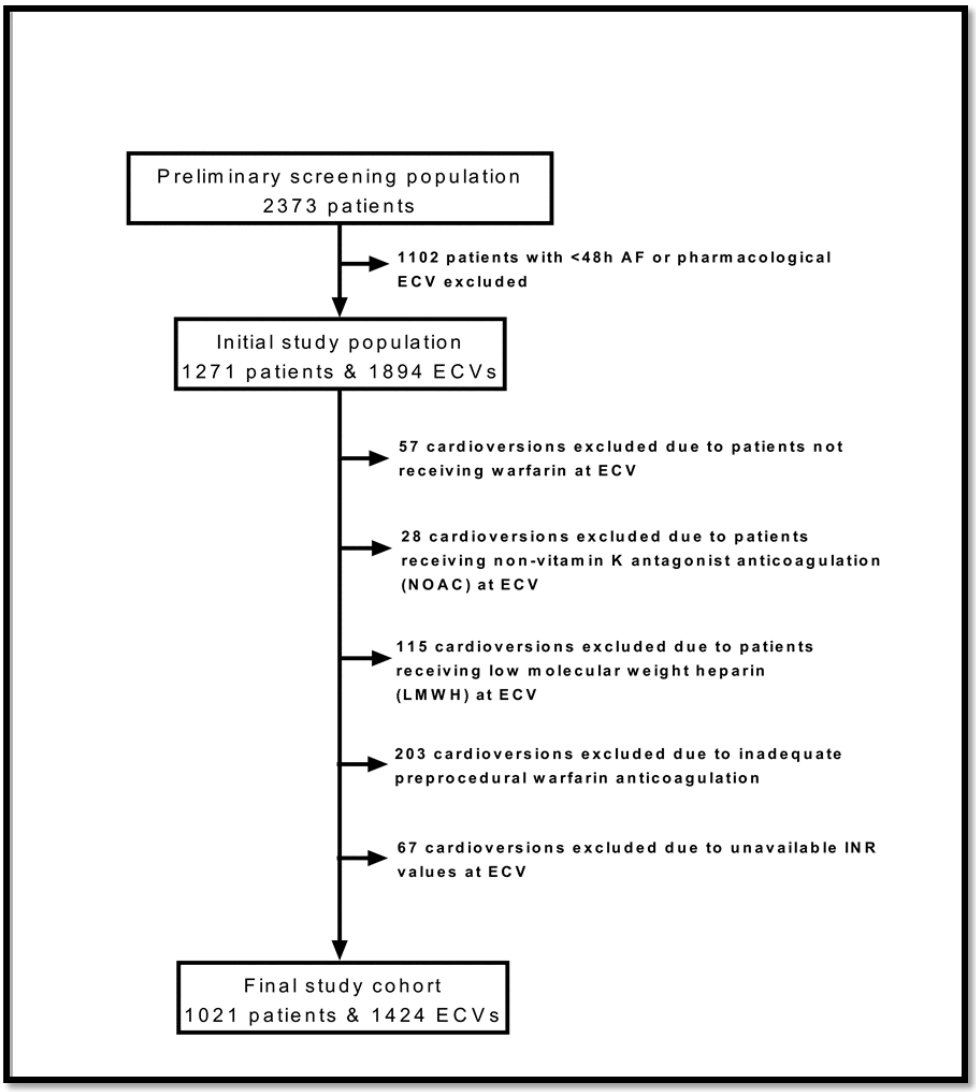

Figure 1 Flow chart illustrating patient selection in Study II.
AF= atrial fibrillation ECV = elective cardioversion

All CVs were performed according to the contemporary guidelines by an attending internist or cardiologist. General anesthesia was provided and supervised by an anesthesiologist, and blood pressure and oxygen saturation were monitored. The positioning (anterior-lateral or anterior-posterior) of the paddles or pads was at the discretion of the clinician performing the CV. The energy ranged from 70 to 360 J and 70 to 200 J with monophasic and biphasic devices, respectively. Solely biphasic defibrillators were used after 2004. A control ECG was recorded after each CV.

4.2 Study population of Study III

Study III study population comprised the study cohorts of all three FinCV studies. The patient data for the FinCV ([http://]www.ClinicalTrials.gov, identifier NCT01380574) and FinCV3 ([http://]www.ClinicalTrials.gov, identifier NCT02911545) studies were collected from Turku University Hospital, Kuopio University Hospital, Helsinki University hospital, Satakunta Central Hospital, Central Finland Central Hospital, North-Kymi Hospital and Helsinki City Hospital from the 2003–2010 and 2011–2016 timeframes, respectively. Patient records were first screened with the ICD-10 code for AF and NCSP code for CV as with the FinCV2 study. Patients were manually enrolled subsequently according to the study-specific inclusion criteria: all patients treated in the emergency room for an acute (<48h) AF in whom electrical or pharmacological CV was attempted (FinCV) and all patients with AF using NOACs and undergoing electrical or pharmacological CV (FinCV3). These studies, together with the study population of the FinCV2 study, comprised 5441 patients and 10852 CVs.

All patients with an unknown AF episode duration or undergoing pharmacological CV were excluded, since Study III focused on the timing of electrical CV in AF. Additionally, patients not on OAC (VKA or NOAC) at the time of the index CV were excluded. Consequently, the final study population of the third publication included 2530 patients and 4356 CVs (Figure 2). The composite study cohort evenly comprised CVs of acute (<48 hours) AF and AF episodes lasting over 48 hours (52.4% vs. 47.6%, respectively).

The study methods and data gathering process in the three studies were otherwise similar.

