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Poor anticoagulation relates to extended access times for cardioversion and is associated with long-term major cardiac and cerebrovascular events

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ABSTRACT

Background: Patients undergoing elective electrical cardioversion (ECV) for atrial fibrillation have a temporarily increased risk of thromboembolism. Current guidelines recommend adequate anticoagulation for ≥3 consecutive weeks precardioversion, i.e. consecutive INR values 2.0–3.0 in patients with vitamin K antagonists (VKA). We aimed to evaluate the occurrence and impact of subtherapeutic INRs precardioversion and to study factors associated with these unwanted fluctuations.

Methods: We recruited 346 consecutive patients undergoing elective ECV in the Maastricht University Medical Centre between 2008 and 2013. Predictors of subtherapeutic INR values were identified and incorporated into a logistic regression model.

Results: A subtherapeutic INR precardioversion occurred in 55.2% of patients. The only statistically significant predictor was VKA-naivety (Odds Ratio (OR) 4.78, 95% Confidence Interval (CI) 2.67–8.58, $p < 0.001$). In patients with ≥1 subtherapeutic INR precardioversion, time from referral until cardioversion was 91.1 ± 42.8 days, compared to 41.7 ± 26.6 days ($p < 0.001$) in patients without subtherapeutic INRs.

No thromboembolic events occurred <30 days after the ECV. Independent predictors for the combined endpoint of cardiovascular death, ischemic stroke and the need of blood transfusion ($n = 30$, median follow-up of 374 days) were coronary artery disease in the history (OR 3.35, 95%CI 1.54–7.25, $p = 0.002$) and subtherapeutic INR precardioversion (OR 3.64, 95%CI 1.43–9.24, $p = 0.007$).

Conclusions: The use of VKA often results in subtherapeutic INRs precardioversion and is associated with a significant delay until cardioversion, especially in patients with recent initiation of VKA therapy. Furthermore, subtherapeutic INR levels prior to ECV are associated with the combined endpoint of cardiovascular death, ischemic stroke and the need of blood transfusion.

1. Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is a major health problem, not merely due to its vastness but also because of the associated risks, in particular of thromboembolism (TE). Besides the intrinsic TE risk, there is an independent, transient risk of TE in AF patients in case of cardioversion. Of note, all types of cardioversion — i.e. spontaneous, pharmacological and electrical — carry a similar TE risk [1,2].

The temporarily increased TE risk pericardioversion is mainly believed to be caused by stasis of blood in the fibrillating atria, especially in the left atrial appendage. Even following restoration of sinus rhythm, mechanical dysfunction of the atria — so-called atrial stunning — may persist, thereby prolonging the temporary increased TE risk [3]. Thus, pericardioversion oral anticoagulation is warranted to significantly decrease the rate of thromboembolic complications from 5.3% to 0.8–1.0% [4,5].

Current international guidelines recommend adequate anticoagulation for at least three weeks prior, and four weeks following cardioversion in patients with AF of >48 h or of unknown duration [6]. When using vitamin K antagonists (VKA), this means achieving and maintaining an INR between 2.0 and 3.0 during the above defined pericardioversion window. However, the well-known VKA hurdles

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result in large inter- and intraindividual fluctuations of anticoagulation levels [7,8] and proof particularly challenging during initiation [9]. Importantly, sub- and supratherapeutic levels are clearly related to increased mortality and serious adverse outcomes, such as thromboembolism and major bleeding [8,10].

Furthermore, inadequate anticoagulation management can also cause a time delay to cardioversion [11–13] and thereby postpone alleviating AF related symptoms, which is usually the primary goal of cardioversion [14]. Whether the same delay has a significant effect on the total AF duration and consequent success of conversion to, and long-term maintenance of, sinus rhythm — explained by structural and electrical remodeling [11] — remains debatable [15–17].

The objective of this study is to evaluate the occurrence, extent and impact of subtherapeutic INR values prior to and following elective electrical cardioversion (ECV) and to study factors associated with these unwanted fluctuations.

2. Methods

2.1. Study design

We recruited consecutive unique patients with atrial fibrillation and flutter undergoing elective, direct current cardioversions between December 2008 and February 2013 in the Maastricht University Medical Centre in the Netherlands using the prospective Maastricht Cardioversion Registry. Ethical approval for the registry was obtained from the Institutional Review Board. Patients were eligible for inclusion given an age ≥18 years and persistent AF or atrial flutter confirmed by a 12-lead electrocardiogram (ECG). Exclusion criteria were AF duration <48 h or the need for urgent cardioversion because of hemodynamic instability.

Patients already using VKA were scheduled for weekly INR measurements and VKA-naive patients were prescribed acenocoumarol and referred to local Thrombosis Services. Our hospitals elective cardioversion protocol is in line with the international guidelines on AF recommending three weeks of adequate anticoagulation (INR 2.0–3.0) prior to and four weeks following cardioversion. We defined subtherapeutic anticoagulation as any INR < 2.0 from the moment the patient was referred for cardioversion.

On the scheduled day of cardioversion, a 12-lead ECG was performed to determine heart rhythm and a venous blood sample was drawn to determine INR and potassium levels. In case of an INR < 2.0 or significant potassium disturbances, cardioversion was postponed. In case of spontaneous conversion to sinus rhythm, cardioversion was canceled.

