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Management and outcome of major bleeding in patients receiving vitamin K antagonists for venous thromboembolism.

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Abstract

Background The optimal management of major bleeding in patients receiving vitamin K antagonists (VKA) for venous thromboembolism (VTE) is unclear.

Methods We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry to assess the management and 30-day outcomes after major bleeding in patients receiving VKA for VTE.

Results From January 2013 to December 2017, 267 of 18,416 patients (1.4%) receiving long-term VKA for VTE had a major bleeding (in the gastrointestinal tract 78, intracranial 72, hematoma 50, genitourinary 20, other 47). Overall, 151 patients (57%) received blood transfusion; 110 (41%) vitamin K; 37 (14%) fresh frozen plasma; 29 (11%) pro-haemostatic agents and 20 (7.5%) a vena cava filter. During the first 30 days, 59 patients (22%) died (41 died of bleeding) and 13 (4.9%) had a thrombosis. On multivariable analysis, patients with intracranial bleeding (hazard ratio [HR]: 4.58; 95%CI: 2.40-8.72) and those with renal insufficiency at baseline (HR: 2.73; 95%CI: 1.45-5.15) had an increased mortality risk, whereas those receiving vitamin K had a lower risk (HR: 0.47; 0.24-0.92). On the other hand, patients receiving fresh frozen plasma were at increased risk for thrombotic events (HR: 4.22; 95%CI: 1.25-14.3).

Conclusions Major bleeding in VTE patients receiving VKA carries a high mortality rate. Intracranial bleeding and renal insufficiency increased the risk. Fresh frozen plasma seems to increase this risk for recurrent VTE.

Introduction

Bleeding is the most feared complication in patients receiving anticoagulant therapy for venous thromboembolism (VTE). In the literature, the rate of major and fatal bleeding in VTE patients receiving long-term therapy with vitamin K antagonists (VKA) ranged around 2-5 events and 0.5-1.0 deaths per 100 patient-years.[1–3] Current management of patients with major bleeding usually starts with immediate discontinuation of VKA therapy, followed by an intervention (endoscopy, coiling, surgery) and treatment with blood transfusion, vitamin K, prothrombin complex concentrate, fresh frozen plasma, or insertion of a retrievable vena cava filter (to be removed once the contraindication is no longer present), all based on the type and severity of the bleeding.[4–8] In these emergency situations, the optimal treatment is unclear and may vary per center. In addition, restarting anticoagulation is also a matter of debate, given the risk of both recurrent VTE and bleeding. In this critical scenario, neither the ideal time to re-start anticoagulant therapy nor the influence of prohaemostatic agents on outcome have been consistently investigated.

RIETE (Registro Informatizado Enfermedad TromboEmbolica) is a multicenter, ongoing, international registry of patients with objectively confirmed, acute VTE.[9–12] Since its inception in 2001, the aim of RIETE is to record data including the clinical characteristics, treatment and outcomes in patients diagnosed with VTE. In the current study, we assessed the management and outcomes occurring during the first 30 days after major bleeding in patients receiving VKA for acute VTE.

Methods

Patients and Data Source

We used the data from RIETE, the largest existing prospective VTE registry. Details about methodology of RIETE have been discussed elsewhere (ClinicalTrials.gov identifier: NCT02832245).[13] In brief, RIETE is a multicenter registry of patients with diagnosed acute deep vein thrombosis (DVT) or pulmonary embolism (PE). Initially started in Spain, RIETE currently has 205 collaborating centers from 27 countries. The protocol for enrolling patients at RIETE for research purposes has been approved by the ethics committees at the participating sites. The study protocol for this manuscript was drafted by two authors (FM and AS) and reviewed by all coauthors.

