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Clinical manifestations and outcomes of severe warfarin overanticoagulation – from the EWA Study

Running title: Relevance of Severe Warfarin Overanticoagulation

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Abstract

Introduction

Severe warfarin overanticoagulation is a risk factor for bleeding, but there is little information on its manifestations, prognosis and factors affecting the outcome. We describe the manifestations and clinical outcomes of severe warfarin overanticoagulation in a large group of patients with atrial fibrillation (AF).

Materials and methods

All international normalized ratio (INR) samples (n=961 431) in the Turku University Hospital region between 2003-2015 were screened. A total of 412 AF patients with INR ≥9 were compared to 405 patients with stable warfarin anticoagulation for AF. Electronic patient records were manually reviewed to collect comprehensive data.

Results

Of the 412 patients with INR≥9, bleeding was the primary manifestation in 105 (25.5%). Non-bleeding symptoms were recorded in 165 (40.0%) patients and 142 (34.5%) had no symptoms. A total of 17 (16.2%) patients with a bleed and 67 (21.8%) without bleeding died within 30 days after the event. Intracranial haemorrhage strongly predicted death within 30 days. Other significant predictors were non-bleeding symptoms, active malignancies, recent bleed, history of myocardial infarction, older age, renal dysfunction and a recent treatment episode.

Conclusions

Bleeds are not the major determinant of the poor prognosis in severe overanticoagulation, as coincidental INR≥9 findings also associate with high mortality.

Key words: atrial fibrillation, anticoagulation, bleed, complication, warfarin

Key messages:

- Only a quarter of AF patients with INR ≥ 9 suffered a bleeding event and the clinical manifestation of INR ≥9 had a significant impact on patient outcome.
- The 30-day mortality rate in patients with INR≥9 was high ranging from 9.2% to 32.7%.
- Several significant predictors of 30-day mortality after INR ≥9 were identified.

Introduction

Anticoagulants are the most common reason for emergency department visits due to adverse drug effects (1). International normalized ratio (INR) fluctuations are common during long-term warfarin anticoagulation and high INR values associate with major bleeding complications as well as increased mortality (2-6). However, causes of death in large atrial fibrillation (AF) trials are mostly related to factors other than bleeding (7). In our previous report we identified several risk factors for very high INR values (≥9) in patients with AF (8). Nevertheless, little is known about the clinical manifestations of excessive warfarin anticoagulation (EWA) or the outcome of these patients, especially in patients without bleeding complications. The aim of our study was to investigate the clinical manifestations and outcome of severe warfarin overanticoagulation (INR ≥9), to identify risk factors for short-term mortality and to study the relationship between clinical manifestation and patient outcomes. Studies focusing on severe overanticoagulation are scarce with limited number of patients and thus the present EWA Study provides novel and clinically relevant information on this phenomenon(5, 6).

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Materials and Methods

This study is a prespecified analysis of the Excessive Warfarin Anticoagulation study (The EWA Study, ClinicalTrials.gov Identifier: NCT02761941) which belongs to a series of study protocols assessing anticoagulation-related complications in the treatment of AF (8-10). In this study, we investigated a patient group of 412 patients with severe overanticoagulation, defined as INR ≥ 9, during warfarin treatment in patients with AF (The EWA Group). Patients were identified with computer searches

from Turku University Hospital and Turku City Hospital laboratory database of 961 431 INR samples between 2003-2015. From this database, we also identified a Control group including all patients (n=405) with AF on long-term (at least 730 days), regularly controlled (maximum INR test interval 60 days) warfarin anticoagulation without INR elevations >4. The event date used for data collection in the Control group was the date with the highest INR value (between 2.7-4.0) in each patient. Detailed patient selection criteria and the patient characteristics are described in our previous report on the EWA Study (8). After initial screening process, all individual electronic patient records were reviewed using a standardized protocol to collect specific information on clinical manifestations and patient management during the high INR event. The short- and long-term outcomes were also recorded, as well as a 90-day follow up on thromboembolic and bleeding complications. Mortality data was collected from the Official Statistics of Finland managed by the National Statistical Service in Finland.

