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Thromboembolic Events With Recombinant Activated Factor VII in Spontaneous Intracerebral Hemorrhage

Results From the Factor Seven for Acute Hemorrhagic Stroke (FAST) Trial

Michael N. Diringer, MD; Brett E. Skolnick, PhD; Stephan A. Mayer, MD; Thorsten Steiner, MD; Stephen M. Davis, MD; Nikolai C. Brun, MD, PhD; Joseph P. Broderick, MD

Background and Purpose—Patients with intracerebral hemorrhage have a high risk of thromboembolic events (TEs) due to advanced age, hypertension, atherosclerosis, diabetes, and immobility. Use of recombinant activated factor VII (rFVIIa) could increase TEs in high-risk patients. Factor Seven for Acute Hemorrhagic Stroke (FAST) trial data were reviewed to define the frequency of and risk factors for TE with rFVIIa.

Methods—Eight hundred forty-one patients presenting <3 hours after spontaneous intracerebral hemorrhage were randomized to 20 or 80 $\mu\text{g}/\text{kg}$ of rFVIIa or placebo. Those with Glasgow Coma Scale score <5, planned early surgery, coagulopathy, or recent TE were excluded. Myocardial, cerebral, or venous TEs were subject to detailed reporting and expedited local review. Additionally, a blinded Data Monitoring Committee reviewed all electrocardiograms, centrally analyzed troponin I values, and CT scans.

Results—There were 178 arterial and 47 venous TEs. Venous events were similar across groups. There were 49 (27%) arterial events in the placebo group, 47 (26%) in the 20- $\mu\text{g}/\text{kg}$ group, and 82 (46%) in the 80 $\mu\text{g}/\text{kg}$ group ($P=0.04$). Of the myocardial events, 38 were investigator-reported and 103 identified by the Data Monitoring Committee. They occurred in 17 (6.3%) placebo and 57 (9.9%) rFVIIa patients ($P=0.09$). Arterial TEs were associated with: receiving 80 $\mu\text{g}/\text{kg}$ rFVIIa (OR=2.14; $P=0.031$), signs of cardiac or cerebral ischemia at presentation (OR=4.19; $P=0.010$), age (OR=1.14/5 years; $P=0.0123$), and prior use of antiplatelet agents (OR=1.83; $P=0.035$). Ischemic strokes possibly related to study drug occurred in 7, 5, and 8 patients in the placebo, 20 $\mu\text{g}/\text{kg}$, and 80- $\mu\text{g}/\text{kg}$ groups, respectively.

Conclusions—Higher doses of rFVIIa in a high-risk population are associated with a small increased risk of what are usually minor cardiac events. Demonstration of the ability of rFVIIa to improve outcome in future studies should be driven by its effectiveness in slowing bleeding outweighing the risk of a small increase in arterial TEs. (*Stroke*. 2010; 41:00-00.)

Key Words: clinical trials ■ Data Monitoring Committee ■ intracerebral hemorrhage (ICH) ■ myocardial ischemia ■ recombinant activated factor VII (rFVIIa) ■ thromboembolic events

Patients with intracerebral hemorrhage (ICH) have an inherently increased risk of thromboembolic events. Factors that contribute to that risk include advanced age, hypertension, atherosclerotic disease, diabetes, and immobility. Options to prevent thromboembolic events are limited after acute ICH and factors that might increase the risk of such events are generally avoided. Recent experience with the use of recombinant activated factor VII (rFVIIa) in spontaneous and Coumadin-associated ICH¹ has raised concern that its administration could result in an increase in thromboembolic events. A critical review of safety in the setting of a large, randomized controlled study will provide important informa-

tion about risk of thromboembolic events associated with ICH and the relationship to rFVIIa treatment in this high-risk population.

A Phase IIb proof-of-concept trial of rFVIIa in 400 patients with acute ICH demonstrated reduced hematoma growth and improved clinical outcome.² We recently reported an increased frequency of thromboembolic events when that trial was combined with several early dose-ranging studies³ (7% versus 2% for rFVIIa- and placebo-treated patients, respectively; $P=0.12$) and a higher frequency of arterial thromboembolic events in the highest dose range (120 to 160 $\mu\text{g}/\text{kg}$) compared with placebo (10% versus 2%, $P=0.013$). A much

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larger Phase III trial (Factor Seven for Acute Hemorrhagic Stroke [FAST] trial, n=841) confirmed the reduction in hematoma growth but failed to demonstrate improved outcome.⁴ We now report on the thromboembolic events that occurred in that trial.