Study Design

We conducted a retrospective study of prospectively collected data from patients with acute VTE enrolled in the RIETE registry. Data were collected from January 2013 to December 2017, corresponding to the time when the data for the management of major bleeding was collected in the database. First, we compared the clinical characteristics of patients receiving long-term therapy with VKA, according to the presence or absence of major bleeding. Secondly, we assessed the time course and management of bleeding among the different sites of bleeding. Then, we compared the 30-day outcomes and tried to identify independent predictors of outcome. The primary outcome was all-cause mortality. Secondary outcome was the development of thrombotic events (including VTE recurrences, myocardial infarction, ischemic stroke or limb amputation).

Bleeding events were classified as 'major' if they were overt and required transfusion of two units or more of blood, or were retroperitoneal, spinal or intracranial, or when they were fatal. [13] Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. [13] All episodes of clinically suspected symptomatic DVT recurrences were investigated by repeat compression ultrasonography or contrast venography. Recurrent PE was confirmed by helical CT pulmonary angiography, ventilation-perfusion lung scan or pulmonary angiography. Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days after symptomatic PE diagnosis, in the absence of any alternative cause of death. Subsequent myocardial infarction was defined as the presence of typical chest pain in combination with a transient increase of creatine kinase-MB or troponin and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 hours, and had an acute cerebrovascular lesion on brain CT or MRI.

Variables

Patients enrolled in RIETE had data collected from around the time of index VTE diagnosis that included but were not limited to: demographics; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days before) major bleeding; risk factors for VTE including active cancer (newly diagnosed or under treatment [i.e. surgery, chemotherapy, radiotherapy, hormonal or support therapy]), recent immobility (bed rest with bathroom privileges for ≥4 days in the 2-months prior to VTE diagnosis), surgery (major

surgery within the 2 months prior to VTE); results at hospital admission that included haemoglobin, platelet count and serum creatinine levels. RIETE also collected treatment data that included anticoagulant use (drugs, doses and duration), vena cava filter use and management of bleeding. Treatment received at bleeding was reported as pro-haemostatic agents (prothrombin complex concentrates or activated Factor VII), fresh frozen plasma, vitamin K, blood or platelet transfusions or inferior vena cava filter. Unfortunately, however, there is no information in RIETE on the clinical characteristics of patients at the moment of bleeding (such as systolic blood pressure levels or renal function).

Treatment and Follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type, dose and duration of therapy were recorded. After major bleeding, all patients were followed-up in the outpatient clinic for at least 30 days. During each visit, investigators assessed the occurrence of symptomatic, objectively confirmed VTE recurrences, ischemic arterial events or major bleeding.

Statistical analysis

Continuous variables were reported as mean and standard error (or non-parametric counterparts where needed) and categorical variables were reported as frequency counts and percentages. Odds ratios (OR) with 95% confidence intervals (CI), as well as p-values (Mann-Whitney test or t-test for continuous variables and Cochran-Mantel-Haenszel tests for categorical variables) were presented for each variable analyzed. Logistic regression analyses were

performed to identify independent predictors for death within the first 48 hours and for the occurrence of thrombotic events (arterial or venous) within the first 30 days. All variables achieving a significance level of ≤0.1 on univarite analysis were considered for inclusion in the logistic regression model. All analyses were conducted using SPSS software (version 20, SPSS Inc., Chicago, Illinois).

Results

From January 2013 to December 2017, 18416 VTE patients receiving long-term therapy with VKA were recruited in RIETE. Of them, 267 (1.4%) had major bleeding during VKA therapy. Among patients that subsequently bled, 160 (60%) initially presented as PE and 101 as only DVT (proximal in 94, 93%). The most frequent sites of major bleeding were: the gastrointestinal (GI) tract (n=78), intracranial (n=72), haematoma (n=50) and genitourinary (n=20). Compared with patients that did not bled, those with major bleeding were 10 years older and more likely to have recent major bleeding, to be using antiplatelets or corticosteroids concomitantly, or to have active cancer, anemia, abnormal platelet count or renal insufficiency at baseline (Table I).

