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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).

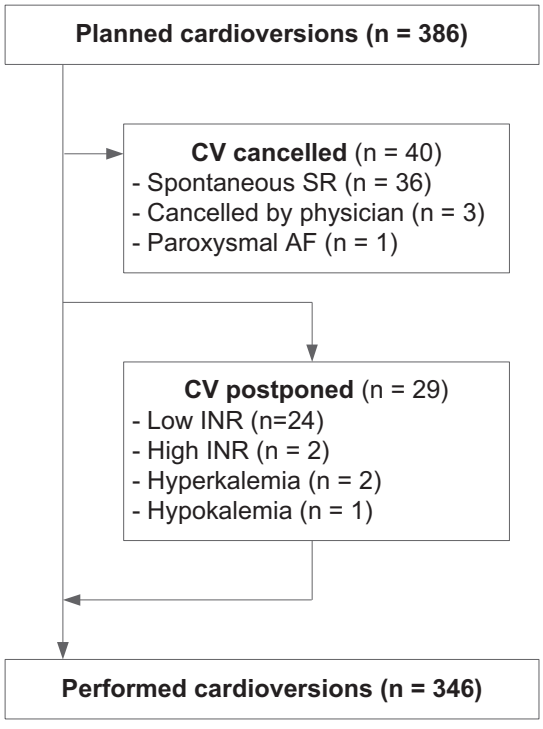

Fig. 1. Study flow chart.

Table 1
Baseline characteristics.

	Subtherapeutic INR (n = 191)[a]	No subtherapeutic INR (n = 155)	p value
Demographics			
Age at ECV	66.9 ± 10.5	68.0 ± 10.2	0.336
Age at first presentation AF[b]	65.6 ± 11.0	64.9 ± 11.8	0.598
Female sex	60 (31.4%)	55 (35.5%)	0.424
CHA_2DS_2-VASc			
0	15 (7.9%)	13 (8.4%)	0.694
1	44 (23.0%)	25 (16.1%)	0.079
2	39 (20.4%)	40 (25.8%)	0.181
3	41 (21.5%)	31 (20.0%)	0.715
4	22 (11.5%)	26 (16.8%)	0.086
5	19 (9.9%)	15 (9.7%)	0.582
6	9 (4.7%)	4 (2.6%)	0.300
7	2 (1.0%)	1 (0.6%)	0.688
8–9	0	0	
Body mass index	28.9 ± 5.3 (n = 176)	28.8 ± 5.1 (n = 145)	0.822
Patient history			
Hypertension	108 (56.5%)	85 (54.8%)	0.751
Heart failure	43 (22.5%)	32 (20.6%)	0.675
Type II diabetes	33 (17.3%)	16 (10.3%)	0.065
Coronary artery disease	60 (31.4%)	47 (30.3%)	0.827
Ischemic CVA	6 (3.1%)	7 (4.5%)	0.504
Hemorrhagic CVA	0 (0%)	1 (0.6%)	0.448
TIA	9 (4.7%)	11 (7.1%)	0.345
Hypercholesterolemia	41 (21.5%)	23 (14.8%)	0.114
Peripheral thromboembolism	6 (3.1%)	0	*0.035*[*]
COPD	12 (6.3%)	9 (5.8%)	0.854
OSAS	8 (4.2%)	6 (3.9%)	0.882
Echocardiography at baseline			
LVEF	47.6 ± 12.4 (n = 188)	51.2 ± 12.0 (n = 151)	*0.007*[*]
LA dimension, mm	45.5 ± 6.6 (n = 183)	45.9 ± 6.4 (n = 144)	0.575
Medication at baseline			
VKA-naivety	70 (37.2%, n = 188)	17 (11.0%, n = 154)	*<0.001*[*]
Acetylsalicylic acid	2 (1.0%)	3 (1.9%)	0.660
AAD			
Amiodarone	22 (11.5%)	28 (18.1%)	0.085
Sotalol	12 (6.3%)	14 (9.0%)	0.335
Flecainide	3 (1.6%)	7 (4.5%)	0.119
Beta blocker[c]	159 (83.2%)	119 (76.8%)	0.132
Digitalis	54 (28.3%)	42 (27.1%)	0.808
Verapamil/diltiazem	10 (5.2%)	15 (9.7%)	0.113
Isosorbide mononitrate	25 (13.1%)	20 (12.9%)	0.959
ACE-inhibitor	74 (38.7%)	56 (36.1%)	0.618
ATII receptor antagonist	61 (31.9%)	49 (31.6%)	0.949
Diuretic	92 (48.2%)	72 (46.5%)	0.751
Dihydropyridine	29 (15.2%)	19 (12.3%)	0.434
Statin	79 (41.4%)	75 (48.4%)	0.191

Abbreviations: AAD = anti-arrhythmic drugs, ACE = angiotensin converting enzyme, AF = atrial fibrillation, ATII = angiotensin II, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, ECV = electrical cardioversion, LA = left atrium, LVEF = left ventricular ejection fraction, OSAS = obstructive sleep apnea syndrome, TIA = transient ischemic attack, VKA = vitamin K antagonist.