The protocols for the proof-of-concept and FAST trials were nearly identical but with 2 important differences. First, in the FAST trial, the 160- $\mu\text{g}/\text{kg}$ dose group was dropped and a 20- $\mu\text{g}/\text{kg}$ dose group was added in an attempt to evaluate whether lower doses would reduce thromboembolic complications while retaining the hemostatic effect. Second, half-way through the proof-of-concept trial, patients were excluded if they had any history of thromboembolic events; in the FAST trial, that restriction was eliminated and patients were excluded only if they had a thromboembolic event within 30 days of drug administration; thus, a higher risk population was enrolled in the FAST trial.

In this article, we review data from the FAST trial to help define the frequency of and risk factors for thromboembolic events in this higher-risk population. We present the process undertaken to evaluate thromboembolic events, explore the relationship between thromboembolic events and dose of rFVIIa, and attempt to identify risk factors for their occurrence. Further trials of rFVIIa may be performed and off-label use of rFVIIa continues for a number of conditions associated with life-threatening hemorrhage. It is therefore important to understand the frequency and clinical impact of thromboembolic events (TEs) in high-risk patients.

Materials and Methods

The details of the trials have been reported elsewhere.⁴ The FAST trial enrolled 841 subjects. They are summarized subsequently.

Patient Selection

Patients were eligible for enrollment in the trial if they presented with symptoms due to a spontaneous ICH evident on CT scan performed within 3 hours of symptom onset. Exclusion criteria included age <18 years; Glasgow Coma Scale score ≤ 5 ; planned early surgery; ICH secondary to coagulopathy (including oral anti-coagulant use); sepsis, crush injury, or disseminated intravascular coagulation; pregnancy, or pre-existing disability. Patients were excluded only if they had symptomatic thromboembolic or vaso-occlusive disease within 30 days of their ICH.

Study Intervention

Patients were randomized to 20 or 80 $\mu\text{g}/\text{kg}$ of rFVIIa or placebo. A single intravenous dose was administered within 1 hour of the CT scan and no later than 4 hours after symptom onset. The protocol recommended that ICH medical management conform to American Heart Association guidelines.⁵

Clinical Assessments

Clinical assessments were performed on enrollment, at the time of drug administration, 1 and 24 hours later, on Days 2, 3, 15 (or at discharge, if that occurred earlier), and on Day 90.

Safety Assessments

The Data Monitoring Committee (DMC) performed an interim analysis after enrollment of every 75 patients and evaluated 4 end points, including death, all TEs, venous and arterial TEs, occurring within 15 days of drug administration. The incidence of each of these outcomes was compared with the placebo group.

Predefined events of special interest, including myocardial infarction/ischemia, ischemic stroke, deep vein thrombosis (DVT), and

pulmonary embolism, were subject to detailed reporting and expedited review. All of these events identified by local investigators were reported to the independent DMC. The DMC established committees to classify these events of special interest occurring in a 5-day window after trial drug administration for myocardial ischemia, cerebral infarction, and DVT and pulmonary embolism events. The classification was performed by the DMC members without knowledge of the treatment allocation and was made based on those potential thrombotic events that were reported by the investigators as adverse events (serious or nonserious adverse events). In addition, all electrocardiograms, centrally analyzed cardiac troponin I values, and 72-hour CT scans were reviewed in comparison to baseline studies to identify unreported cases of myocardial or cerebral ischemia. These are reported as DMC-identified events.

The DMC classified all myocardial events as ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or "biochemical markers only" (troponin I $>0.3 \mu\text{g}/\text{L}$ and electrocardiograms without signs of STEMI or NSTEMI). Cerebral infarction was defined as an acute focal neurological deficit due to focal cerebral ischemia caused by arterial thrombosis or embolism or by venous infarction. Clinical or radiographic evidence that indicated that the deficit had persisted for at least 24 hours was required.

The impact of each adverse event was rated by the investigators using the following regulatory definitions: "recovered"—fully recovered, with treatment the condition returned to the level observed at the time of enrollment; and "recovered with sequelae"—as a result of the adverse event, the subject had persistent and significant disability/incapacity.