Median duration of anticoagulant therapy in patients that did not develop major bleeding was 176 days (range, 99-316 days). Mean duration was 262±298 days. Median time from VTE diagnosis to major bleeding was 95 days (range, 19-252) (Table II). It was shorter in patients with hematoma (15 days, 8-97) and longer in those with intracranial bleeding (136 days, 66-423). At bleeding, 36% of patients had INR levels above 3.0, with no differences according to bleeding site. Anticoagulant therapy was immediately discontinued in all patients. In addition,

57% of patients received packed red blood cells, 41% vitamin K, 14% fresh frozen plasma, 11% pro-haemostatic agents (prothrombin complex concentrates [PCC], aPCC or Factor VIIa), 7.5% received a vena cava filter, 3.7% underwent surgery and 3.7% embolization. Patients with intracranial bleeding (n=72) were more likely to receive pro-haemostatic agents (21%) or a vena cava filter (13%) than those with bleeding in other sites (n=195).

After major bleeding, 17% of patients restarted anticoagulant therapy (average, 13 days later), with some differences according to site of bleeding. During the first 30 days after major bleeding, 59 patients (22%) died (Table III). The causes of death were: bleeding itself (n=41), disseminated cancer (n=6), multiorganic failure (n=2), renal insufficiency (n=2), myocardial infarction (n=1), heart failure (n=1), respiratory insufficiency (N=1), unknown (N=5). Most deaths (50 of 59, 85%) occurred within the first 10 days after bleeding (Figure 1). The mortality rate ranged from 42% in patients with intracranial bleeding to 6.0% in those with hematoma. Among survivors, 3 patients had a major re-bleeding (none of these died of bleeding), 10 developed VTE recurrences (3 PE, 7 DVT) and 5 suffered from an ischemic arterial event (ischemic stroke 2, myocardial infarction 2, limb amputation 1) during the first 30 days after bleeding. One myocardial infarction was fatal.

On univariable analysis, age ≥75 years, concomitant use of antiplatelets at baseline, renal insufficiency, initial VTE presentation as PE and intracranial bleeding were all associated with a higher mortality rate, while the use of vitamin K was associated with a lower mortality (Table IV). Moreover, patients with

unprovoked VTE or receiving fresh frozen plasma had a higher rate of thrombotic (arterial or venous) events within the first 30 days. On multivariable analysis, patients with CrCl levels <50 mL/min at baseline (hazard ratio [HR]: 2.73; 95%CI: 1.45-5.15) and those with intracranial bleeding (HR: 4.58; 95%CI: 2.40-8.72) had an increased mortality risk, whereas those receiving vitamin K were at a lower risk (HR: 0.47; 95%CI: 0.24-0.92) (Table V). Finally, patients receiving fresh frozen plasma were at increased risk for thrombotic events during the first month (HR: 4.22; 95%CI: 1.25-14.3).

Discussion

Our data, obtained from a large series of VTE patients receiving VKA therapy, revealed that the development of major bleeding carries a high mortality rate (59 of 267 patients, 22%), particularly during when it occurred within the first 10 days (50 of 59, 85%). Thus, rapid and aggressive bleeding management is mandatory to reduce its mortality. However, only half of the patients received pharmacological treatment to antagonize VKA. Furthermore, no uniform transfusion strategy seemed to be applied in the different hospitals. For instance, out of the 24 patients that were treated with PPC, only 17 received vitamin K concomitantly. Moreover, 37 patients (14%) received FFP, whereas PCC is faster acting and preferred over FFP in VKA-related bleeding.[14]

Although it is unsure whether aggressive prohemostatic treatment would reduce the mortality rate, current guidelines recommend a clear step up strategy of transfusion and prohemostatic treatment in case of major bleeding.[15,16] Unfortunately, clinical practice in these emergency situations seems resistant, as

was also shown in the Rely study, where in the VKA arm only few patients received vitamin K or PCC despite major bleeding.[17,18] As expected, patients with intracranial bleeding had a high mortality rate, as were those with renal insufficiency. Also in our study, there was no benefit of any therapy on mortality, although the numbers of patients may be too small to show any effect. In the literature, there is some controversy on this issue: while one study found that PPC had a survival benefit over FFP in patients with intracranial bleeding (not in those with extracranial bleeding)[19], Sarode et al. found no survival benefit.[14] Only vitamin K, as previously reported, was associated with a lower mortality.[20–25] Selection of patients with better outcome that received vitamin K could be a logical explanation for this finding, since a biological mechanism is hard to imagine. Unexpectedly however, less than half of the patients in our cohort did receive vitamin K. This is consistent with other series. [26,27]

