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Quality of individual INR control and the risk of stroke and bleeding events in atrial fibrillation patients: A nested case control analysis of the ACTIVE W study

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ABSTRACT

Introduction: Time in therapeutic range (TTR) for international normalized ratio (INR) is an accepted quality measure of anticoagulation control in patient populations, but its usefulness for predicting stroke and bleeding in individuals is not well understood.
Materials and Methods: In a nested case control analysis among ACTIVE W study patients, cases with stroke and cases with bleeding were separately matched with controls. Several anticoagulation quality measures were compared, overall and in a time-dependent manner.
Results: 32 cases with ischemic stroke and 234 cases with bleeding in the analysis were matched in a 4:1 ratio to 122 and 865 controls, respectively. Follow-up duration was 257 ± 154 days for the stroke analysis and 222 ± 146 days for the bleeding analysis. Compared with their respective controls, the study mean TTR of both stroke cases (53.9% ± 25.1 vs 63.4% ± 24.8; $p = 0.055$) and bleeding cases (56.2% ± 25.4 vs 63.4% ± 26.8; $p < 0.001$) was lower. Time below range for stroke and time above range for bleeding were only greater in the last month leading up to the event, not over the entire study period. Rather, over the entire study period bleeding cases spent more time below range than controls (26.8% ± 25.9 vs 20.8% ± 24.0; $p = 0.001$).
Conclusions: TTR was lower in individual AF patients with stroke or bleeding compared with matched controls in ACTIVE W. Maintaining a high TTR, with equal importance to avoid low and high INRs, is a relevant goal of individual patient treatment to prevent stroke and bleeding.

Introduction

Vitamin K antagonists (VKAs) reduce vascular events with an acceptable risk of bleeding in patients with atrial fibrillation (AF). The benefits of VKA therapy depend on maintaining the International Normalized Ratio (INR) within a relatively narrow range [1]. There is good evidence that the optimal INR target range is between 2 and 3 for AF patients [2]. Considering INR data at the time of the event, an INR below 2 decreases the benefit of VKA for prevention of strokes whereas an INR above 3 increases the risk for serious bleeding [3]. Due to the pharmacokinetic variability of warfarin and its interaction with many drugs and foods, it is difficult to maintain the INR in this therapeutic range despite regular INR measurements and dose adjustments [4].

The time in therapeutic range (TTR) is increasingly used as a measure of the quality of anticoagulation control. The approach proposed by Rosendaal to calculate TTR uses linear interpolation between successive INRs to summarize the quality of anticoagulation control over months or even years of VKA therapy for individuals or populations [5]. Multiple studies have demonstrated that mean (or median) TTR predicts stroke and bleeding outcomes in AF populations. In a post-hoc analysis of the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W), patients treated at centres which achieved a TTR above 65% derived a significant benefit from VKA therapy compared to the combination of clopidogrel and aspirin for the prevention of vascular events, whereas those treated with a VKA at centers with TTR of <65% derived no benefit [6]. Other studies also showed worse patient outcomes with lower values for TTR [7–9].

However, it remains uncertain how useful TTR is for predicting events in individual patients and whether timely changes in treatment based on observed TTR could avoid future adverse events. Further, there is uncertainty about the importance of time below range for predicting stroke and time above range for predicting bleedings, and what role INR variability and large INR fluctuations play. Therefore, the purpose of this study was to investigate the association between individual patients' TTR and other anticoagulation quality measures with stroke and bleeding events in AF patients enrolled in the ACTIVE W study, using a nested case control approach.

Abbreviations: ACTIVE W, the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; VKA, vitamin K antagonist; AF, atrial fibrillation; INR, international normalized ratio; TTR, time in therapeutic range; SD, standard deviation.

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Materials and Methods

The ACTIVE W randomized controlled trial compared VKA – which was the locally used vitamin K antagonist - with the combination of clopidogrel and aspirin for the prevention of vascular events in AF patients and was prematurely terminated because of superiority of VKA. The design and main results of the ACTIVE W have been reported in detail [10,11].

Study population

ACTIVE W patients were included in this analysis if they were randomized to VKA and did not have VKA permanently discontinued before the end of the study or before the occurrence of an ischemic stroke or major or minor bleeding. Two types of cases were selected:

1. Patients with ischemic stroke, and
2. Patients with a bleeding episode, either a major bleeding or a minor bleeding requiring adjustment of study VKA medication. Minor bleedings not requiring VKA therapy adjustment were not captured as an endpoint in ACTIVE W, since these are judged to be clinically less important.

