



## Full Length Article

## Intensity of anticoagulation and risk of thromboembolism after elective cardioversion of atrial fibrillation



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## ABSTRACT

**Background:** Elective cardioversion (ECV) for atrial fibrillation (AF) is associated with a relatively low risk of thromboembolic complications. However, the optimal intensity of anticoagulation for ECV is unknown. We sought to assess the risk of thromboembolism in low (INR 2.0–2.4) vs. high (INR  $\geq$  2.5) therapeutic range in a large retrospective cohort study.

**Methods:** This multi-centre “real world” study included 1424 ECVs in 1021 patients. The primary outcome was a stroke or a transient ischaemic attack (TIA) or a systemic embolus during the 30-day follow-up after ECV.

**Results:** Altogether 4 (0.3%) strokes, 2 (0.1%) TIAs and 2 (0.1%) bleeds were detected during the 30-day follow-up after ECV. No systemic emboli were detected. There were 2 deaths (0.1%), one associated with a stroke. Median time to stroke/TIA was 4 (IQR 9.5) days and the median CHA<sub>2</sub>DS<sub>2</sub>-VAsc-score was 2 (IQR 1.25) among patients with thromboembolic events. Mean INR at ECV was 2.7 (SD 0.54) in the study cohort. Patients with INR 2.0–2.4 at ECV had more thromboembolic events compared with patients with INR  $\geq$  2.5 (5/529 (0.9%) vs. 1/895 (0.1%),  $p = 0.03$ ). Comprehensive postprocedural INR data was available for 733 (71.8%) patients and 1007 cardioversions. At least one subtherapeutic (<2.0) INR value was detected within 21 days after 230 (22.8%) ECVs and this drop in INR level was associated with a higher risk for thromboembolic events compared with continuous therapeutic post-cardioversion anticoagulation (1.7% vs 0.3%,  $p = 0.03$ ).

**Conclusions:** Our results suggest that the intensity of periprocedural anticoagulation is associated with the risk of thromboembolic events after ECV.

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## 1. Introduction

Annual stroke rate in atrial fibrillation (AF) without anticoagulation is approximately 3% [1], but the risk can be reduced close to 1% with adequate anticoagulation [2]. Elective cardioversion (ECV) for >48 h AF

increases the risk of stroke substantially and the reported rates of thromboembolic events after ECV have varied between 3 and 7% in non-anticoagulated patients [3,4]. In spite of the increased post-cardioversion risk, the target INR (2.0–3.0) for ECV has been similar to the general anticoagulation recommendations in the long-term management of AF, and is based on consensus of observations made in observational studies investigating anticoagulation for stroke prevention in AF [5,6]. Current guidelines recommend a minimum of 3 weeks of therapeutic anticoagulation prior to ECV and 4 weeks after the procedure with frequent INR controls for warfarin [5]. However, little is known how periprocedural INR levels predict thromboembolic events.

In this study, we sought to evaluate whether the intensity of periprocedural anticoagulation with vitamin K antagonists in adequately anticoagulated patients predicts thromboembolic events after ECV of AF in contemporary clinical practice. Our hypothesis was that a more intense periprocedural anticoagulation is associated with a lower incidence of thromboembolic events.

**Abbreviations:** ECV, Elective cardioversion; AF, Atrial fibrillation; INR, International normalized ratio; TIA, Transient ischaemic attack; CHA<sub>2</sub>DS<sub>2</sub>-VAsc, Congestive heart failure, hypertension, age  $\geq$  75 years (doubled), diabetes mellitus, prior stroke, transient ischaemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless <65 years and no other risk factors); SD, Standard deviation; ICD-10, International classification of diseases; TTR, Time in therapeutic range; PINRR, Percentage of INR measurements in therapeutic range; ECG, Electrocardiogram; J, Joule; ISTH, International Society on Thrombosis and Haemostasis; IQR, Inter-quartile range; NOAC, Non-Vitamin K antagonist oral anticoagulant.

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## 2. Methods

The FinCV2 study ([<http://www.ClinicalTrials.gov>, identifier NCT02850679]) is part of an ongoing study program exploring thrombotic and bleeding complications of AF in Finland [7–11].

The current study is a prespecified report from FinCV2 study. Data was collected from patient registries in Turku University Hospital and two regional hospitals from a time period of 2003–2014 and in Kuopio University Hospital from a period of 2013–2015. Firstly, admission records and databases were used to review all patients above 18 years of age with >48 h AF who underwent ECV in the participating hospitals during the study period (ICD-10 code I48 for AF and TFP20 Nordic Classification of Surgical Procedures code for cardioversion). In addition, only patients living in the hospital catchment area were included in order to get the comprehensive follow-up data after the cardioversion. Each of the hospitals is the only referral hospital responsible for the acute care of patients presenting with cardiac or stroke events in their catchment areas.

Preliminary screening resulted in 2373 patients. Thus, the initial study cohort of 1271 patients with 1894 ECVs performed for AF with a duration >48 h was then manually identified. After the initial screening, all patient files were reviewed individually. Comprehensive data on duration of AF, relevant clinical characteristics and, medications, together with cardioversion and periprocedural anticoagulation details were collected from the patient records. The present study focused on patients with adequate warfarin anticoagulation (INR maintained within therapeutic range (2.0–3.0) consistently for  $\geq 3$  weeks, tested at least once a week) prior to the ECV.