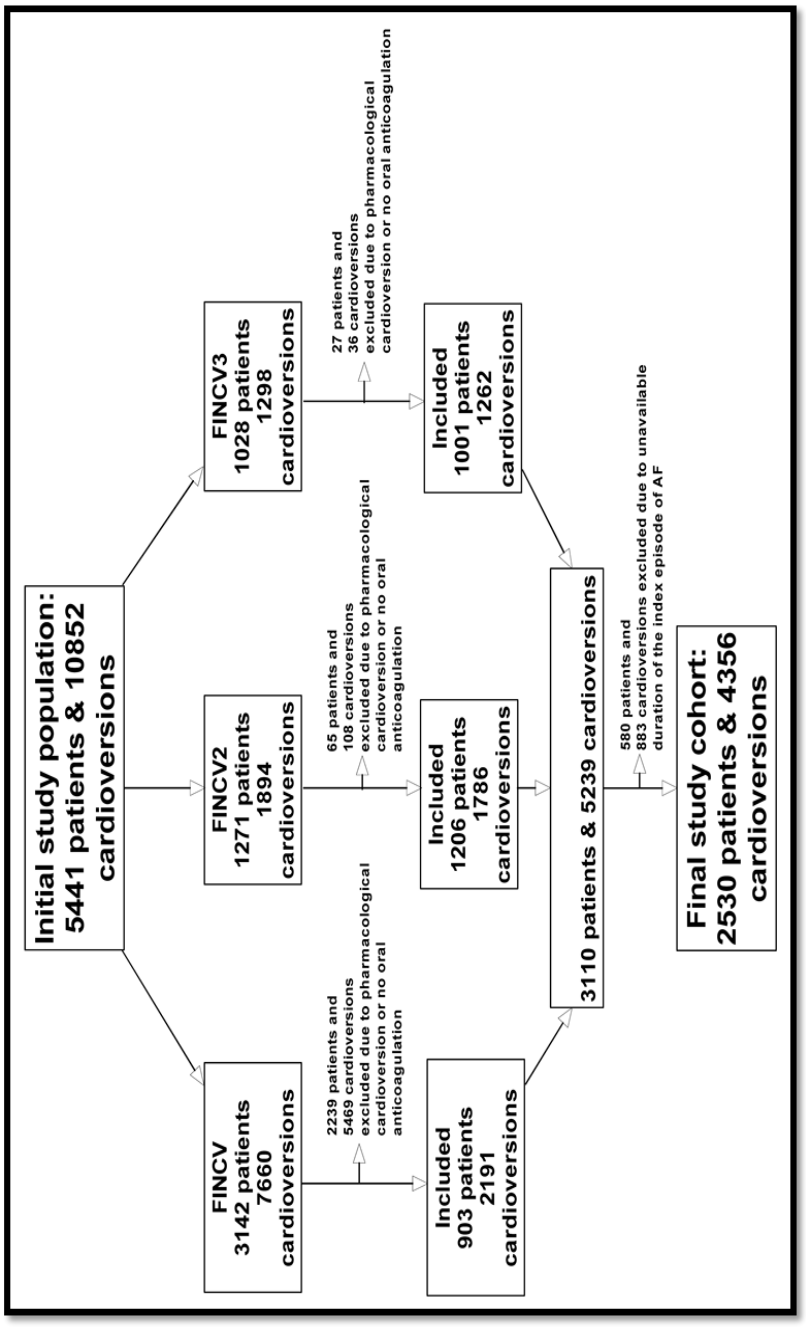

Figure 2 Flow chart showing the patient selection in the third article.

4.3 Ethics

The study was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the National Institute for Health and Welfare's Ethics Committee. The study adheres to the Declaration of Helsinki. Informed consent was not required due to the retrospective nature of the study.

4.4 Definitions

The attending clinician confirmed all AFs by a 12-lead or ambulatory ECG. The study did not segregate AF and atrial flutter. Estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula. An unsuccessful CV was defined as the inability to sustain sinus rhythm until discharge from the procedural department despite an initially successful CV. A relapse of AF within the 30-day follow-up period after a successful index CV confirmed by ECG or pacemaker log was defined as an AF recurrence. An ischemic, non-hemorrhagic stroke or TIA confirmed by the attending neurologist with imaging or systemic embolism diagnosed by the attending vascular surgeon with imaging was qualified as a thromboembolic event. The definition of acute arrhythmic complication included asystole lasting >5 seconds, ventricular tachycardia or ventricular fibrillation occurring immediately after the index CV.

Notably, Study III aggressively pursued more definite endpoints; thus, TIAs or systemic embolisms were not collected as thromboembolic events.

4.5 Statistical analysis

Normally distributed continuous variables were reported as mean ± SD, whereas skewed continuous variables were denoted as median [IQR]. Categorical variables were reported as absolute and relative (percentage) frequencies. Normality in continuous covariates was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests. The unpaired t-test or Mann-Whitney test was used to compare continuous variables, whereas Pearson x^2 or Fisher's exact test were applied to compare categorical variables in the study subgroups, as appropriate. Logistic regression with backward selection was used to identify the independent predictors of the study outcomes. Baseline variables with $p < 0.10$ level

in univariate analysis were entered into the logistic regression models. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

The Hosmer-Lemeshow test was used in Study III to estimate the calibration of the regression models.

IBM SPSS Statistics software version 22.0 and SAS 9.4 statistical software (SAS Institute Inc., Cary, North Carolina) were used to perform all analyses, as appropriate.

5 RESULTS

5.1 Prediction of ineffective elective cardioversion of atrial fibrillation (I)

A composite endpoint, the ineffective elective CV defined as an unsuccessful CV, or a recurrence of AF within 30-days follow up after a successful elective CV, served as the primary outcome of Study I and was used to assess the clinical efficacy of elective CV in patients with AF lasting over 48 hours. Altogether, 303 (15.2%) CVs were unsuccessful, and AF recurred after 549 (32.4%) initially successful CVs within the 30-day follow up. Thus, the primary endpoint of ineffective elective CV occurred in 852 (42.6%) cases.

Several independent predictors were identified for the primary endpoint, procedural failure and unsuccessful sinus rhythm maintenance. In the multivariate model, >5 years' history of AF, an index AF episode lasting >30 days and ventricular rate >60 bpm, whereas female sex, use of AAs, history of kidney failure and eGFR <60 ml/min independently predicted unsuccessful CV and recurrence of AF after successful CV, respectively. Finally, age <65 years (OR 1.31, CI95% 1.07–1.62, p=0.01), female sex (OR 1.44, CI95% 1.15–1.80, p<0.01), ventricular rate >60 bpm (OR 1.92, CI95% 1.08–3.41, p=0.03) and use of AAs (OR 1.48, CI95% 1.14– 1.93, p<0.01) were the independent predictors for the primary endpoint in the multivariate analysis. Since creatinine values were unavailable in 955 (47.8%) CVs, eGFR was included in the multivariate model in a separate analysis. Consequently, low (<60 ml/min) eGFR (OR 1.59, CI95% 1.08–2.33, p=0.02), ventricular rate >60 bpm (OR 2.93, CI95% 1.33–6.47, p=0.01) and use of AAs (OR 1.50, CI95% 1.09– 2.08, p=0.01) predicted ineffective elective CV, while age and female sex ceased to remain significant predictors.