In all patients with major bleeding anticoagulant treatment was stopped. This carries a risk of recurrent VTE. In our study, 4.9% of patients had a recurrent event in the first 30 days after the major bleeding. On the other hand, only three patients had a re-bleeding beyond the first 48 hours. The development of thrombotic events is most likely due to the sudden discontinuation of anticoagulant therapy, that persisted for several days (median, 7 days), and the concomitant use of fresh frozen plasma or prohaemostatic agents. The influence of these agents on outcome in patients with major bleeding has been evaluated in a number of studies, revealing some superiority of prothrombin complex concentrates over fresh frozen plasma in terms of international normalized ratio or effective haemostasis, but no study reported any difference in mortality.[14,28–

31] In our study, the use of fresh frozen plasma (and not of prothrombin complex concentrate) was associated with an 4-fold increased thrombotic risk. This is a previously not reported effect and must be evaluated in the future using properly designed randomized trials. Strikingly, only 46 patients (17%) in our cohort restarted anticoagulant therapy, and, as expected, this was lower in patients with intracranial bleeding. There was no association between the time to restart anticoagulation and VTE or mortality, probably due to small numbers.

Our study has a number of limitations. First, RIETE is an observational registry, and data from registries are susceptible to selection bias if a non-representative sample of patients is selected for analysis. However, RIETE captures a broad range of patients from multiple medical centers, countries, and treatment settings, making it less likely that the study cohort is made up of a skewed population. Second, there is no external adjudication of the major bleeding events, which are reported by the treating physicians. However, prior studies showed that adjudicated data usually match well with onsite outcome assessment.[32–34] Third, patients in the RIETE database were selected in several countries, and the variation of clinical practice in different countries could potentially affect the study outcomes. For instance, the dosing and regimen of prohaemostatic treatment can vary according form country to country, and even per center, underlying disease process, and presence of cancer. Fourth, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported. However, we did have access to and adjusted for many important clinical variables and for hospital factors in the multivariate models. Even if some residual confounding exists, it is unlikely that such confounding factors account

for the entire effect size that we observed. Finally, another limitation is that numbers are small, and therefore, the robustness of the findings may be questioned. The main strength of our study is that the population based sample describes the effects of initial therapy of VTE in “real world” clinical care, as opposed to in a protocol driven randomized trial, and enhances the generalizability of our findings.

In summary, in VTE patients presenting with major bleeding during VKA therapy, mortality rate is high, while recurrent VTE occurs after stopping anticoagulant treatment. Despite the high risk of fatal bleeding, only half of the patients receive transfusion or prohaemostatic treatment. Further studies are needed on the timing of re-starting anticoagulation and events (recurrent VTE and major bleeding) to improve the quality of care in these vulnerable patients.

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Table I. Clinical characteristics at baseline in patients who suffered major bleeding during VKA therapy, and in those who did not.