To further evaluate the efficacy of warfarin management, the INR data for 30 days before and 30 days after ECV for patients treated in Turku University Hospital and 2 regional hospitals were explored from the laboratory database provided by Turku University Hospital laboratory service (TYKSLAB). The additional INR data was available for 733 patients and 1007 ECVs. TTRs (time in therapeutic range) and PINRRs (percentage of INR measurements in therapeutic range) were determined for the 30 days before and after ECV.

ECVs were performed according to the contemporary guidelines under general anaesthesia. During and after the procedure, ECG, blood pressure and oxygen saturation were monitored. Paddles or pads were positioned in antero-posterior or antero-lateral configuration. The energy ranged from 70 to 200 J with biphasic defibrillator devices and from 70 to 360 J with monophasic devices. A 12-lead ECG was controlled before and after the procedure. ECVs were performed by biphasic defibrillator after 2004.

### 2.1. Outcomes

For the present analysis, patients were divided into two groups according to the INR at the time of ECV; those with low (2.0–2.4) INR and those with high ( $\geq 2.5$ ) therapeutic INR. All patients were followed up for 30 days after the cardioversion and thromboembolic complications, systemic embolic events, bleeding events (categorized according to the ISTH criteria [12]) and mortality were recorded. The primary outcome was a fatal or non-fatal stroke or a transient ischaemic attack (TIA) adjudicated by the treating neurologist with appropriate imaging or systemic embolus confirmed by the attending vascular surgeon and by imaging.

### 2.2. Ethics

The study received approval of the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. The study conforms to the Declaration of Helsinki. Informed consent was not required due to the retrospective registry set-up of the study.

### 2.3. Statistics

The unpaired *t*-test or Mann-Whitney test was used to compare continuous variables and Pearson  $\chi^2$  or Fisher's exact test to compare categorical variables in the study subgroups, as appropriate. Normality in continuous covariates was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were reported as mean  $\pm$  standard deviation whereas skewed continuous variables were denoted as median [inter-quartile range (IQR)]. Categorical variables were reported with absolute and relative (percentage) frequencies. Baseline variables correlating at  $p < 0.10$  significance level with the dependent variable in univariate models were entered in multivariate logistic regression analysis. All tests were two-sided and significance was set at  $p = 0.05$ . 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.

## 3. Results

After patients with inadequate preprocedural warfarin treatment or partially unavailable INR data as well as patients receiving direct oral anticoagulants or low molecular weight heparin at the time of ECV were excluded, the final study population comprised of 1021 patients and 1424 ECVs (Fig. 1).

Altogether low (2.0–2.4) therapeutic INR and high ( $\geq 2.5$ ) therapeutic INR was measured at the time of 529 and 895 ECVs, respectively. Mean age of study patients was 64 (SD 9.8) and 419 (29.4%) patients were female. The median number of ECVs was 1 per patient with a range of 1–8 and the median time between two procedures was 136 (IQR 504) days. The mean INR at ECV was 2.7 (SD 0.54) and the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc-score was 2.0 (SD 1.6). Transoesophageal echocardiography was performed before 31 (2.2%) ECVs to exclude atrial thrombus. ECV was successful in 1205 (84.6%) cases.

### 3.1. Outcomes

At 30-day follow-up after ECV, 4 (0.3%) strokes and 2 (0.1%) TIAs were detected (Table 1). There were no systemic emboli, but one patient suffered a pulmonary embolism one day after a successful ECV. Additionally, one (0.1%) major bleed and one (0.1%) clinically relevant non-major bleed (1 traumatic subdural haemorrhage and 1 bleeding after dental procedure causing sinus perforation and requiring nasal tamponade) occurred during the follow-up. No spontaneous bleeds were detected. Two patients (0.1%) died during follow-up (1 associated with stroke and 1 with congestive heart failure, renal failure and infection). One death and one major bleed were detected in patients with INR 2.0–2.4 and INR  $\geq 2.5$  at ECV, respectively. Median time to a stroke/TIA was 4 (IQR 9.5) days after ECV. The median CHA<sub>2</sub>DS<sub>2</sub>-VASc-score was 2 (IQR 1.25) in patients suffering thromboembolic events. All thromboembolic events occurred after successful ECVs.

### 3.2. Intensity of anticoagulation and risk of thromboembolism

The risk for a thromboembolic event was higher in the group of patients with low (2.0–2.4) therapeutic INR at ECV than in those with INR  $\geq 2.5$  at ECV (5/529 (0.9%) vs. 1/895 (0.1%),  $p = 0.03$ ) (Fig. 2). Baseline characteristics of these patient groups were similar, but patients without prior AF episodes had more often ( $p < 0.05$ ) low therapeutic INR values at ECV (Table 2.) The results did not change when only the first ECV of each patient was analysed (5/389 (1.3%) vs. 0/632 (0%),  $p = 0.01$ ). In the 733 patients with additional INR data, mean TTR (2.0–3.0) was 76% during 30 days prior to ECV. The relatively low TTR value was explained by high (>3.0) INR values measured during the preprocedural time period.

During the 21 days after ECV, a drop in INR to subtherapeutic (<2.0) level was detected in 230 (22.8%) cardioversions and the risk for a

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