Statistical Analysis

The proportion of adverse events in the rFVIIa-treated patients was compared with those in the placebo group using Fisher exact test. Trends across dose levels were tested using the Cochran-Armitage test. Mortality in all patients receiving rFVIIa was compared with the placebo group using a 2-sided χ^2 test. Because we found an increase in arterial but not venous events, a separate analysis was performed for arterial TEs.

Logistic regression analysis was performed to identify factors related to the occurrence of arterial TEs. The variables screened were: treatment group; age; gender; ethnicity; body mass index; history of diabetes, hypertension, or thromboembolism; mean arterial pressure; FVII:C levels; signs of ischemia on admission CT; serum cholesterol; prothrombin time/international normalized ratio; troponin I; fibrinogen; platelet count; prothrombin fragment 1+2; and antiplatelet medications (eg, clopidogrel, Dipyridamol, rofecoxib, aspirin, and other nonsteroidal anti-inflammatory drugs). After screening with univariate analysis, variables with $P < 0.25$ were entered into the regression model. The model was then reduced by removing the least significant covariate such that only covariates with a probability value < 0.10 were included in the final model. For the final model, covariates were considered to have a significant effect at the 5% level ($P < 0.05$), whereas covariates with probability values between 0.05 and 0.10 were considered not to have a significant effect on the outcome but to be of sufficient importance for the model fit to be retained in the final model.

Results

Study Population

The 3 groups were similar in terms of age, race, gender, disease severity (Glasgow Coma Scale score, ICH volume; Table 1). Time to treatment after symptom onset also did not differ across groups. Only the percentage of subjects with intraventricular hemorrhage differed with more in subjects randomized to rFVIIa treatment.

Risk for TEs

Eighty-two percent of the patients enrolled had a history of hypertension, 32% had a history of antiplatelet therapy, and 19%

Table 1. Baseline Characteristics and Timing of Treatment*

	rFVIIa		
	Placebo (N=268)	20 μg/kg (N=276)	80 μg/kg (N=297)
Age, years	65±14	65±14	65±13
Male, %	63	61	61
Race, %			
White	67	72	69
Black	9	9	9
Asian	21	16	18
Unknown/other	3	3	3
IVH present, %	29	35	41
GCS score	15 (6–15)	14 (6–15)	14 (6–15)
GCS 6–8, %	3	6	6
Onset-to-treatment time, minutes	160±38	161±37	160±36
Baseline ICH volume, mL	22±24	24±26	23±26

*Values are mean±SD, median (range), or percent. Values may not add up to 100 percent because of rounding.

IVH indicates intraventricular hemorrhage; GCS, Glasgow Coma Scale.

had a history of diabetes mellitus, whereas only 12% had a TE history with 5% having had a prior myocardial infarction.

Thromboembolic Events

A total of 225 (26.7%) TEs occurred; 59 (7%) were reported by the investigators and an additional 176 (20.9%) identified by DMC review (Table 2). Of these events, 178 (79%) were arterial and 47 (21%) venous. The rate of venous events did not differ across groups (Table 2). Of the 178 arterial TEs, 49 (27%) were in the placebo group, 47 (26%) in the 20-μg/kg group, and 82 (46%) in the 80-μg/kg group (P=0.04).

Myocardial Ischemia and Infarction

There were 38 investigator-reported myocardial events (based on clinical judgment, local troponin I, and/or local electrocardiographic interpretation) in 37 patients (Table 3). In 2 cases, the DMC did not agree because the diagnostic

Table 2. All TEs (Investigator-Reported and DMC-Identified)

No. (%)	rFVIIa			Total Events
	Placebo (N=268)	20 μg/kg (N=276)	80 μg/kg (N=297)	
Arterial				
Myocardial event	41 (15)	36 (13)	64 (22)*	141 (17)
Cerebral infarction	8 (3)	11 (4)	18 (6)	37 (4)
Total arterial	49 (18)	47 (17)	82 (28)	178 (21)
Venous				
DVT	14 (5)	11 (4)	11 (4)	36 (4)
Pulmonary embolism	3 (1)	4 (1)	4 (1)	11 (1)
Total venous	17 (6)	15 (5)	15 (5)	47 (6)
Total	66 (25)	62 (22)	97 (32)	225 (27)

*The frequency of arterial events was significantly higher in the 80-μg/kg group compared with placebo (P=0.04, χ² test).