5.2 Intensity of anticoagulation and risk of thromboembolism after elective cardioversion of atrial fibrillation (II)

5.2.1 Occurrence of thromboembolisms and mortality

The second publication focused on periprocedural intensity of VKA anticoagulation in patients with AF lasting over 48 hours undergoing elective CV. Mean age in the whole study population was 64 (SD 9.8) years, and 419 (29.4%) patients were female. The mean INR at the index CV was 2.7 (SD 0.54), and the mean CHA_2DS_2-VASc-score was 2.0 (SD 1.6). TOE was performed prior to 31 (2.2%) elective CVs to exclude atrial thrombus.

Altogether, four (0.3%) strokes and two (0.1%) TIAs were detected within the 30-day follow up (Table 7). No systemic embolisms were seen, but one pulmonary embolism was observed. All thromboembolic events occurred after successful CVs, and the median time to a thromboembolism was 4 [IQR 9.5] days after the index CV. The median CHA_2DS_2-VASc-score was 2 [IQR 1.25] in patients with thromboembolic events. While none of the bleeding complications were spontaneous, one (0.1%) major bleed (traumatic subdural hemorrhage) and one (0.1%) clinically relevant, non-major bleed (dental procedure causing sinus perforation and requiring nasal tamponade) was detected. Two (0.1%) patients died within the 30-day follow up (one mortality was associated with a stroke and the other with congestive heart failure, kidney failure and sepsis).

Table 7 Characteristics of the thromboembolic events after elective CV.

	Event	Age/Sex	Time after CV (days)	CHA_2DS_2-VASc-score	TOE	INR (CV)	INR (Event)	Other
Pt 1	Stroke	53M	12	1	No	2.4	1.4	Traumatic subdural hemorrhage before stroke
Pt 2	Stroke	65M	5	2	No	2.1	1.9	Warfarin pause due to cataract surgery
Pt 3	Stroke	73M	11	2	No	2.2	4.4	-
Pt 4	Stroke	75M	3	2	No	2.8	2.4	-
Pt 5	TIA	70M	1	1	No	2.2	1.9	-
Pt 6	TIA	53F	2	0	No	2.2	2.2	-

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless <65 years and no other risk factors); TOE = transesophageal echocardiography; INR = international normalized ratio; Pt = patient; M = male; F = female; TIA = transient ischemic attack

5.2.2 Intensity of anticoagulation and risk of thromboembolism

Study II's study population was divided into two groups according to the therapeutic intensity of anticoagulation prior to the index CV: patients with INR 2.0–2.4 and INR ≥2.5 at the time of the index CV, respectively. Table 8 depicts the baseline characteristics of the two study groups.

Table 8 Baseline characteristics of patients with low (2.0–2.4) therapeutic INR vs high (≥2.5) therapeutic INR at elective CV.

	INR 2.0-2.4 (N=529)	**INR ≥2.5 (N=895)**	**p**
Age >75 years	88 (16.6)	134 (15.0)	0.60
Female	150 (28.4)	269 (30.1)	0.51
First AF episode	279 (52.7)	419 (46.8)	0.03
Prior cardioversion	211 (39.9)	404 (45.1)	0.10
CHA_2DS_2-VASc-score ≥2	304 (57.5)	529 (59.1)	0.58
Duration of the index AF episode <90 days [a]	202 (65.4)	341 (66.7)	0.51
Duration of AF disease ≤1year	262 (57.7)	404 (52.6)	0.09
History of heart failure	67 (12.7)	127 (14.2)	0.47
Hypertension	300 (56.7)	473 (52.8)	0.17
History of kidney disease	30 (5.7)	54 (6.0)	0.82
Diabetes	73 (13.8)	142 (15.9)	0.32
Prior stroke/TIA	38 (7.2)	52 (5.8)	0.31
Coronary artery disease	74 (14.0)	144 (16.1)	0.32
Medication at discharge			
Aspirin	14 (2.6)	16 (1.8)	0.41

[a] exact duration not available in 604 (42.4%) cardioversions.

Values in parentheses are %, INR = international normalized ratio; AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless <65 years and no other risk factors); TIA = transient ischemic attack

Patients with low (2.0–2.4) therapeutic INRs had a higher risk for thromboembolic events than patients with high (≥2.5) therapeutic INRs (5/529 (0.9%) vs. 1/895 (0.1%), p=0.03) (Figure 3), and the results did not change when only the first CV of each patient was analyzed. A drop in INR to subtherapeutic (<2.0) level was detected in 230 (22.8%) cases 21 days after the index CV in the 733 patients with the additional comprehensive INR data. Furthermore, the mean TTRs and percentage of INR measurements in therapeutic range (PINRRs) were lower in patients with postprocedural subtherapeutic (<2.0) INRs compared to those with all INRs ≥2.0 (55% vs. 79%, p <0.01 and 45% vs. 73%, p<0.01, respectively). The risk for thromboembolic events was markedly higher in the patients with postprocedural drops to subtherapeutic INRs than in patients with therapeutic postprocedural INRs (1.7% vs. 0.3%, p=0.03) (Figure 3). Low (2.0–2.4) therapeutic INR at the time of elective CV predicted the drop in INR to subtherapeutic (<2.0) level within 21 days after elective CV (OR 1.93, CI95% 1.38–2.69; p <0.01).