Definitions

Recent antibiotic or antifungal therapy included antibiotic therapy during the preceding 14 days of the index event date or antifungal therapy in the preceding 7 days. Alcohol abuse was defined as an alcohol related diagnosis or a hospital/health center visit due to excessive alcohol use. Recent medical treatment was defined as an outpatient clinic visit with or without hospitalization during the preceding 30 days. Patients living independently at home without requiring outside help in everyday life were classified as independent. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation to classify renal function according to KDIGO (Kidney Disease Improving

Global Outcomes) clinical practice guidelines (11). The definition of intracranial bleed included intracerebral, subarachnoid or subdural bleeding event. Recent bleeding event included all bleeds in the preceding 30 days that were reported by the patient or led to either hospitalization or outpatient clinic visit. All bleeding events during severe overanticoagulation were classified using the International Society on Thrombosis and Haemostasis / Scientific and Standardization Committee (ISTH/SSC) bleeding score(12). Patients suffering from other than bleeding-related symptoms (e.g. shortness of breath, fever or nausea) were assigned to the Other symptoms-group.

Statistical analysis

Continuous variables were reported as mean ± standard deviation if they were normally distributed, and as median [inter-quartile range (IQR)] if they were skewed unless stated otherwise. Categorical variables were described with absolute and relative (percentage) frequencies. Chi-square test and Fisher's exact test were used for categorical variables as appropriate. For all variables with more than 0.5% missing data, the exact number of patients with missing data is marked in the table. A binary stepwise logistic regression analysis (backward Wald) was performed to identify independent predictors of 30-day mortality and bleeding complications in patients with very high INR values. Variables strongly correlated with the dependent variable by univariate analyses ($p < .1$) were entered in the model as covariates. We included prior myocardial infarction and age over 75 years in the multivariate model and excluded coronary artery disease and not-independent -living due to significant intercorrelations. All tests were two-sided and statistical significance was set at 5%. Kaplan-Meier survival curves were constructed to display the time-to-

event relationship for the occurrence of death. This manuscript was written following STROBE guidelines for the reporting of observational studies(13). Statistical analyses were performed with SPSS software (version 23.0, SPSS, Inc., Chicago, Illinois) and SAS software (version 9.2, SAS Institute, Inc., Cary, North Carolina).

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland. Informed consent was not required, because of the register-based nature of the study. The study complies with the Declaration of Helsinki as revised in 2002.

Results

Severe excessive warfarin anticoagulation was observed in 412 AF patients (The EWA Group) comprising 3.0 % of all 13618 patients living in the Turku University Hospital region with at least one INR value of ≥2 as an indirect marker of warfarin anticoagulation. The previous INR value before the event was 2.72±0.37 in the Control Group and 3.04±1.44 in the EWA Group (p<.001).

Manifestations

Symptoms other than bleeding were recorded in 165 (40.0%) patients, whereas severe overanticoagulation was a coincidental finding without any symptoms in 142 (34.5%) patients. Bleeding was the primary clinical manifestation of EWA in 105 (25.5%) patients. Only 4 patients (1.0%) in the Control group suffered a bleeding event on the index event date. Patient characteristics according to EWA manifestation type are presented in Table 1.

A total of 112 bleeding events were observed in 105 patients during severe overanticoagulation. Major bleeds (ISTH 3-4) comprised 49.1% of all bleeds. A third of all bleeds (33.0%) were from the gastrointestinal-tract, half of which (n=19) were severe (ISTH 4). Cutaneous bleeds, urinary tract bleeds or nosebleeds comprised 41.1% of all bleeds, the majority of them being classified as minor (ISTH 1-2). Only 5 patients suffered an intracranial bleeding event. Bleeding types, frequencies and severity classifications are listed in Table 2. Independent predictors of bleeding complications associated with EWA in a multivariate analysis were use of tramadol (OR 3.63; 95% confidence interval (CI) 1.28-10.3, p=.015) and a bleeding event within 30 days before EWA episode (OR 5.87; 95% CI 1.93-17.9, p=.002), while a history of malignancy was of borderline significance (OR 1.67; 95% CI 0.99-2.81 p=.053).

In EWA episodes without symptoms, previous INR was >3 in 29.6% of the patients (n=42, mean INR 2.91 (95% CI 2.69-3.14)) and the median interval between the previous sample and EWA was 15 [IQR 19] days. Previous INR was >3 in 24.8% (n=26, mean INR 2.67 (95% CI 2.46-2.89)) of the patients with bleeding symptoms, and in 38.8% (n=64, mean INR 3.38 (95% CI 3.13-3.62)) of patients with non-bleeding symptoms, while the INR sample intervals were 16 [IQR 26] and 9 [IQR 15] days respectively.