For the analysis of ischemic stroke, controls (without ischemic stroke) were matched to cases based on the decile of age and prior history of stroke or transient ischemic attack. For the analysis of bleeding, controls were matched to cases (without major or minor bleed) based on the decile of age and prior history of bleeding. Deciles of age were 10 equally sized age groups based on the age in the overall ACTIVE W study: <57, 57–62, 62–66, 66–69, 69–71, 71–74, 74–76, 76–79, 79–82, >82 years.

The aim was to match each case to 4 controls, which was achieved for 88% of ischemic stroke and 78% of bleeding cases, and the remaining cases had 3 or less controls. To be able to compare time trends between cases and controls, the follow-up duration for controls was censored so that it was the same duration as the case to which they were matched.

Outcome definitions [10]

Ischemic stroke was defined as acute onset of neurological deficit compatible with occlusion of a major cerebral artery with exclusion of hemorrhagic stroke by imaging.

Major bleeding was defined as any bleeding requiring transfusion of at least two units of red blood cells or equivalent of whole blood, or associated with a variety of more severe outcomes.

Minor bleeding was any non-major bleeding requiring modification of the study drug regimen.

All major outcomes (not minor bleedings) were adjudicated by a blinded committee and all strokes were adjudicated by neurologists.

Anticoagulation quality measures

TTR was calculated with Rosendaal's linear interpolation method [4]. An interpolated INR value was assigned to each follow up day. TTR was the mean percentage of days that the INR for an individual patient was in the therapeutic range of 2–3. Time off VKA therapy was censored, including the first 4 weeks after restarting. We also calculated the proportion of time below the therapeutic INR range, proportion of time above the therapeutic range, the mean INR of both the actual and the interpolated values, and the standard deviation (SD) of the mean INR of both the actual and the interpolated values. Finally, to further explore the role of INR variability, we calculated the proportion of large leaps (>0.5, >1.0 and >1.5 INR units) between consecutive INR values, not on an individual level but in the overall groups.

Statistical analysis

Statistical analyses were performed with SPPS statistical software (SPSS Inc, release 14.0.1). Individual anticoagulation quality measures are reported as mean ± SD, and individual proportions of INR leaps as median (10th - 90th percentile). TTR, time below range, time above range and mean INR were also calculated per month leading up to the event. Individual anticoagulation quality measures were compared between cases and controls using linear mixed models to take into account the selection of matched controls. When more than one individual anticoagulation quality measure was significantly different in univariable analysis, multivariable conditional logistic regression was done to assess which measure had the most significant independent effect. Conditional logistic regression was used to account for the random effect of matching.

Ethical approval

The ethics committees at all ACTIVE W study sites approved the study and all ACTIVE W study participants signed informed consent.

Results

There were 42 patients with an ischemic stroke and 305 with either a major or minor bleeding among 3371 patients who were randomized to VKA in ACTIVE W. Of these cases, 7 cases with ischemic strokes and 41 with bleeding were excluded from further analysis due to absence of INR data and respectively 3 and 30 additional cases due to failure to find any controls based on our matching criteria. Therefore, 32 cases with ischemic stroke and 234 cases with bleeding were included in the analysis and were matched to 122 and 865 controls, respectively. Follow-up duration was on average 257 ± 154 days for the stroke analysis and 222 ± 146 days for the bleeding analysis, and was similar in cases and controls (Table 1).

Table 1
Comparison of individual anticoagulation quality measures between cases and matched controls.

	Bleeding			Ischemic stroke		
	Bleeding	Control	p-value	Stroke	Control	p-value
N	234	865		32	122	
Follow-up duration (days)	220 ± 148	222 ± 145	0.792	259 ± 171	256 ± 150	0.918
TTR (%)	56.2 ± 25.4	63.4 ± 26.8	<0.001	53.9 ± 25.1	63.4 ± 24.8	0.055
Time below range (%)	26.8 ± 25.9	20.8 ± 24.0	0.001	26.9 ± 25.3	22.0 ± 22.7	0.295
Time above range (%)	17.0 ± 21.3	15.7 ± 20.6	0.424	19.2 ± 18.6	14.5 ± 18.2	0.199
Mean INR*	2.51 ± 0.64	2.48 ± 0.50	0.466	2.49 ± 0.61	2.43 ± 0.38	0.475
Mean Time between INRs (days)	21.6 ± 12.5	25.4 ± 15.3	0.001	20.7 ± 11.3	22.9 ± 12.4	0.334
SD of mean INR	0.74 ± 0.50	0.65 ± 0.40	0.001#	0.88 ± 0.59	0.64 ± 0.36	0.014#

Results are group mean ± standard deviation.
* Patients with only one INR value were included in the calculation of mean INR and numbers were higher for ischemic stroke (34) and their controls (128) as well as for bleedings (261) and their controls (963). # Comparisons were tested using the coefficient of variance ([SD of the mean INR / mean INR] x 100) rather than the actual SD value, to standardize values.