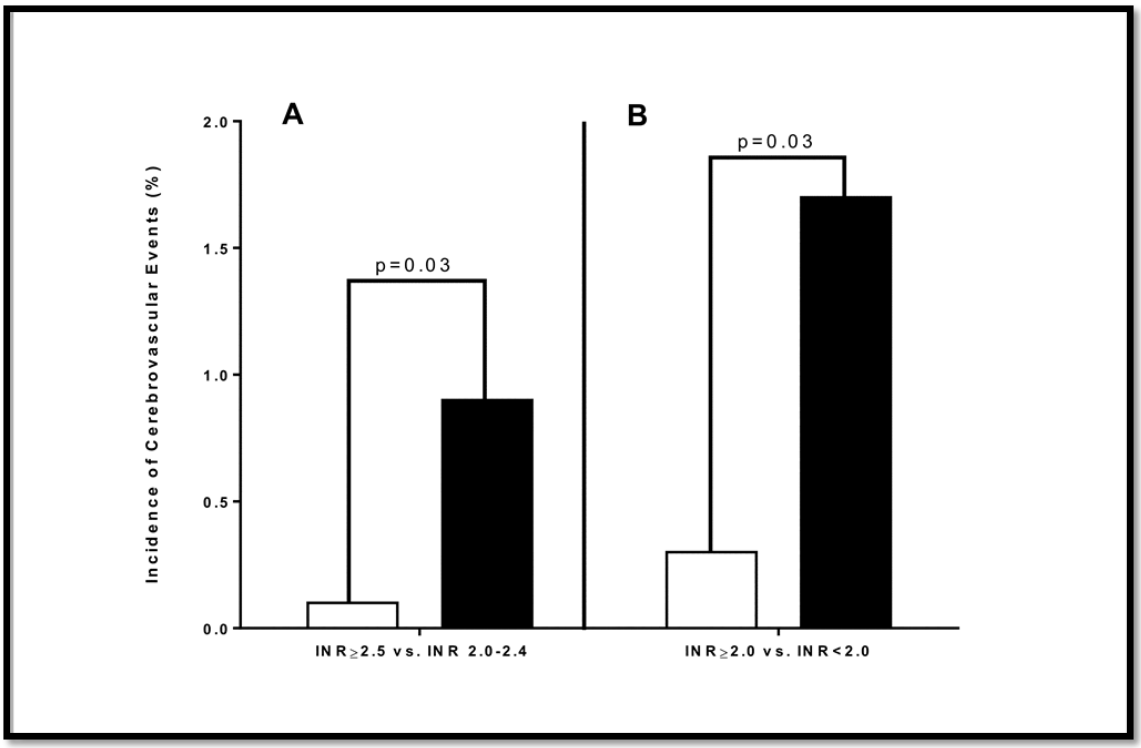

Figure 3 Incidence of thromboembolic events in patients with high (≥2.5) therapeutic INRs (full color) compared to those with low (2.0–2.4) therapeutic INRs (no color) at elective cardioversion (ECV) (Panel A), and in patients with therapeutic (≥2.0) vs. subtherapeutic (<2.0) INRs within 21 days after ECV (Panel B).

5.3 Optimal timing for cardioversion in atrial fibrillation (III)

5.3.1 Study population characteristics and adverse outcomes

The study population was divided into four groups according to the duration of the index AF episode to better assess the effect of the delay between AF detection and CV on patient outcomes in the composite cohort of Study III: <24 hours, 24–48 hours, 48 hours – 30 days and >30 days and comprised 1767, 516, 632 and 1441 CVs, respectively. Table 9 presents the baseline characteristics of the study groups. Patients with shorter (<24h or 24–48h) index AF episodes were more likely to be women and use AAs, as well as have a history of hypertension, coronary or peripheral artery disease, prior stroke or myocardial infarction. On the contrary, patients with longer (48h – 30d or >30d) index AF episodes had lower CHA_2DS_2-VASc-scores and ventricular rate at the time of CV but more often had a history of congestive heart failure or kidney failure.

Study III's primary endpoint was the composite adverse outcome, defined as postprocedural mortality, thromboembolic event, unsuccessful CV, acute arrhythmic complication and/or AF recurrence after successful CV within the 30-day follow up. Overall, 448 (10.3%) CVs were not successful, and sinus rhythm maintenance failed after 1194 (30.6%) initially successful CVs within the 30-day follow-up period. The rate of thromboembolisms was five (0.1%), and four (0.1%) patients died during follow up. No episodes of ventricular fibrillation or ventricular tachycardia were observed. Asystole lasting >5 seconds was detected after 32 (0.7%) CVs. The rate of composite adverse outcome was 1669 (38.4%) within the 30-day follow-up period.

5.3.2 Timing of cardioversion and prediction of adverse outcomes

Table 10 depicts the relationship between the timing of CV and adverse events. There was no association between index AF episode duration and the rate of postprocedural mortality, thromboembolisms or acute arrhythmic complications. However, the relationship between AF episode duration and unsuccessful CV showed a J-shaped curve; the lowest procedural failure rate was in patients with an index AF episode lasting 24–48 hours (Figure 4), and the corresponding results concerning timing of CV and recurrence rate of AF within the 30-day follow-up period were similar. Concordantly, there was a significant association between the timing of CV and the composite adverse outcome; patients with AF lasting 24–48 hours had the best patient outcomes (Figure 4).

Table 9 Baseline characteristics of CVs according to duration of index episode of AF.

	<24h (N=1767)	24-48h (N=516)	48h-30d (N=632)	>30d (N=1441)	p
Age mean years	64 (12)	64 (10)	63 (11)	64 (10)	<0.01
median years	66 [1]	64 [12]	63 [14]	65 [14]	<0.01
Age >75 years	294 (16.7)	62 (12.1)	73 (12.7)	223 (16.7)	<0.01
Female	796 (45.0)	197 (38.2)	159 (25.2)	401 (28.2)	<0.01
Prior cardioversion[a]	1301 (75.8)	330 (69.6)	246 (81.5)	347 (49.2)	<0.01
CHA_2DS_2-VASc-score ≥2	1190 (67.3)	327 (63.4)	305 (48.3)	766 (53.2)	<0.01
Ventricular rate (/min)					
<60/min	23 (1.4)	12 (2.5)	16 (3.0)	46 (3.5)	<0.01
median	109 [33]	102 [32]	91 [33]	86 [25]	<0.01
History of heart failure	147 (8.3)	66 (12.8)	110 (17.7)	193 (13.8)	<0.01
Hypertension	989 (56.0)	271 (52.5)	295 (47.0)	775 (54.3)	<0.01
Chronic kidney disease	34 (1.9)	13 (2.5)	29 (4.7)	70 (5.1)	<0.01
Diabetes	226 (12.8)	81 (15.7)	87 (13.9)	213 (15.2)	0.18
Cirrhosis	0 (0.0)	2 (0.4)	0 (0.0)	4 (0.3)	0.49
Prior stroke	244 (13.8)	58 (11.3)	31 (5.0)	39 (2.8)	<0.01
Coronary artery disease	632 (35.8)	178 (34.5)	78 (12.6)	164 (11.7)	<0.01
Prior myocardial infarction	201 (11.4)	73 (14.1)	43 (6.9)	88 (6.3)	<0.01
Peripheral artery disease	475 (26.9)	131 (25.5)	19 (3.1)	26 (1.9)	<0.01
Pacemaker	157 (8.9)	58 (11.3)	67 (11.0)	69 (5.0)	<0.01
Medication at CV					
Beta-blocker	1542 (87.3)	430 (83.5)	543 (86.2)	1262 (88.0)	0.06
Digoxin	175 (9.9)	58 (11.5)	88 (15.3)	246 (19.4)	<0.01
Verapamil	37 (2.1)	17 (3.4)	4 (0.7)	13 (1.0)	<0.01
Any antiarrhythmic agent[b]	466 (26.4)	132 (26.1)	132 (22.9)	122 (9.7)	<0.01

