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

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Key words: atrial fibrillation; stroke; anticoagulation**;** therapeutic range; international normalized ratio

Abbreviations:

ECV = elective cardioversion; AF = atrial fibrillation; INR = international normalized ratio; TIA = transient ischaemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 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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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≥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_2DS_2-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≥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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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 >48h AF increases the risk of stroke substantially and the reported rates of thromboembolic events after ECV have varied between 3-7% 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.

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].

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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 >48h 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 >48h 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 ≥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

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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 200J with biphasic defibrillator devices and from 70 to 360J with monophasic devices. A 12-lead ECG was controlled before and after the procedure. ECVs were performed by biphasic defibrillator after 2004.

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 (≥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.

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

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Welfare. The study conforms to the Declaration of Helsinki. Informed consent was not required due to the retrospective registry set-up of the study.

Statistics

The unpaired t-test or Mann-Whitney test was used to compare continuous variables and Pearson x^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 ± standard deviation whereas skewed continuous variables were denoted as median [inter-quartile ranger (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.

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 (Figure 1).

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Altogether low (2.0-2.4) therapeutic INR and high (≥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_2DS_2-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.

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≥2.5 at ECV, respectively. Median time to a stroke/TIA was 4 (IQR 9.5) days after ECV. The median CHA_2DS_2-VASc-score was 2 (IQR 1.25) in patients suffering thromboembolic events. All thromboembolic events occurred after successful ECVs.

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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≥2.5 at ECV (5/529 (0.9%) vs. 1/895 (0.1%), p=0.03) (Figure 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 thromboembolic event was significantly higher in these patients than in those with all INR measurements ≥2.0 after ECV (1.7% vs 0.3%, p=0.03) (Figure 2). Correspondingly, the mean TTRs and PINRRs were lower in patients with a subtherapeutic INR during the 30 days after ECV when compared to those with all INRs ≥2.0 (55% vs 79%, p<0.01 and 45% vs 73%, p. <0.01, respectively). In a multivariate analysis, low (2.0-2.4) INR at ECV (OR 1.93, CI95% 1.38-2.69; p<0.01) predicted a drop in INR to subtherapeutic (<2.0) level within 21 days after ECV.

DISCUSSION

In this large retrospective multi-center study patients with low (2.0-2.4) therapeutic INR at ECV or those with subtherapeutic (<2.0) INR measurements within 21 days after ECV had an increased risk for thromboembolic events (Figure 2). Importantly, every fourth patient

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experienced a drop of INR to subtherapeutic level after ECV, and low periprocedural INR levels appeared to predict the drop in INR after ECV.

Modern oral anticoagulation has reduced AF-related stroke risk to 0.1-0.2%/month in the long-term treatment [2]. The risk of thromboembolic complications after ECV performed during therapeutic oral anticoagulation has ranged from 0.3% to 0.9% in previous trials [13-15]. This means that patients undergoing ECV are exposed to a 1.5-4.5 -fold higher risk for stroke during the post-cardioversion month compared to patients without a cardioversion and there is a clinical need to reduce ECV related strokes. The magnitude of the problem is illustrated by a recent finding that 6.4% of all strokes associated with paroxysmal or persistent AF are preceded by a cardioversion [10]. In line with this reasoning, inadequate pericardioversion anticoagulation may have contributed to the poor outcome in the rhythm control arm of the AFFIRM study [16].

Thrombus formation in the left atrial appendage is responsible for the majority of thromboembolic events after cardioversion. In spite of the solid theoretical background, several clinical trials have concluded that performing transoesophageal echocardiography to exclude thrombus formation prior to ECV does not reduce the rate of stroke compared to conventional anticoagulation regime [13,15]. Early cardioversion may, however, be advantageous in this respect, since the risk for stroke has shown to be low (0.1% per month) in patients undergoing cardioversion within 48 hours after the onset of AF during long-term oral anticoagulation [11]. This finding is probably explained by less atrial stunning and thrombus formation after the conversion of shorter episode of AF to sinus rhythm.

One important finding of our study was the high incidence of subtherapeutic INR values during the most vulnerable period of atrial stunning after the cardioversion. This finding may

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reflect the more floppy general attitude on anticoagulation after achieving the sinus rhythm and therefore assuming a lower risk of thromboembolism. The use of non-Vitamin K antagonist oral anticoagulants (NOACs) should help to ensure stable therapeutic periprocedural anticoagulation in patients with good drug compliance. The conventional dosing of NOACs has, however, provided no significant advantage over vitamin K antagonist anticoagulants in this setting, although numerically the event rates have been slightly lower and less delays to cardioversion have been reported [14,15,17].