Treatment

Warfarin was temporarily or permanently discontinued in all patients with severe overanticoagulation. Vitamin K (oral, intramuscular or intravenous) was administered in 353 (85.7%) patients with an EWA episode, without statistically significant

difference between Bleeding- (88.6%, n=93), Other symptoms- (85.5%, n=141) and No-symptoms groups (83.8, n=119) (p=.568). Other medications (prothrombin complex concentrate, solvent detergent (S/D) treated human plasma or tranexamic acid) were used to counteract overanticoagulation in 41.9% (n=44) of patients with a bleeding event, 5.9% (n=4) without symptoms and 29.4% (n=20) in patients with symptoms other than bleeding. Five (4.8%) patients with bleeding complications did not receive any drugs to reverse warfarin effect.

Outcomes

The 30-day mortality rate was 20.4% (n=84) in the EWA Group and 0.2% (n=1) in the Control Group. A total of 17 (16.2%) patients with bleeding as the primary symptom and 67 (21.8%) without a bleed died within 30 days of severe overanticoagulation event. Bleeding as the clinical manifestation of the EWA episode did not have a statistically significant effect on short-term outcome in the multivariate analysis. Nearly a third (n= 54, 32.7%) of patients presenting with symptoms other than bleeding died within 30 days after EWA. Coincidental symptomless finding of INR ≥9 was associated with the best 30-day outcome, as there were 13 deaths (9.2%) within 1 month of EWA. At 12 months, the mortality rates were 40.5% (n=167) in the EWA Group and 1.7% (n=7) in the Control group. The survival advantage of the Control group over EWA group persisted through long-term follow up and at 4 years, 20 patients (4.9%) had died in the Control group and 257 (62.4%) in the EWA group. The cumulative survival analysis for both groups, as well as for each manifestation type of EWA is presented in Figure 1.

Independent predictors of 30-day mortality in patients with EWA are presented in Table 3 and the results of the univariate analysis in Supplementary table 1. Intracranial haemorrhage was the only bleed to independently predict short-term mortality, as no other bleeding type (even the most severe [ISTH class 4]) predicted death in 30 days after EWA. Only 8 (1.9%) patients suffered an ischaemic stroke and one patient (0.2%) had a peripheral embolism in the 90 days following the EWA episode. There was no association between the use of vitamin K or other drugs used for warfarin reversal, and thromboembolic complications, short-term mortality or duration of hospital stay.

Discussion

To our knowledge, the current observational study is the largest analysis on severe warfarin overanticoagulation. Our observational study shows that severe overanticoagulation during warfarin treatment associates with high mortality in patients with AF, even when the high INR value is detected in routine controls without any symptoms. We identified several clinical risk factors for 30-day mortality as well as for bleeding complications during EWA. Our results suggest that even though very high INR predisposes to severe bleeds, the majority of deaths are explained by other factors than bleeding complications – with the obvious exception of intracranial bleeds (5). Long-term follow-up revealed a persisting difference in mortality rate between the groups.

The observed high mortality of patients experiencing non-bleeding-related symptoms during the EWA event may be explained with the poor prognosis of the underlying critical illnesses which may cause INR elevations even without warfarin (14).

Therefore it was not a surprise that these patients had a 4-fold increase in the risk of death within 30 days and the mortality rate was very high (35.1%). Even though the poor outcomes of these critically ill patients explain the high overall mortality associated with EWA, it was unexpected that bleedings - except for intracranial haemorrhages - did not predict short-term mortality. Our findings in these patients with extreme anticoagulation intensity are in line with a recent meta-analysis by Gómez-Outes et al reporting that only 6% of deaths in modern anticoagulation studies in AF patients are caused by bleedings (7). Also in accordance with previous studies, intracranial bleeding event during EWA was the strongest predictor of 30-day mortality in our study (4, 15).

Among all clinical manifestation types of EWA, subjects with coincidental asymptomatic finding of INR value ≥ 9 had the best prognosis. This is expected, since these EWA episodes were detected in routine controls before symptomatic complications had occurred and the overanticoagulation was less frequently related to acute illness. Nevertheless, to put the better prognosis of this patient group in perspective, the 30-day mortality rate (9.2%) after symptomless INR ≥9 episode was much higher than for example after acute ST-elevation myocardial infarction (.9%-3.1%) in contemporary clinical trials (16, 17). The poor prognosis of all EWA manifestation types highlights the importance of recognizing the previously reported clinical risk factors for severe overanticoagulation(8).