[a] data is missing in 1158 (26.6%) cases, [b] Antiarrhythmic agents comprised flecainide, amiodarone, propafenone, quinidine or disopyramide and dronedarone.

Values in parentheses are % or standard deviation when appropriate and values in brackets are interquartile range; CV = cardioversion; AF = atrial fibrillation; VKA = vitamin-K antagonist; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless <65 years and no other risk factors).

A duration of over 48h of the index AF episode predicted unsuccessful CV and recurrence of AF within the 30-day follow up (OR 1.79, CI95% 1.41-2.26 and OR 1.38, CI95% 1.16-1.64, p<0.01 for both comparisons, respectively) in the multivariate logistic regression analysis. Furthermore, prior pacemaker implantation, beta blocker medication and AA medication, congestive heart failure, kidney failure, prior myocardial infarction, peripheral artery disease, digoxin and AA medication independently predicted unsuccessful CV and recurrence of AF within 30-days follow up, respectively. Younger age was associated with both a lower rate of unsuccessful CV and recurrence of AF as well as a lower rate of composite adverse outcome.

Table 10 Adverse outcomes of CVs according to duration of the index AF episode.

Outcomes	**<24h (N=1767)**	**24-48h (N=516)**	**48h-30d (N=632)**	**>30d (N=1441)**	**p-value/H-L test**
Composite adverse outcome	645 (36.5)	160 (31.1)	283 (45.0)	581 (40.4)	<0.01
Adjusted OR (95%CI)	1.33 (1.07-1.66)	Reference	2.00 (1.52-2.60)	1.89 (1.49-2.40)	0.37
Unsuccessful CV	150 (8.5)	28 (5.4)	70 (11.1)	200 (13.9)	<0.01
Adjusted OR (95%CI)	1.81 (1.16-2.84)	Reference	2.10 (1.17-3.60)	3.60 (2.27-5.90)	0.74
Asystole >5 s	15 (0.8)	4 (0.8)	6 (0.9)	7 (0.5)	0.58
Adjusted OR (95%CI)	1.00 (0.33-3.03)	Reference	1.24 (0.33-4.65)	0.54 (0.15-1.92)	0.84
Thromboembolic event	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	0.29
Adjusted OR (95%CI)	-	Reference	-	-	-
Mortality	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.2)	0.18
Adjusted OR (95%CI)	-	Reference	-	-	-
AF recurrence	481 (29.8)	129 (26.5)	209 (37.3)	375 (30.3)	<0.01
Adjusted OR (95%CI)	1.23 (0.97-1.56)	Reference	1.83 (1.36-2.46)	1.64 (1.25-2.14)	0.26

Values in parentheses are %; CV = cardioversion; AF = atrial fibrillation; H-L: Hosmer-Lemeshow test p-value

Finally, an index AF episode lasting over 48 hours (OR 1.49, CI95% 1.28-1.74, p<0.01), congestive heart failure (OR 1.52, CI95% 1.22-1.89, p<0.01), chronic kidney disease (OR 1.56, CI95% 1.07-2.27, p=0.02), peripheral artery disease (OR 1.23, CI95% 1.01-1.49, p=0.04), beta blocker medication (OR 1.43, CI95% 1.16-1.76, p<0.01) and AA medication (OR 1.73, CI95% 1.46-2.05, p<0.01) were independent predictors for the development of composite adverse outcome in the multivariate logistic regression analysis.