The target pericardioversion anticoagulation level is based on consensus opinion and does not differ from the general anticoagulation recommendations in the long-term management of AF in spite of the higher temporary risk of thromboembolic complications after successful cardioversion. Our findings support the view that the higher intensity of periprocedural anticoagulation - even within the current therapeutic range - may reduce the risk of thromboembolic complications. These observations are in line with an earlier study where no embolic events were detected after 779 ECVs with periprocedural INR ≥ 2.5 whereas 7 (0.9%) embolic events occurred after 754 ECVs with INR <2.5 [18]. Similarly, the risk of thromboembolism was numerically lower (0.3% vs 0.8%) during chronic anticoagulation with high dabigatran dose (150mg twice daily) than with the lower dose (110mg twice daily) [19]. In the light of present and earlier findings it seems unlikely that a short period of more intensive anticoagulation causes redundant rise in the risk for bleeds during the peri- and post-cardioversion treatment [6], since the monthly rates for bleeds have been similar (0.1-0.3% per month) in trials investigating anticoagulation of non-valvular AF [2] and venous thromboembolism with higher doses of NOACs [20,21]. Nevertheless, the efficacy and safety of the more intensive periprocedural anticoagulation of ECV in AF needs to be assessed in a prospective randomized trial.

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This study has all the limitations of a retrospective study. The total number of embolic events is low for definite conclusions and an interruption of anticoagulation treatment occurred in two patients with thromboembolic events. Furthermore, comprehensive periprocedural INR data was unavailable in all patients reducing the sample size. Events were not independently adjudicated, however, all events were diagnosed by the treating neurologist with appropriate imaging or systemic embolus confirmed by the attending vascular surgeon and by imaging. Moreover, all patients were from the catchment area of the participating hospitals and thus all thromboembolic events are treated in the same hospital. Despite the limitations, we feel that this data can guide future research and treatment decisions in patients undergoing ECV.

CONCLUSIONS

Our results provide indirect evidence that the increased risk of thromboembolic events related to ECV might be reduced by more aggressive anticoagulation and careful follow-up during the periprocedural period. However, further research is needed to definitely assess the efficacy and safety outcomes of the hypothesis. Our study demonstrates the importance of rigorous and good quality INR control after a successful ECV in stroke prevention.

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Disclosures

All authors have approved submission of the manuscript, and the manuscript has not been published and is not being considered for publication elsewhere. The authors do not have any conflicts of interest in connection with the submitted article.

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Table 1. Characteristics of the thromboembolic events after ECV

	Event	Age/Sex	Time after ECV (days)	CHA_2DS_2-VASc -score	TEE	INR (ECV)	INR (Event)	Other
Pt 1	Stroke	53M	12	1	No	2.4	1.4	Traumatic subdural haemorrhage 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	-

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ECV= elective cardioversion; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 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); TEE = transoesophageal echocardiography; INR = international normalized ratio; Pt = patient; M = male; F = female; TIA = transient ischaemic attack

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Table 2. Baseline characteristics of patients with low (2.0-2.4) therapeutic INR vs high (≥2.5) therapeutic INR at ECV.

	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

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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 ischaemic 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 ischaemic attack

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Figure legends

Figure 1. Flow chart illustrating patient selection in the study.

AF = atrial fibrillation; ECV = elective cardioversion

Figure 2. 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).