Table 3. Myocardial Events, Causal Relationship With rFVIIa as Judged by DMC, and Impact on Outcome

	Placebo	20 μg/kg	80 μg/kg	Total Events
	No. of patients (%); No. of events			
Investigator-reported				
Biochemical marker only	...	2 (0.7); 2	2 (0.7); 2	4 (0.5)
NSTEMI	6 (2.2); 7	10 (3.6); 10	9 (3.0); 9	26 (3.0)
STEMI	2 (0.7); 2	1 (0.4); 1	5 (1.7); 5	8 (1.0)
DMC-identified				
Biochemical marker only	23 (8.6); 23	13 (4.7); 13	26 (8.8); 26	62 (7.4)
NSTEMI	7 (2.6); 7	10 (3.6); 10	21 (7.1); 21	38 (4.5)
STEMI	2 (0.7); 2	...	1 (0.3); 1	3 (0.4)
All events				
Biochemical marker only	23 (8.6); 23	15 (5.1); 15	28 (9.4); 28	65 (7.7)
NSTEMI	13 (4.9); 14	20 (7.2); 20	30 (10.1); 30	63 (7.5)
STEMI	4 (1.5); 4	1 (0.4); 1	6 (2.0); 6	11 (1.3)
Relationship to drug				
Investigator-reported				
Unlikely	2	4	4	10 (1.2)
Possible	7 (2.6)	9 (3.3)	12 (4.0)	28 (3.3)
Unrelated			2 (0.7)	2 (0.2)
DMC-identified				
Unlikely	3	8	3	14 (1.7)
Possible	29 (10.8)	15 (5.4)	45 (15.1)	89 (10.6)
All events				
Unlikely	5	12	7	24
Possible	36 (13.4)	24 (9.4)	57 (19.2)	117 (13.9)
Impact of events on outcome				
Myocardial event and alive	12 (4.3)	13 (4.7)	20 (6.7)	45 (5.4)
Myocardial event and dead	5 (1.9)	8 (2.9)	16 (5.4)	29 (3.5)
No myocardial event and alive	205 (76.5)	212 (76.8)	215 (72.4)	632 (75.2)
No myocardial event and dead	46 (17.2)	43 (15.6)	46 (15.5)	135 (16.1)

criteria were not fulfilled. An additional 103 myocardial events in 103 patients were detected by retrospective DMC review of all electrocardiograms and centrally measured troponin I levels (Table 3).

When combining all DMC and investigator-identified myocardial events, the frequency of STEMI was 4 (1.5%), one (0.4%), and 6 (2.0%) in the placebo, 20-μg/kg, and

Table 4. Causal Relationship Between Treatment and Cerebral Infarction Events

No. (%)	Treatment Groups			Total
	Placebo	20 $\mu\text{g}/\text{kg}$	80 $\mu\text{g}/\text{kg}$	
Investigator-reported				
Unlikely	0	2 (0.72)	1 (0.34)	3 (0.36)
Possible	7 (2.61)	1 (0.36)	8* (2.69)	16 (1.90)
Unrelated	0	1 (0.36)	1 (0.33)	2 (0.24)
DMC-identified				
Unlikely	2 (0.75)	3 (1.1)	7 (2.4)	12 (1.4)
Possible	0	4 (1.45)	0	4 (0.5)
Total	9 (3.4)	11 (4.0)	17 (5.7)	37 (4.4)

*One patient with 2 events.

80- $\mu\text{g}/\text{kg}$ groups, respectively (Table 3). The frequency of NSTEMI and STEMI events combined was 18 (6.4%) for placebo, 21 (7.6%) for 20 $\mu\text{g}/\text{kg}$, and 36 (12.1%) for 80 $\mu\text{g}/\text{kg}$ rFVIIa-treated patients ($P=0.015$). Of the myocardial events, the DMC considered 117 of the 141 events to be possibly related to study drug (either placebo or rFVIIa) administration, corresponding to 36 (13%), 26 (9%), and 57 (19%) in the placebo, 20- $\mu\text{g}/\text{kg}$, and 80- $\mu\text{g}/\text{kg}$ groups, respectively (Table 3).

In patients who had a STEMI or NSTEMI, associated mortality by Day 90 was higher in the rFVIIa groups than in the placebo group. This appeared to be a function of dose (Table 3). Outcome from the 40 cardiac events reported by the investigator was 24 recovered, 6 not recovered, one recovering, one recovered with sequelae, 6 fatal, and 2 unknown. Patient death associated with a cardiac event occurred in one placebo, 2 in the 20- $\mu\text{g}/\text{kg}$, and 3 in the 80- $\mu\text{g}/\text{kg}$ dose of rFVIIa.