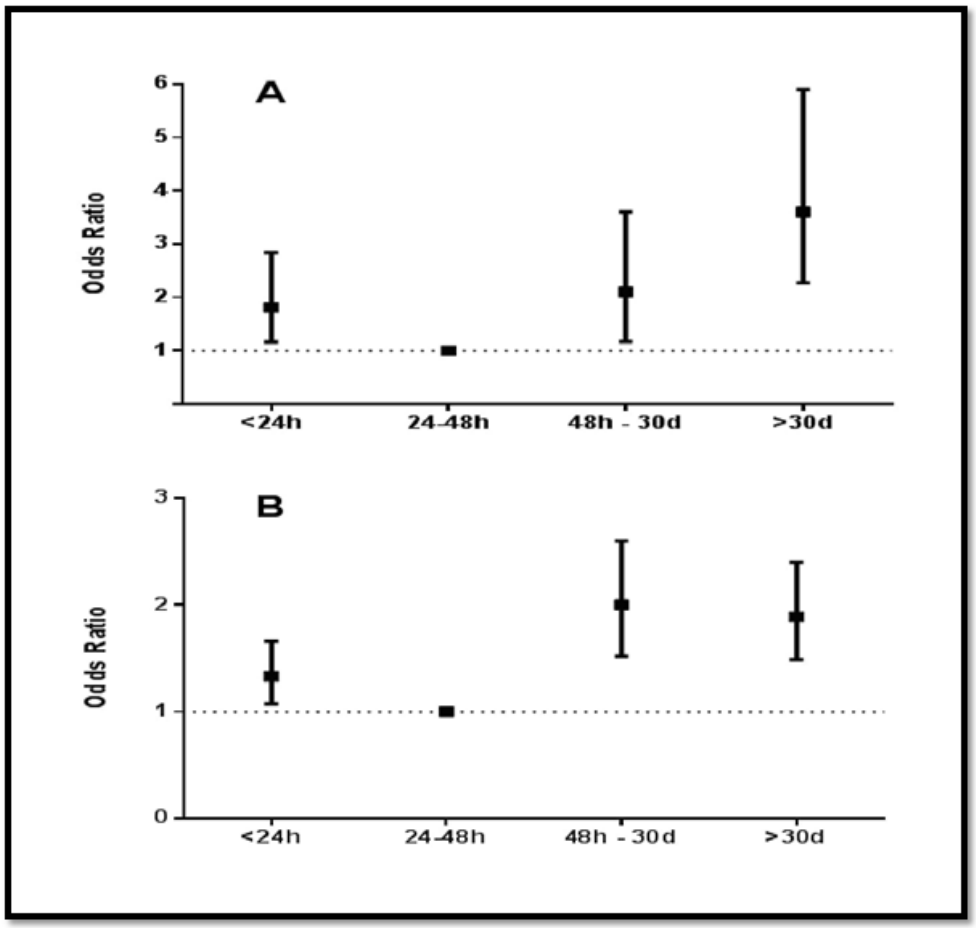

Figure 4 Adjusted odds ratios with 95% confidence intervals of unsuccessful CV (A) and composite adverse outcome (B) according to duration of the index AF episode.

5.3.3 Comparison of AF episodes with known vs unknown duration

An additional analysis was performed to compare the study outcomes between the study cohort patients with known index AF episode duration with the excluded patients with AF episodes of unknown duration. The excluded patient cohort had generally fewer coexisting conditions and a smaller burden of AF or medications. There were more unsuccessful CVs (17.5% vs. 10.3%, $p < 0.01$) and fewer (0.1% vs. 0.7%, $p = 0.03$) episodes of asystole lasting over 5 seconds in the excluded patient cohort compared to the study patient cohort. Otherwise, the rate of adverse outcomes between the cohorts was similar.

6 DISCUSSION

6.1 Prediction of ineffective elective cardioversion of atrial fibrillation (I).

In Study I, our "real-life" data demonstrated that almost every sixth elective CV in AF patients was unsuccessful and that a third of the patients experienced a relapse of AF within one month after an initially successful elective rhythm conversion. Altogether, nearly half of the patients were in AF at the end of the study follow-up period. These findings are in line with previous studies and demonstrate the still persisting problem with efficacy outcomes of elective CV in AF – mainly with maintenance of sinus rhythm even in short-term follow up after CV.

The procedural failure rate of elective CV (15.2%) in our data demonstrates that the risk for unsuccessful elective CV has remained largely the same for five decades (Table 4). No further progress has been made in the field of procedural efficacy since the wider introduction of biphasic defibrillators in clinical cardiology almost 20 years ago. For this reason, research on clinical predictors of ineffective CV cannot be emphasized enough. Apropos, our results showed that longer overall disease history or episode duration of AF are associated with a lower success rate of elective CV. This finding is in line with discoveries made in previous studies and with the atrial remodellation theory (Van Gelder et al., 1991; Wijffels et al., 1995; Frick et al., 2001; Fumagalli et al., 2002; Elhendy et al., 2002; Kuppahally et al., 2009). Thus, it is reasonable to pursue the minimization of the delay between AF detection and CV to improve the chances of procedural success. Another potentially beneficial factor in improving the procedural success rate of CV in AF patients is the favoring of anterior-posterior positioning of electrodes over anterior-lateral positioning. Although the positioning of the electrodes was not controlled in our study, it was noticed during the data gathering phase that anterior-lateral positioning was surprisingly popular despite evidence favoring the other configuration (Inácio et al., 2016).

Our observations on the failure rate of sinus rhythm maintenance (32.4%) after successful elective CV as well as on most of the risk factors for recurrence of AF identified in our study have been previously demonstrated (Table 5). Unsurprisingly, AA medication was associated with increased failure rate in sinus rhythm maintenance and the primary composite endpoint, contrary to their purpose. The association did not change even if AAs were analyzed separately. Additionally, patients with prior AF ablations had more recurrences. These findings demonstrate the effect of a high AF disease burden in some patients in an unselected "real-life" patient cohort. Although the median number of CVs in this cohort was one, the total number of procedures ranged from 1 to 10 per patient, indicating that the characteristics of some symptomatic patients' refractory and often

intensively managed AF disease may be emphasized in statistical analysis. A more unexpected finding was the association between a low ventricular rate and a higher efficacy of elective CV. Similar associations have not been described in the literature before, and the FinCV study also demonstrated no association between ventricular rate and procedural efficacy in a much larger cohort of patients with acute (<48 hours) AF. Thus, while the finding may be incidental, it nonetheless requires further elucidation (Jaakkola et al., 2015). A very interesting finding was that a history of kidney failure as well as a low (<60ml/min) GFR at the time of the index CV predicted unsuccessful sinus rhythm maintenance and the primary composite endpoint. Very little data on the effect of kidney failure on efficacy of CV in AF exists in previous literature, and our study demonstrated this association for the first time in a "real-life" registry study. However, one small trial on selected patients with kidney failure demonstrated that progressive renal insufficiency was associated with increased rate of AF recurrence after successful CV. Our findings call for further research on the clinical potential and background mechanism of the plausibly modifiable predictor of procedural efficacy.

The reason for using a composite endpoint of ineffective CV as the primary outcome was based on the rationale of the concept from a clinical perspective. The initial procedural failure and early recurrence of AF after successful CV are equally undesirable outcomes for a patient. The high (42.6%) rate of ineffective CV was not unexpected in a cohort of consecutively enrolled patients and, together with the yield of risk factors, offers potential clinical implications. Certain patient groups are likely to have difficulties in sustaining sinus rhythm after CV due to clustering of risk factors. Our data suggests, e.g., that women with moderate kidney failure are at approximately 60% risk to relapse into AF within one month after elective CV. Such high-risk patients with debilitating symptoms might benefit from AFCA, while less symptomatic patients might benefit from deferral of rhythm management of AF altogether. One primary aim of this study was to create a basis for a predictive score for procedural efficacy of elective CV. As with other previous attempts, our study failed to deliver enough data for formulation of a scoring system (Disertori et al., 2010). However, Jaakkola et al. were able to overcome this obstacle in the FinCV cohort of patients with AF episodes lasting less than 48 hours undergoing CV and effectively created a scoring system (the AF-CVS Score) for ineffective acute CV, defined likewise as a failed CV or an early recurrence of AF (Jaakkola et al., 2017).