	Major bleeding	No major bleeding	OR (95%CI)
Patients, N	***267***	***18,149***	
Clinical characteristics,			
Mean age (years ±SD)	75.2±13.3	64.7±18	<0.0001
Age ≥75 years	172 (64%)	6,680 (37%)	3.11 (2.42-4.00)
Male gender	117 (44%)	8,921 (49%)	0.81 (0.63-1.03)
Underlying diseases,			
Recent major bleeding	12 (4.5%)	254 (1.4%)	3.32 (1.83-5.99)
Concomitant therapy,			
Antiplatelets	72 (27%)	3,125 (17%)	1.78 (1.35-2.33)
Corticosteroids	32 (12%)	1,452 (8.0%)	1.57 (1.08-2.27)
NSAIDs	23 (8.6%)	1,295 (7.1%)	1.23 (0.80-1.89)
Risk factors for VTE,			
Active cancer	56 (21%)	2,066 (11%)	2.07 (1.53-2.78)
Transient risk factors	87 (33%)	5,876 (32%)	1.01 (0.78-1.31)
Unprovoked VTE	124 (46%)	10,207 (56%)	0.67 (0.53-0.86)
Prior VTE	49 (18%)	2,779 (15%)	1.24 (0.91-1.70)
Baseline blood tests,			
Anemia	136 (51%)	4,854 (27%)	2.84 (2.23-3.62)
Abnormal platelet count*	20 (7.5%)	804 (4.4%)	1.74 (1.10-2.77)
CrCl levels <50mL/min	98 (37%)	3,669 (20%)	2.29 (1.78-2.94)
Initial VTE presentation,			
Pulmonary embolism	160 (60%)	10,299 (57%)	1.14 (0.89-1.46)

*Platelet count <100,000/µL or >450,000/µL

Abbreviations: VTE, venous thromboembolism; SD, standard deviation; CrCl, creatinine clearance; OR, Odds ratio; CI, confidence intervals.

Table II. Management of bleeding according to bleeding site.

	Intra-cranial	Gastro-intestinal	Haema-toma	Genito-urinary	Other	Any
Patients, N	***72***	***78***	***50***	***20***	***47***	***267***
Time since VTE,						
Median days (range)	136 (66-423)	100 (29-260)	15 (8-97)	104 (35-288)	102 (20-300)	95 (19-252)
INR at bleeding,						
INR <2.0	17 (24%)	17 (22%)	15 (30%)	3 (15%)	6 (13%)	58 (22%)
INR 2.0–3.0	21 (29%)	20 (26%)	6 (12%)*	7 (35%)	13 (28%)	67 (25%)
INR >3.0	20 (28%)	27 (35%)	22 (44%)	7 (35%)	20 (43%)	96 (36%)
Not reported	14 (19%)	14 (18%)	7 (14%)	3 (15%)	8 (17%)	46 (17%)
Therapy at bleeding,						
VKA drugs	72 (100%)	77 (99%)	49 (98%)	20 (100%)	46 (98%)	264 (99%)
LMWH+VKA drugs	0	1 (1.3%)	1 (2.0%)	0	1 (2.1%)	3 (1.1%)
Management,						
Pro-hemostatic agents	15 (21%)	3 (3.8%)†	6 (12%)	0	5 (11%)	29 (11%)
PCC	11 (15%)	2 (2.6%)†	6 (12%)	0	5 (11%)	24 (9.0%)
aPCC	3 (4.2%)	0	0	0	0	3 (1.1%)
Factor VIIa	1 (1.4%)	1 (1.3%)	0	0	0	2 (0.75%)
Fresh frozen plasma	10 (14%)	16 (21%)	3 (6.0%)	2 (10%)	6 (13%)	37 (14%)
Vitamin K	28 (39%)	29 (37%)	25 (50%)	9 (45%)	19 (40%)	110 (41%)
Vitamin K and PCC	6 (8.3%)	1 (1.3%)	6 (12%)	0	4 (8.5%)	17 (6.4%)
Protamine sulfate	1 (1.4%)	0	0	0	0	1 (0.37%)
Transfusion						
Blood transfusion	2 (2.8%)	64 (82%)‡	38 (76%)‡	15 (75%)‡	32 (68%)‡	151 (57%)
Platelet transfusion	1 (1.4%)	3 (3.8%)	0	0	3 (6.4%)	7 (2.6%)
Surgery	6 (8.3%)	1 (1.3%)	1 (2.0%)	0	2 (4.3%)	10 (3.7%)
Embolization	1 (1.4%)	2 (2.6%)	3 (6.0%)	0	4 (8.5%)	10 (3.7%)
Other measures,						
IVC filter ≤3 days	9 (13%)	2 (2.6%)*	5 (10%)	1 (5.0%)	3 (6.4%)	20 (7.5%)
Resumption of therapy,						
Restart, n (%)	4 (5.5%)	16 (21%)	18 (36%)	3 (15%)	5 (11%)	46 (17%)
Mean days (±SD)	11±7.8	10±15	18±18	1.7±1.2	15±11	13±15
Median days (IQR)	11 (4-18)	6 (3-9)	13 (7-23)	1 (1-3)	7 (7-23)	7 (4-18)

*p <0.05; †p <0.01; ‡p <0.001

Pro-hemostatic agents = PCC, aPCC or activated factor VII.