[a] Data are presented as means ± standard deviation or no. (%). N = 191 or 155, unless otherwise specified.

[b] Confirmed by ECG recording.

[c] Sotalol excluded.

[*] Statistically significant, $p < 0.05$.

In patients with ≥1 subtherapeutic INR value prior to cardioversion, time from referral until cardioversion was 91.1 ± 42.8 days, compared to 41.7 ± 26.6 days ($p < 0.001$) in patients without a subtherapeutic INR value before cardioversion. The relationship between the number of subtherapeutic INRs and the time to cardioversion is depicted in Fig. 2. In VKA naive patients, time from referral until cardioversion was 84.5 ± 40.6 days, compared to 63.6 ± 44.0 days ($p < 0.001$) in patients already on vitamin K antagonists before referral to cardioversion.

3.2. Anticoagulation management postcardioversion

INR measurements 1, 2, 3, and 4 weeks after cardioversion could be retrieved in 87.9%, 85.5%, 72.8% and 37.0% of the patients, respectively. A subtherapeutic INR was found in 11.5%, 11.1%, 11.1% and 12.5% of these patients. In total, 30.0% of patients with available follow-up on INR

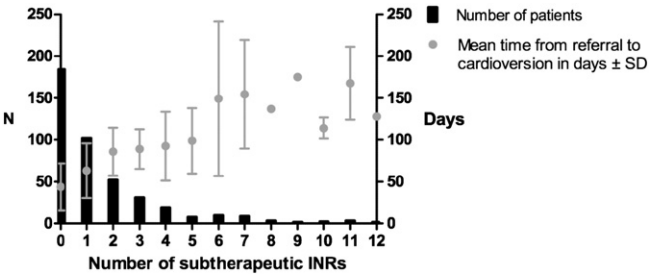

Fig. 2. Mean time from referral to cardioversion for patients subdivided by the number of subtherapeutic INRs (right y-axis) and the sample size per group (left y-axis).

values postcardioversion showed at least one subtherapeutic INR. Possible predictors for subtherapeutic INR values postcardioversion were assessed using logistic regression in a similar manner to the analysis of precardioversion subtherapeutic INRs. However, no statistically significant predictors could be identified.

3.3. Mortality, strokes and events requiring blood transfusion during follow-up

The median follow-up was 374 days (147–818 days), 31 patients (9.0%) were lost to follow-up. A total of 20 patients died during follow-up, of whom 5 died of cardiovascular causes. One death occurred 4 days after cardioversion. This patient lived alone and was found dead at home by her family. Autopsy showed severe coronary artery disease and myocarditis. Cerebral autopsy showed no signs of ischemic stroke, thus a direct relationship with the cardioversion could not be established. No other deaths occurred within 30 days after the cardioversion.

Ischemic stroke occurred in 5 patients (1.5%) during follow-up. None of the strokes occurred within 30 days following cardioversion (range of 204–1658 days). Thus, no direct relationship with the cardioversion could be established.

No hemorrhagic strokes occurred during follow-up. A total of 22 patients received blood transfusion postcardioversion. None of these occurred within 30 days after cardioversion. Median time to transfusion was 420 days (139–762 days).

For the combined endpoint of cardiovascular death, ischemic stroke and the need of blood transfusion ($n = 30$), statistically significant predictors were subtherapeutic INR values prior to ECV (OR 3.64, 95%CI 1.43–9.24, $p = 0.007$) and coronary artery disease in the history (OR 3.35, 95%CI 1.54–7.25, $p = 0.002$).

4. Discussion

In this cohort of patients undergoing elective electrical cardioversion we observed that subtherapeutic INR levels prior to cardioversion occurred frequently (55.2%) and were associated with a significant prolongation of the time from referral until cardioversion (91 vs. 42 days, $p < 0.001$). In nearly a quarter of these patients, the subtherapeutic INR value was preceded by a supratherapeutic INR value (>3.5). This implies that VKA dose adjustments should be made with precaution in patients on the waiting list for elective cardioversion, since one subtherapeutic INR value means a delay of cardioversion of at least 4 weeks.