6.2 Intensity of anticoagulation and risk of thromboembolism after elective cardioversion of atrial fibrillation (II)

Our Study II results showed that in patients with adequate therapeutic VKA anticoagulation prior to rhythm conversion, the intensity of periprocedural anticoagulation is associated with the risk of stroke after elective CV in AF patients. Patients with INR values in the lower (2.0–2.4) therapeutic range at the time of the index CV had more strokes than patients with higher (≥2.5) therapeutic values. Furthermore, the patients with INRs in the low (2.0–2.4) therapeutic range had an increased risk for unstable postprocedural anticoagulation and subtherapeutic (<2.0) INRs. Strikingly, the analysis of the subcohort with comprehensive INR data demonstrated that almost every fourth patient experienced a drop in INR values to subtherapeutic (<2.0) levels, and these patients were also at an increased risk for stroke.

The extra stroke risk associated with elective CV in AF has been established in a multitude of trials (Bjerkelund et al., 1969; Weinberg et al., 1989; Arnold et al., 1992; Table 6). Anticoagulated patients undergoing elective CV are exposed to 1.5–4.5 -fold higher risk for stroke (Tables 2 and 6) in comparison with the general anticoagulation management of AF. The elevated risk persists for the first postprocedural month and subsequently settles to the general risk level until the next rhythm conversion is performed. Thus, patients with symptomatic AF undergoing serial CVs may actually be at increased risk for stroke for a major part of a year. Nevertheless, the current anticoagulation recommendations do not regard the extra risk associated with elective CVs as requiring special attention, although a considerable number of strokes occur after CVs (Palomäki et al., 2016). Notably, insufficient anticoagulation after CVs may partly have explained the poor outcome in the rhythm control arm of the AFFIRM study (Wyse et al., 2002). The optimal intensity of anticoagulation in elective CV in AF has not, in fact, been tested in a proper research setting. The contemporary anticoagulation guidelines regarding elective CV have been derived from trials investigating general anticoagulation for stroke prevention in AF (EAFT study group, 1995). Therefore, there is a consensus opinion but little evidence.

Our findings endorse the hypothesis that a more intensive periprocedural anticoagulation may reduce the risk of stroke after elective CV of AF and are in line with the results published in a previous trial (Gallagher et al., 2002). Together, the risk for stroke (0–0.1%) in these studies in more intensively anticoagulated patients appears numerically closer to the general stroke risk in anticoagulated AF patients (Table 2). Similarly, in the subanalysis of the RE-LY trial, AF patients with higher dosing (150mg twice daily) of dabigatran appeared to have a trend towards better efficacy in stroke prevention after elective CVs compared with patients with lower (110mg twice daily) doses (0.3% vs.

0.8%) (Nagarakanti et al., 2011). Although, the risk for major bleeds in anticoagulated patients appears to be inherently increased during the first month after elective CV compared to general management of AF (Tables 2 and 6), a significant increase in the rate of bleeding complications is unlikely in patients with temporarily more intensive periprocedural anticoagulation. For example, the rate of major bleeds in the 1995 EAFT study was 1 per 100 patient-years compared to 3 per 100 patient-years in patients with INR ranging between 2.0–2.9 and 3.0–3.9, respectively (EAFT study group, 1995). Furthermore, the trials investigating the effect of higher dose NOACs in patients with venous thromboembolisms have not exhibited an excess rate of major bleeds (0.1–0.3% per month), either (Schulman, et al., 2009; Büller et al., 2012). Thus, it might be plausible to increase the INR target range to e.g. 2.5–3.5 in VKA anticoagulation or NOAC anticoagulation to transitorily higher doses in the periprocedural period of elective CV for better safety outcomes. However, this setting has to first be tested in RCTs for definite conclusions.

A very important finding in our study was that the INR levels dropped below 2.0 in many patients during the critical postprocedural period after elective CV when the incidence of stroke is at its highest and proper anticoagulation is needed the most. This finding highlights the inherent issue with VKA anticoagulation: The unstable and often difficult-to-manage INR levels may lead to adverse outcomes. Clinicians may also exhibit more lenient behavior toward INR monitoring after a successful CV. The first INR control is often scheduled in two weeks after the CV, even though the weekly INR controls are most critical right after the rhythm conversion. NOACs are a favorable choice in this regard, since they exhibit more stable and reliable anticoagulation and have been linked to shorter delays to CV, although no survival benefit for use of NOACs over VKAs in elective CV exists. Another approach to improve stroke prevention after CV would be to pursue early rhythm conversion, since evidence suggests that prompt CV may be associated with a lower rate of adverse outcomes (Nuotio et al., 2014). This strategy would only benefit a small part of the AF community, however, due to the high rate of asymptomatic recurrences. Further clinical supervision and education for a more rigorous postprocedural INR monitoring in AF patients on VKAs is warranted for clinicians treating AF patients for this reason, NOACs are an increasingly prevalent solution to adequate postprocedural anticoagulation in AF patients, yet many patients are still using VKAs and require better management to avoid unnecessary strokes after elective CVs.

6.3 Optimal timing for cardioversion in atrial fibrillation (III)

The optimal timing of CV in AF was explored in Study III using a composite registry that included patients with both AF episodes lasting under and over 48 hours from all FinCV studies. The primary endpoint of composite adverse outcome was used to assess the rate of and predictors for both efficacy and safety outcomes of CV, which occurred in over one third of the cases. Most importantly, the risk of adverse events doubled in patients with an index AF episode lasting over 48 hours compared to patients with AF lasting less than 48 hours. The most favorable time for rhythm conversion is between 24 and 48 hours after detection of AF, according to our results.