Cerebral Ischemia

Investigators reported 21 cerebral infarctions in 20 patients based on their clinical evaluations. On DMC retrospective review of all CT scans, 16 additional cerebral infarctions

Table 5. Causal Relationship Among Investigator-Reported DVTs, Pulmonary Emboli, and Trial Drug as Judged by DMC

No. (%)	Treatment Groups			Total
	Placebo	20 $\mu\text{g}/\text{kg}$	80 $\mu\text{g}/\text{kg}$	
DVT				
Not applicable	1 (0.4)	0	0	1 (0.1)
Not evaluable	0	1 (0.4)	0	1 (0.1)
Unlikely	7 (2.6)	5 (1.8)	6 (2.0)	18 (2.1)
Possible	7 (2.6)	6 (2.2)	5 (1.7)	18 (2.1)
Total	15 (5.6)	12 (4.3)	11 (3.7)	38 (4.5)
Pulmonary emboli				
Unlikely	2 (0.7)	0	2 (0.7)	4 (0.5)
Possible	1 (0.4)	4 (1.4)	2 (0.7)	7 (0.8)
Total	3 (1.1)	4 (1.4)	4 (1.3)	11 (1.3)

Table 6. Multivariate Analysis of Risk Factors for Arterial TEs

Factor	OR	95% CI	P
Age/5 years	1.14/year	1.03–1.27	0.012
Platelet count/ $10^{-7}/\text{L}$ increase	1.47	0.97–2.19	0.069
Male gender	1.70	0.94–3.20	0.083
Antiplatelet agents	1.83	1.04–3.20	0.035
Signs of ischemia at baseline*	4.19	1.46–10.54	0.010
20 $\mu\text{g}/\text{kg}\dagger$	1.23	0.57–2.68	0.599
80 $\mu\text{g}/\text{kg}\dagger$	2.14	1.09–4.41	0.031

*Ischemic changes on admission CT or electrocardiogram.

†Relative to placebo.

were detected (Table 4). In an assessment of both the investigator- and DMC-identified events, 7 of the cerebral infarctions were classified as pre-existing (signs of infarction already present on the baseline CT), 4 to be surgery-related, 21 as thromboembolic, and 5 due to mass effect. The frequency of these events did not differ across groups. Seven in the placebo group and 13 rFVIIa-treated patients were considered possibly related to drug administration. Three of the 8 patients with possibly related cerebral infarction in the 80- $\mu\text{g}/\text{kg}$ group died, whereas all but one of the other patients with cerebral infarcts survived.

Outcome from the 21 cerebral infarctions reported by the investigator was 6 recovered, 7 not recovered, 3 recovering, 3 recovered with sequelae, and 2 fatal both in the 80- $\mu\text{g}/\text{kg}$ group.

DVTs and Pulmonary Emboli

There were DVTs in 15 (5.6%) placebo and in 22 (3.8%) active treatment patients ($P=0.45$, Fisher exact test). None of the investigator-reported DVTs had a fatal outcome (Table 5). Pulmonary embolism occurred in 3 (1.1%) of placebo and in 8 (1.4%) of active treatment patients ($P>0.99$, Fisher exact test). Fatal outcomes from pulmonary embolisms were similar in placebo and active treatment groups.

Other TEs

Fourteen other TEs were reported by the investigators, 5 cases of thrombophlebitis in the placebo group and 6 in the rFVIIa-treated patients. In the 80- $\mu\text{g}/\text{kg}$ group, there was also one case each of intracardiac thrombus, renal and retinal artery thrombi.

Risk Factors for Arterial TEs

An increased risk of arterial thromboembolism was noted for the 80- $\mu\text{g}/\text{kg}$ rFVIIa group (OR=2.14; $P=0.031$) and patients with signs of ischemia at baseline (cardiac or cerebral) had a substantially increased risk of having an arterial TE (OR=4.19; $P=0.01$). Furthermore, a higher risk of arterial thromboembolism was associated with increasing age (OR=1.14/5 years; $P=0.0123$) and prior use of platelet aggregation inhibitors (OR=1.83; $P=0.035$). No statistically significant interactions between dose and the other covariates were found (Table 6).