Abbreviations: VTE, venous thromboembolism; INR, International normal ratio; PCC, Prothrombin complex concentrate; aPCC, activated Prothrombin complex concentrate; IVC, Inferior vena caval; SD, standard deviation; IQR, interquartile range; CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; OR, Odds ratio; CI, confidence intervals.

Table III. Thirty-day outcomes after major bleeding, according to bleeding site.

	Intra-cranial	Gastro-intestinal	Haema-toma	Genito-urinary	Other	Any
Patients, N	***72***	***78***	***50***	***20***	***47***	***267***
30-day events,						
Death	30 (42%)	15 (19%)†	3 (6.0%)‡	2 (10%)†	9 (19%)*	59 (22%)
Fatal bleeding	27 (38%)	7 (9.0%)‡	1 (2.0%)‡	0	6 (13%)†	41 (15%)
Major re-bleeding	0	2 (2.6%)	0	0	1 (2.1%)	3 (1.1%)
Recurrent PE	3 (4.2%)	0	0	0	0	3 (1.1%)
Recurrent DVT	1 (1.4%)	3 (3.8%)	1 (2.0%)	1 (5.0%)	1 (2.1%)	7 (2.6%)
Ischemic stroke	1 (1.4%)	1 (1.3%)	0	0	0	2 (0.7%)
Myocardial infarction	1 (1.4%)	0	1 (2.0%)	0	0	2 (0.7%)
Limb amputation	0	1 (1.3%)	0	0	0	1 (0.4%)
Any thrombotic event	4 (5.6%)	5 (6.4%)	2 (4.0%)	1 (5.0%)	1 (2.1%)	13 (4.9%)

*p <0.05; †p <0.01; ‡p <0.001

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis.

Table IV. Predictors of death and of thrombotic events within the first 30 days after bleeding.

	Death		Thrombotic events	
	Dead	Alive	Thrombotic events	No thrombotic events
Patients, N	***59***	***208***	***13***	***254***
Clinical characteristics				
Age ≥75 years	43 (73%)	129 (62%)	7 (54%)	165 (65%)
Male gender	29 (49%)	88 (42%)	3 (23%)	114 (45%)
Body weight <60 kg	13 (22%)	27 (13%)	2 (15%)	38 (15%)
Underlying diseases				
Recent major bleeding	2 (3.4%)	10 (4.8%)	0	12 (4.7%)
Concomitant therapy				
Antiplatelets	21 (36%)	51 (25%)	3 (23%)	69 (27%)
Corticosteroids	5 (8.5%)	27 (13%)	1 (7.7%)	31 (12%)
Risk factors for VTE				
Active cancer	17 (29%)	39 (19%)	2 (15%)	54 (21%)
Transient risk factors	20 (34%)	67 (32%)	1 (7.7%)	86 (34%)
Unprovoked VTE	22 (37%)	102 (49%)	10 (77%)	114 (45%)*
Prior VTE	15 (25%)	34 (16%)	3 (23%)	46 (18%)
Baseline blood tests				
Anemia	33 (56%)	103 (50%)	6 (46%)	130 (51%)
Abnormal platelet count	4 (6.8%)	16 (7.7%)	1 (7.7%)	19 (7.5%)
CrCl levels <50ml/min	31 (53%)	67 (32%)†	6 (46%)	92 (36%)
VTE at baseline				
Pulmonary embolism	40 (68%)	120 (58%)	5 (38%)	155 (61%)
Time to bleeding <15 days	14 (24%)	41 (20%)	3 (23%)	52 (20%)
Site of bleeding				
Intracranial	30 (51%)	42 (20%)‡	4 (31%)	68 (27%)
INR at bleeding				
INR <2.0	16 (27%)	42 (20%)	4 (31%)	54 (21%)
INR 2.0–3.0	11 (19%)	56 (27%)	1 (7.7%)	66 (26%)
INR >3.0	16 (27%)	80 (38%)	5 (38%)	91 (36%)
Treatment of bleeding				
PCC	7 (12%)	17 (8.2%)	0	24 (9.4%)
aPCC	1 (1.7%)	2 (0.96%)	0	3 (1.2%)
Factor VIIa	0	2 (0.96%)	0	2 (0.79%)
Pro-hemostatic agents	8 (14%)	21 (10%)	0	29 (11%)
Fresh frozen plasma	5 (8.5%)	32 (15%)	5 (38%)	32 (13%)*
Vitamin K	17 (29%)	93 (45%)*	5 (38%)	105 (41%)
Other measures,				
IVC filter ≤3 days	2 (3.4%)	18 (8.7%)	3 (23%)	17 (6.7%)
Restart therapy <10 day				
Yes	1 (100%)	31 (65%)	1 (33%)	22 (48%)