As we have reported previously, hospital treatment episodes or emergency department/health care center visits independently predict severe overanticoagulation in the following 30 days(8). Our current results show that these

treatments episodes are also independent predictors of 30-day mortality in this patient group. The medical condition itself in combination with possible operations and medications (such as antibiotics or antifungals) used for managing the condition all probably contribute to the worse outcome of these patients. This finding highlights the importance of frequent and systematic INR controls during and following these treatment episodes.

The predictors of overanticoagulation describe the characteristic of patients in each subgroup (Table 1) and reflect the underlying mechanism of overanticoagulation (8). Comorbidities such as renal failure, heart failure or treatment of an active disease process prior to the overanticoagulation (antibiotics or antifungals, recent medical treatment) were logically most frequent in the “Other symptoms” group. Alcohol consumption and active malignancies were most common in patients with bleeding symptoms and mechanical heart valves and active smoking in asymptomatic patients.

Interestingly a bleeding event during EWA did not have an effect on 30-day mortality, but a prior bleeding event (in the preceding 30 days) increased the risk 3.4-fold. This increased risk of patients with recent bleeding events is probably related to underlying comorbidities and acute diseases, which may predispose to bleeding events even during lower anticoagulation intensity. Furthermore, the consequential treatment interventions may also have an effect on prognosis when INR level later reaches ≥9. This finding emphasizes the importance of anticoagulation stability in patients who are prone to bleedings during warfarin treatment.

As expected, active malignancies independently predicted short-term mortality after EWA, since cancer associates with poor prognosis also in patients without warfarin. As active malignancies have also been shown to predict severe overanticoagulation, the risks and benefits have to be weighted carefully when considering warfarin for these patients (8). Moreover, patients with a history of myocardial infarction and AF are known to be at increased risk of cardiovascular death (7, 18). When these patients with cardiovascular diseases experienced an EWA episode, the risk of 30-day mortality was high (2.9-fold) compared to patients without a history of infarction.

Older age (≥75 years) was expectedly an independent predictor of short-term mortality. Different acute conditions in elderly patients – such as dehydration or infections – may cause only subtle and nonspecific symptoms that may delay diagnosis and treatment interventions(19). Besides being a well established risk factor for bleeding and all-cause mortality, renal impairment is also a risk factor for severe overanticoagulation in AF patients (8) (20, 21). Considering this background, it was a logical finding that there was a 2-fold increase in the risk of death after EWA in patients with severe renal impairment (eGFR<30).

The causes of death are often multifactorial even in patients with a bleeding event and are subject to interpretation for several reasons. Determining the causalities and associations of different comorbidities in the process is a subjective interpretation often even after autopsy. For instance, active bleeding is a prothrombotic condition, which can modify the clinical presentation of the disease process in the final stages of life, thus obscuring the significance of overanticoagulation and bleeding.

Recent bleeding event is a well-established risk factor for subsequent bleeding in anticoagulated patients reflecting their general susceptibility to bleeding(22, 23). As the intensity of anticoagulation increases, the threshold for haemorrhages is lowered and bleedings should manifest more easily in patients with a history of bleeding(24). In line with this reasoning, recent bleeding event was the strongest (5.9) risk factor of bleeding complication during EWA episode. Even though the rate of major bleeding events in our study was higher than in contemporary AF trials due to the extreme anticoagulation intensity, the majority of patients did not experience bleeding during the EWA episode (4, 7, 25-28). Of note, INR elevations seem to develop rapidly prior to the bleeding event and thus it may be challenging to prevent bleeding complications by more frequent INR controls to detect overanticoagulation before bleedings become evident (29). Furthermore, majority of bleeding events in anticoagulated patients occur during therapeutic anticoagulation intensity from occult bleeding sites revealed already by low intensity anticoagulation (4, 30). This may also explain the finding that recent initiation of warfarin treatment was not an independent risk factor for bleeding in our study, as most bleedings in this scenario probably occur before INR reaches the level ≥9 (31, 32). Moreover, extreme warfarin anticoagulation intensity did not have an effect on the bleeding sites since bleeding types were similar to those in several earlier anticoagulation studies (3, 30, 31, 33-36).

It would be straightforward to think that the standard treatment of administering vitamin K would benefit these patients. In accordance with previous reports, the administration of vitamin K or other counteracting drugs had no effect on occurrence of complications (death, thromboembolism or length of hospital stay) (5, 37). It

should be noted, however, that most of the patients received vitamin K and it was impossible to analyze reasons for not using vitamin K in the retrospective study setting.