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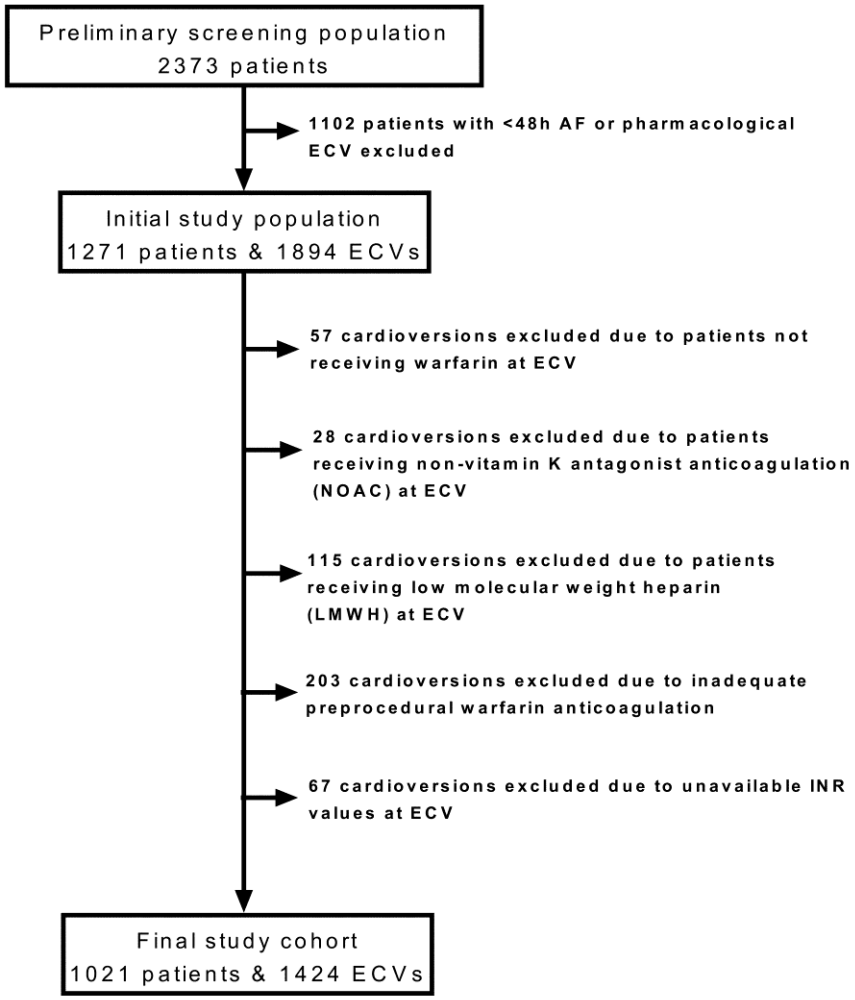

Fig. 1

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Figure 2.

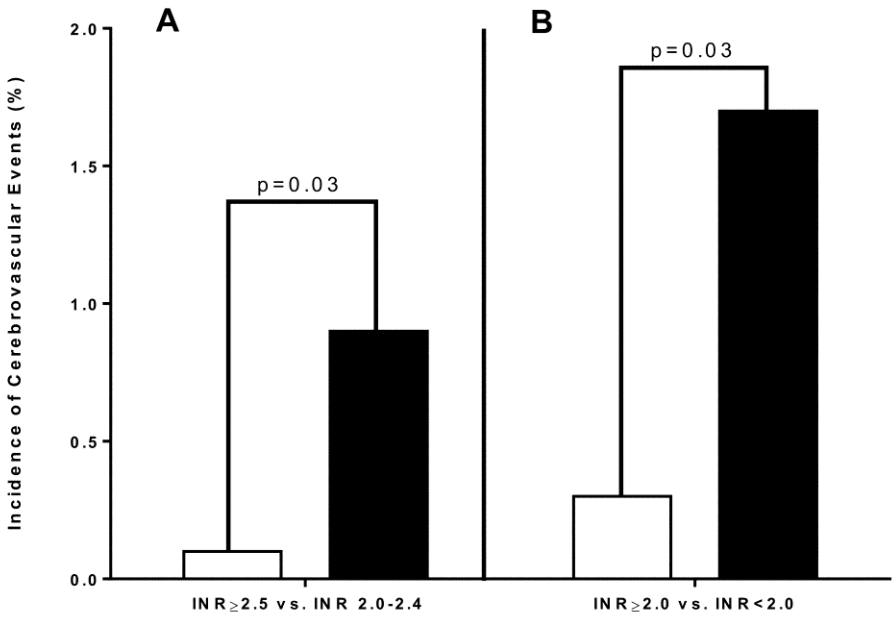

Fig. 2

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Highlights:

- Risk of thromboembolic events in cohort of AF patients undergoing ECV was explored.
- The incidence of thromboembolic events was 0.4%.
- Patients with INR 2.0-2.4 at ECV had higher risk than those with INR≥2.5.
- A drop in INR to low (<2.0) levels was detected after 22.8% cardioversions.
- The INR drop was also associated with an increased risk for a thromboembolic event.

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