Differences between patients with- vs. without the events: °p <0.1; *p <0.05; ‡p <0.001**.**

Abbreviations: VTE, venous thromboembolism; INR, International normal ratio; PCC, Prothrombin complex concentrate; aPCC, activated Prothrombin complex concentrate; IVC, Inferior vena caval.

Table V. Multivariable analyses.

	All-cause death within 30 days		Thrombotic events within 30 days	
	Adjusted OR (95%CI)	**p value**	**Adjusted OR (95%CI)**	**p value**
Risk factors for VTE				
Transient risk factors	-	-	0.30 (0.03-3.54)	0.341
Unprovoked VTE	-	-	1.93 (0.39-9.58)	0.420
Baseline blood tests,				
CrCl levels <50mL/min	2.73 (1.45-5.15)†	0.002	-	-
Site of bleeding				
Intracranial	4.58 (2.40-8.72)‡	0.000	-	-
Treatment of bleeding				
Fresh frozen plasma	-	-	4.22 (1.25-14.3)	0.020
Vitamin K	0.47 (0.24-0.92)*	0.028	-	-
Other measures,				
IVC filter ≤3 days	-	-	3.52 (0.82-15.1)	0.089

*p <0.05; †p <0.01; ‡p <0.001

Abbreviations: VTE, venous thromboembolism; IVC, Inferior vena caval; CrCl, creatinine clearance; OR, Odds ratio; CI, confidence intervals.

Figure 1. Cumulative rate of fatal bleeding and thrombotic events during the first 30 days after major bleeding.

Days		*2*	*7*	*10*	*15*	*30*
Fatal bleeding	**Intracranial**	19 (26%)	23 (32%)		26 (36%)	28 (40%)
	No intracranial	10 (5.1%)	12 (6.1%)	12 (6.1%)	12 (6.1%)	14 (7.2%)
Thrombotic events	**Intracranial**	3 (4.2%)	3 (4.2%)		4 (5.6%)	4 (5.6%)
	No intracranial	3 (1.5%)	7 (3.6%)	7 (3.6%)	7 (3.6%)	9 (5.2%)

Highlights:

- The optimal management of major bleeding in patients receiving vitamin K antagonists for venous thromboembolism is still unclear.
- Major bleeding occurred in 1.4% of patients, and the mortality rate ranged from 6.0% (in patients with haematoma) to 42% (in those with intracranial bleeding).
- Only 41% of patients received vitamin K , 11% received prohemostatic agents and 7.5% underwent a vena cava filter.
- On multivariate analysis, patients receiving vitamin k were at a lower risk to die, and those receiving fresh frozen plasma at increased risk for thrombotic events.