Strengths and limitations

The strengths of this study include exceptionally good coverage of all INR samples collected in the southwestern Finland (475 580 inhabitants). Turku University Hospital laboratory service provider (TYKSLAB) performs all the INR measurements regardless of the place of residence in the district. All the major complications related to EWA episodes are treated in the same hospitals where our study data was also gathered. Statistics of Finland is the official governmental agency, whose purpose is to store reliable and up-to-date data on the death rate and causes of death in Finland. In addition, the vast majority of people living in the southwestern Finland tend not to move to elsewhere.

This study has all the inherent limitations of the retrospective study. As the data was collected by study personnel retrospectively, we had to rely on the data and diagnoses recorded by physicians treating the patients. Treatment decisions were at the treating physicians' discretion and factors not covered by the case report form may affect the results. Warfarin dosage and level of adherence to medication were not available. Despite these limitations, findings from our "real world" study offer solid observations on how these frail patients were treated and what affected their outcome in short and long term.

Conclusions

Severe overanticoagulation is a dangerous complication of warfarin treatment for AF and it appears that bleeding is not the major determinant for the poor prognosis. Some risk factors for excessive anticoagulation are modifiable, emphasizing the importance of identifying high-risk-patients and considering alternative treatment strategies in an attempt to improve treatment safety.

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Table 1 legend:

$CHA_2DS_2$2-VASc, Congestive heart failure, Hypertension, Age 75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); eGFR, estimated glomerular filtration rate (ml/min/1.73 m2); SD, standard deviation

[a]Data missing on 27 patients (3.3%)

[b]Living at home independently without outside help in daily routines

[c]Hospitalization or outpatient visit during the preceding 30 days

[d]Alcohol related diagnosis or a hospital/health care center visit due to alcohol use

[e]Bleeding event during the preceding 30 days

[f]Antifungal therapy during the preceding 7 days

[g]Antibiotic therapy during the preceding 14 days

Table 2 legend:

ISTH, International Society on Thrombosis and Haemostasis / Scientific and Standardization Committee

[a]Haemoptysis, retroperitoneal bleed, outer ear bleed

[b]Subdural bleed or intracerebral bleed

Table 3 legend:

eGFR, estimated glomerular filtration rate (ml/min/1.73 m2); MI, myocardial infarction.

[a]Bleeding event in the preceding 30 days before excessive warfarin anticoagulation

[b] Hospitalization or outpatient visit during the preceding 30 days

Figure 1 title:

Kaplan-Meier Survival Analysis according to manifestation of excessive warfarin anticoagulation.

Figure 1 legend:

EWA, excessive warfarin anticoagulation; Other symptoms, patients suffering other than bleeding-related symptoms.

Table 1. Patient characteristics.

Clinical parameter	Control Group (n=405)	EWA Group (n=412)		
	Stable INR (n=405)	No symptoms (n=142)	Bleeding symptoms (n=105)	Other symptoms (n=165)
Age, y ± SD	76.6±8.5	77.6±10.6	76.2±11.4	78.8±9.8
Female, n (%)	223 (55.1)	71 (50.0)	45 (42.9)	101 (61.2)
CHA_2DS_2-VASc, mean ± SD	3.7±1.6	4.0±1.8	3.6±1.9	4.5±1.6
Chronic heart failure	55 (13.6)	47 (33.1)	25 (23.8)	83 (50.3)
Treatment for hypertension	283 (69.9)	86 (60.6)	59 (56.2)	90 (54.5)
Diabetes	99 (24.4)	39 (27.5)	22 (21.0)	50 (30.3)
History of ischaemic stroke	57 (14.1)	25 (17.6)	22 (21.0)	35 (21.2)
Coronary artery disease	89 (22.0)	48 (33.8)	22 (21.0)	60 (36.4)
History of myocardial infarction	41 (10.1)	24 (16.9)	15 (14.3)	41 (24.8)
Peripheral artery disease	9 (2.2)	9 (6.3)	7 (6.7)	18 (11.0)
eGFR< 30[a]	5 (1.3)	16 (11.6)	20 (19.0)	50 (30.3)
Independent living[b]	338 (83.5)	85 (59.9)	73 (69.5)	90 (54.5)
History of malignancy	53 (13.1)	32 (22.5)	37 (35.2)	35 (21.2)
Active malignancy	15 (3.7)	15 (10.6)	18 (17.1)	15 (9.1)
Recent medical treatment[c]	67 (16.5)	52 (36.6)	31 (29.5)	72 (46.5)
Alcohol abuse[d]	6 (1.5)	29 (20.4)	27 (25.7)	17 (10.3)
Active smoking	7 (1.7)	6 (4.2)	8 (5.6)	21 (12.7)
Recent bleed[e]	4 (1.0)	0 (0.0)	10 (9.5)	5 (3.0)
Mechanical heart valve	1 (0.2)	9 (6.4)	3 (2.9)	4 (2.4)
Concomitant medication				
Tramadol	4 (1.0)	1 (0.7)	9 (8.6)	6 (3.6)
Paracetamole	146 (36.0)	57 (40.4)	39 (37.1)	74 (44.8)
Antifungal medication[f]	0 (0.0)	9 (6.4)	4 (3.8)	4 (2.4)