All cardioversions were carried out according to protocol. Cardioversion was performed by a cardiology resident using a biphasic waveform defibrillator (Medtronic LIFEPAK® Physio-Control 20) with anterolateral paddle position. Antero-posterior position could be preferred or necessary in selected patients, i.e. in patients with cardiac implantable electronic devices. In case of unsuccessful defibrillation, increasing energy levels were applied with a maximum of three attempts to restore sinus rhythm (200–300–360 J). Propofol or etomidate was used for sedation at the discretion of the anesthesiologist.

Cardioversion was considered successful upon sinus rhythm restoration and maintenance until discharge the same day. A standard follow-up outpatient clinic visit was planned one month following discharge or earlier if deemed clinically necessary. Follow-up was performed until June 2013.

2.2. Data analysis

Baseline demographics, medical history, medication use, echocardiographic findings and specific information about anticoagulation management were obtained from our digital hospital records. Sinus rhythm maintenance was evaluated during follow-up on the basis of all available 12 lead ECGs from the routine follow-up outpatient clinic visits. The occurrence of ischemic or hemorrhagic stroke was also assessed by reviewing the digital hospital records. Clinically relevant bleeding events were retrieved by identifying patients who needed blood transfusion.

During the course of this study, the target range for INRs in AF patients was 2.5–3.5 in the Netherlands, as recommended at that time by the Federation of Dutch Thrombosis Services. However, given the minimum INR value of 2.0 to safely perform a cardioversion, we only considered an INR < 2.0 as subtherapeutic. We reviewed all INR measurements between referral and performance of cardioversion. To evaluate a possible delay we calculated the time between referral and the actual cardioversion.

2.3. Statistical analysis

Data were analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are reported as mean ± standard deviation or median (25–75% quartiles) and categorical variables as number of observed patients (percentage). Chi square test was used for comparison of categorical variables between groups. Fisher's exact test was used if any expected cell count was <5. Normally distributed continuous variables were compared between two groups using the independent samples t-test, whereas not normally distributed continuous variables were compared using the Mann–Whitney U test. The distribution of continuous variables was visually checked for normality.

Predictors of subtherapeutic INR values were identified by incorporating all baseline characteristics with a significant univariate relationship and biologically plausible variables into a logistic regression model, with stepwise reduction of the model for variables with a p value <0.1. All variables in the final model with a p value <0.05 were considered significant independent predictors and were tested for interactions.

3. Results

A total of 386 patients were planned to undergo an elective ECV between 2008 and 2013. Of these, 40 (10.4%) were canceled and 29 (7.5%) were postponed on the day of cardioversion and performed later (see breakdown Fig. 1). Baseline rhythm before cardioversion was atrial fibrillation in 90% and atrial flutter in 10% of the patients. An antero-lateral paddle position was used in 92.5% of cardioversions. One shock was sufficient to restore sinus rhythm in 76% with a total success rate of electrical cardioversion of 90%.

3.1. Anticoagulation management before cardioversion

At least one subtherapeutic INR prior to the cardioversion occurred in 191 of 346 patients (55.2%), with an average of 2.8 ± 2.3 subtherapeutic INR values. The baseline characteristics of these patients and their adequately anticoagulated counterparts are displayed in Table 1. In 23.7% of the patients with inadequate anticoagulation management, the subtherapeutic INR was preceded by a supratherapeutic INR (>3.5). In addition, despite adequate anticoagulation prior to the cardioversion, 29 cardioversions (8.4%) were postponed on the planned day of cardioversion due to a subtherapeutic INR value and were performed later (Fig. 1). The time in therapeutic range (TTR) in the time period between referral and performing of cardioversion was 0.79 ± 0.12 in the patients with subtherapeutic INRs.

Possible predictors for subtherapeutic INR values precardioversion were assessed using logistic regression. After stepwise reduction of the model, the only remaining statistically significant predictor was VKA-naivety (Odds Ratio (OR) 4.78, 95% Confidence Interval (CI) 2.67–8.58, p < 0.001).

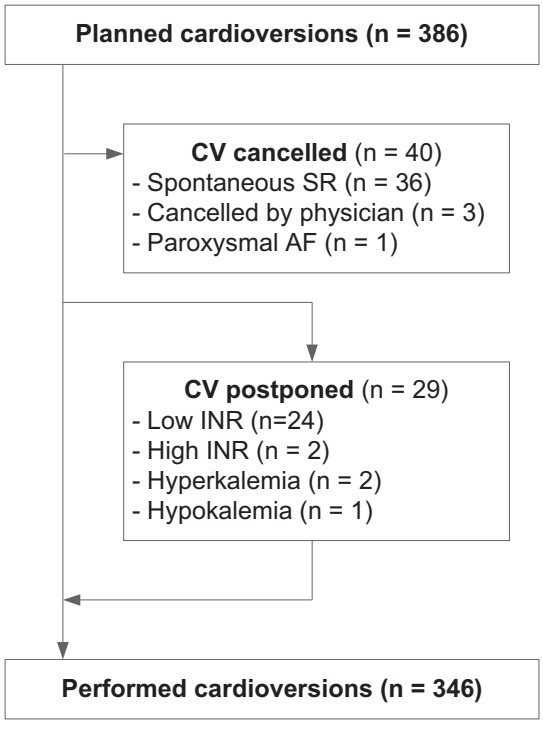

Fig. 1. Study flow chart.