The rate of efficacy outcomes, i.e., unsuccessful CV or recurrence of AF after successful rhythm conversion of CV, were within expectations and comparable with prior studies (Tables 4 and 5). Both efficacy endpoints were significantly associated with the delay between detection of AF and CV. This is consistent with prior studies regarding the procedural failure rate of CV, as Study I showed. The association between AF episode duration and recurrence rate of AF, however, has not previously been demonstrated in a large "real-life" cohort. Shorter AF duration has been linked with improved sinus rhythm maintenance in two small studies before, and only one of these enrolled consecutive patients (Dittrich et al., 1989; Frick et al., 2001). One small randomized trial, on the other hand, found no difference in the rate of permanent AF at 18 months follow up when AF patients with consecutive acute (<24h delay between detection of AF and rhythm conversion) and elective (4-6 weeks delay between detection of AF and rhythm conversion) CVs were compared (Hemels et al., 2006). Furthermore, prior studies have used a much more robust division of AF episode duration in their analyses. The specific division of duration of AF episodes into <24 hours and 24–48 hours, as well as two longer classes of symptom duration, is important, since evidence shows that differences exist in the risk stratification of short AF episodes lasting less than 48 hours. Moreover, a majority of CVs are performed for outpatients with acute (<48 hours) episodes of AF. The rate of procedural failure and recurrence of AF was lowest in patients with the index AF episode lasting 24–48 hours, and only 5% of CVs failed in this timeframe of AF duration. It is very interesting that the procedural efficacy was slightly lower in patients with the shortest AF episodes, although the mechanism for this finding is unclear. It is plausible that the identification and adequate management of underlying triggers, such as alcohol withdrawal symptoms, dehydration, hypokalemia or congestive heart failure, etc., may partly explain why the probability of successful CV increases after the first 24 hours (Mandyam et al., 2012; Krijthe et al., 2013/A; Sibley et al., 2015; Johansson et al., 2017). The cumulative effect of successive administrations of rate control medication such as beta-blockers may also play a role in the delay of the successful CV in the

short term. The difference in efficacy of sinus rhythm maintenance, however, was smaller between patients with AF episodes lasting less than 24 hours and 24–48 hours but much more considerable when comparing patients with AF episodes lasting under and over 48 hours. This is probably explained by a lesser degree of atrial remodellation due to the shorter AF duration.

The occurrence of adverse safety outcomes was scarce in this study and not associated with the timing of CV. Periprocedural mortality or acute arrhythmic complications have not been linked to the delay between AF onset and CV. Comparison of the postprocedural stroke rates between trials exploring rhythm conversion outcomes of acute (<48 hours) AF episodes and AF episodes lasting over 48 hours have suggested that patients with shorter AF episodes have fewer strokes (Airaksinen et al., 2013; Table 6). Furthermore, prompt CV of acute (<48 hours) AF episodes has been associated with a lower rate of stroke. It seems sensible to perform rhythm conversion in AF sooner rather than later to protect patients from excess stroke risk (Nuotio et al., 2014). Overall, our findings suggest that CV in anticoagulated AF patients is a relatively safe procedure, as the combined rate of adverse safety outcomes was less than 1% in a "real world" cohort of over 4300 CVs.

The occurrence of the primary endpoint of composite adverse outcome was mainly driven by the high rate of adverse efficacy outcomes, suggesting that a major effort to improve procedural outcomes should be focused on the prediction of procedural failure and AF recurrence. Our study yielded many viable risk factors for the composite adverse outcome, most of which, however, were not modifiable but rather represented high disease burden in a patient. Furthermore, only younger age was associated with a lower rate of adverse outcomes. Thus, our findings suggest a more conservative approach towards aging AF patients with a high burden of cardiovascular diseases referred for CV. If rhythm control is pursued, younger patients with debilitating symptoms should be more promptly cardioverted in the emergency department setting rather than referred for elective CV to avoid an increased risk for adverse events. Evidently, the risks and benefits of rhythm control treatment of AF have to be carefully weighed in each case, since survival benefit has only been demonstrated in very selected patients and rhythm management of AF has been associated with increased healthcare costs and risk for hospitalizations (Wyse et al., 2002; Marrouche et al., 2017; Poole et al., 2018). Furthermore, each separate CV always brings forth a temporary boost to the risk of stroke which is a very high price to pay for symptom control of AF.

6.4 Limitations

The FinCV studies have all the major limitations associated with retrospective research. Importantly, the recurrence rate of AF after successful CV and the duration of AF epi-

sodes may be underestimated, since asymptomatic AF is frequent. For this reason, all depictions of AF should be interpreted as symptomatic AF. However, this reflects actual clinical practice and is, thus, suitable for use in "real-life" research. The rate of thromboembolic events and mortality was low in our study for definite interpretations, and the thromboembolisms were not independently adjudicated. However, all events were diagnosed by attending neurologists and confirmed with imaging. Furthermore, all patients were living in the catchment area of the hospitals performing the index CVs and, thus, would not undergo diagnostic examinations or receive care in any other hospital for adverse events. Lastly, Study III comprised three different cohorts, enabling possible imbalance in the study population. Nonetheless, the protocols covering the gathering of data, definition of outcomes and management of AF and CVs were similar across all the studies.

6.5 Future prospects

CV has been a cornerstone of rhythm management of AF for over 50 years. With the aging of the population in the developed countries in Europe and the United States, AF will become increasingly prevalent and further burden their healthcare systems.

The rapid development of better AFCA techniques and hybrid therapy options will likely reduce the rate of AF recurrences in the future, although there are no prospective improvements in sight for increasing the probability of successful CV in AF.

Recent changes in anticoagulation recommendations in stroke prevention and the introduction of NOACs provide improved stability of anticoagulation for AF patients. Warfarin, however, will still be used in patients with prosthetic valves. Adequate anticoagulation has effectively reduced the risk of thromboembolisms in the AF population, yet the extra risk associated with CVs is unlikely to completely vanish, and improvements in the risk stratification schemes and anticoagulation regimes in this setting are needed to enhance patient care.

7 CONCLUSIONS

The occurrence of ineffective elective CV in AF is high; further research is needed to identify the patients best suited for rhythm management of AF (I).

The intensity of periprocedural anticoagulation is associated with the risk of stroke after elective CV in AF (II).

A shorter delay between AF detection and CV is associated with better patient outcomes (III).

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ORIGINAL PUBLICATIONS I-III