Recent initiation of VKA was associated with inadequate INRs precardioversion. Time to cardioversion for VKA-naive patients was on average 85 days, compared to 64 days for patients already on VKA. This difference is probably accountable to the initial fluctuation of INRs after starting with VKA therapy and the time needed to acquire stable and adequate INR values.

Despite adequate anticoagulation management prior to the cardioversion, a substantial amount of patients (8.4%) had a subtherapeutic INR value on the day they were planned to undergo the cardioversion. This not only means that the patient has to wait for an additional 4 weeks at best, but also impedes reduction of the waiting list since another patient could have undergone the ECV on that day. This could partly explain the fact that the mean time to cardioversion in the group with adequate anticoagulation management prior to the cardioversion is 42 days, which is still much longer than the required 21 days according to the guidelines [6].

After cardioversion, we observed at least one subtherapeutic INR value in 30% of the patients with known anticoagulation follow-up. No thromboembolic events occurred within 30 days of the ECV, whereas we would have expected 4 events based on a prevalence of 0.8–1.0% [5]. Furthermore, no major bleedings occurred within 30 days of cardioversion.

Factors associated with the combined endpoint of cardiovascular death, ischemic stroke and the need of blood transfusion were subtherapeutic INRs prior to cardioversion and a history of coronary artery disease (CAD). CAD likely acts as a general marker of vascular weakness, resulting in both thromboembolism and bleeding events. Inadequate anticoagulation management prior to the cardioversion could be a marker of long term cardiovascular events, but could also be the underlying mechanism of these events via chronically suboptimal anticoagulation management. This is in line with a previous report showing that time in therapeutic range (TTR) in the initial phase after starting VKA therapy is highly predictive for the long term TTR [18]. Furthermore, subtherapeutic INRs precardioversion are comparable to "labile INR" as used in the bleeding risk score HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly) [19]. Patients with subtherapeutic INRs prior to cardioversion could therefore be seen as the patients who have a higher risk of developing bleeding events on the long run due to frequently occurring supratherapeutic INRs. Switching to a non-VKA oral anticoagulant drug (NOAC) could be beneficial in these patients by eliminating a fluctuating anticoagulation level, not only leading to a reduced access time for elective cardioversion but also possibly leading to less bleeding events by eliminating supratherapeutic INRs.

At the time of inclusion and follow-up of this study, the INR range used by the Federation of Dutch Thrombosis Services for patients with AF was higher than the international recommendations (2.5–3.5 vs. 2.0–3.0). This would in theory translate into a smaller number of subtherapeutic INR levels and subsequent postponement since there is a buffer for the occurrence of subtherapeutic INRs. Also meaning that the prevalence of subtherapeutic INRs can be higher than reported in this study in countries using the internationally recommended INR range. As of January 1st 2016, the INR target range in the Netherlands has been changed and is now the same as used internationally. This could mean that subtherapeutic INR values precardioversion will be more prevalent in the Netherlands from now on when compared to the results found in this study.

Our study highlights the struggles of achieving adequate anticoagulation with VKA in patients undergoing an ECV. The fluctuations in the level of anticoagulation, expressed in INR values, substantially affects the time to cardioversion. However, in our study, no adverse effects on patient outcomes were observed.

NOACs appear to be good alternatives to VKAs in patients planned for ECV, especially for those who are more likely to have subtherapeutic INR values, i.e. patients who have not yet started an anticoagulant drug. Both dabigatran and rivaroxaban have proven to be non-inferior to VKA treatment regarding safety endpoints in patients undergoing electrical cardioversion [5,20,21]. Additionally, NOACs have the advantage of not being dependent on a fluctuating anticoagulation level when taken as prescribed. This advantage can shorten both the time to cardioversion for the patient and the waiting list for elective cardioversion in general.

4.1. Limitations

Not all patients undergoing elective ECV could be included due to missing INR data. Furthermore, only clinically relevant major bleedings were taken into account since minor bleedings could not be uniformly obtained from the patient files.

At the time of inclusion and follow-up of this study, the INR range used by the Federation of Dutch Thrombosis Services was higher compared to international recommendations. This potentially translates into an underestimation of the prevalence of subtherapeutic INR values in countries using the internationally recommended INR range, like the Netherlands at present, possibly leading to an even longer mean time to cardioversion than reported in this study.

5. Conclusions

The use of vitamin K antagonists often results in subtherapeutic INR levels prior to elective ECV 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.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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