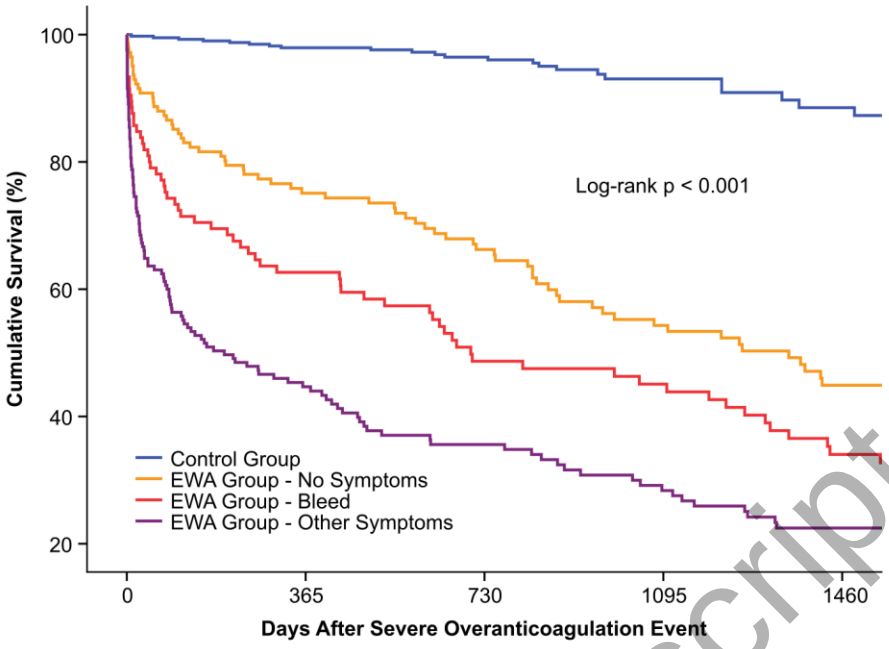
Antibiotic therapy[g]	22 (5.4)	20 (14.1)	18 (17.1)	69 (41.8)

Table 2. Observed number and classification of bleeding complications during severe overanticoagulation.

Bleed	ISTH 1	ISTH 2	ISTH 3	ISTH 4	Total
Gastrointestinal, n (%)	10	6	2	19	37 (33.0)
Cutaneous	6	3	6	2	17 (15.2)
Haematuria	5	8	0	2	15 (13.4)
Epistaxis	6	1	4	3	14 (12.5)
Oral cavity	1	2	3	1	7 (6.3)
Other bleed[a]	2	2	0	3	7 (6.3)
Minor wounds	3	0	1	2	6 (5.4)
Intracranial bleed[b]	0	0	3	2	5 (4.5)
Menorrhagia	1	0	0	1	2 (1.6)
Muscle haematoma	0	1	0	0	1 (0.9)
Haemarthrosis	0	0	0	1	1 (0.9)
Total	34 (30.4)	23 (20.5)	19 (17.0)	36 (32.1)	112

Table 3. Multivariate predictors of 30-day mortality in patients with excessive warfarin anticoagulation

Clinical risk factor	OR (95% CI)	*p* Value
Intracranial bleed	69.2 (6.60-725)	<.001
Active malignancy	4.21 (1.95-9.11)	<.001
Non-bleeding symptoms	4.08 (2.27-7.32)	<.001
Recent bleed[a]	3.38 (1.04-11.0)	.043
History of myocardial infarction	2.99 (1.64-5.43)	<.001
Age ≥ 75 years	2.42 (1.26-4.67)	.008
eGFR < 30	2.00 (1.08-3.70)	.028
Recent medical treatment[b]	1.86 (1.06-3-25)	.030



No. at risk					
Control Group	405	327	227	98	72
EWA Group - No Symptoms	142	100	78	58	41
EWA Group - Bleed	105	60	41	35	25
EWA Group - Other Symptoms	165	66	44	33	24