Discussion

The mechanisms responsible for the therapeutic effect of rFVIIa, namely enhanced hemostasis, may also lead to

unintended consequences such as TEs. This risk is potentially amplified in high-risk populations, typified by patients with ICH. The hemostatic effect of FVIIa is, in part, initiated by binding to tissue factor, which is exposed by endothelial injury but is also potentially exposed on atherosclerotic plaques. Thus, administration of rFVIIa to patients with atherosclerotic lesions may lead to thrombosis at unintended sites such as the coronary or cerebral vasculature. The potential off-label use of rFVIIa makes it essential to understand the clinical impact of this process in high-risk patients.

Uncontrolled reports of all off-label use of rFVIIa have linked it to a number of TEs but did not relate them to risk factors.^{1,6–8} Controlled trials of rFVIIa in presumably lower-risk patients with cirrhosis or severe trauma have not demonstrated increased risk of TEs.^{9–11} However, in our previous trial of rFVIIa in acute ICH, in a higher risk population, we found an association between receiving rFVIIa and arterial TEs.²

The FAST trial has provided important additional data to our understanding of the impact of treatment with rFVIIa on TEs in high-risk patients. First, it is by far the largest controlled trial of rFVIIa to date. Second, the change in doses from the proof-of-concept trial to include 20 $\mu\text{g}/\text{kg}$ provides additional data to understand the risks and benefits of a lower dose. Third, extensive prospective measures and DMC review were used to be sure that we identified all TEs. Finally, the trial enrolled patients at high risk for TEs.⁴

The analysis of the FAST data confirms and extends the findings in the proof-of-concept trial. Patients receiving higher doses of rFVIIa appear to have a small increased risk of arterial TEs. The absolute rate of events identified in the FAST trial was higher than previously reported, reflecting the heightened surveillance by both investigators and careful surveillance by the DMC. Still, the current study, with its larger sample and improved surveillance, demonstrates a similar relative increase in TEs in the patients receiving rFVIIa. Logistic regression analysis showed that the risk of having an arterial thrombotic event was significantly increased in the 80- $\mu\text{g}/\text{kg}$ rFVIIa dose group compared with 20 $\mu\text{g}/\text{kg}$ or placebo.

The relative increase in thrombotic events consisted of a higher incidence of myocardial events in patients receiving rFVIIa. In terms of the most significant myocardial events, there was a total 6 STEMIs in the highest dose rFVIIa group compared with 4 in the placebo group. The remainder were NSTEMI or biochemical events only. Thus, the myocardial events were few, mostly biochemical in nature, and most had a minor impact. The minor nature of these events likely explains in part why only 27% of the myocardial events were identified by the investigators; the remainder were identified retrospectively by centralized troponin I measurements and review of electrocardiograms.

Use of rFVIIa in this population appears to have very low risk of ischemic stroke. The number of new ischemic infarcts that were considered in any way related to the study drug by the investigators or DMC was 7, 5, and 8 in the placebo, 20- $\mu\text{g}/\text{kg}$, and 80- $\mu\text{g}/\text{kg}$ dose groups. There is the possibility, however, that if an ischemic stroke occurs in a patient who has received 80 $\mu\text{g}/\text{kg}$ rFVIIa, the outcome will be worse; the

only patients who had a ischemic stroke possibly related to the drug and later died were in the 80- $\mu\text{g}/\text{kg}$ dose group.

The risk factors for TEs identified in this study support the concept that the increased arterial thrombotic events with rFVIIa in this population are likely to be associated with exposure of endothelial tissue factor due to ruptured or ulceration of atheromatous plaques associated with increased risk of thromboses.¹² Higher dose of rFVIIa, older age, and the use of antiplatelet agents were independently associated with higher risk of arterial TEs (Table 6). A stronger association was found with signs of ischemia at baseline (OR=4.19). The criteria used to define ischemia at baseline were limited to signs of cerebral ischemia on the initial CT scan or abnormalities indicative of ischemia on the initial electrocardiogram. Although the number of such cases is small, it would certainly be prudent to avoid the use of rFVIIa in such patients.

Unlike in our previous report, the current study included both investigator-identified events as well as those identified based on routine centralized monitoring and DMC review. Of note, almost 3 times as many myocardial events were identified by the DMC compared with the investigators. The majority of these were biochemical markers (troponin elevation) identified by the central laboratory and not immediately available to the investigators. The likely explanation for this difference is 2-fold. First, routine mandatory testing for adverse events will have a higher sensitivity for identifying events (although possibly a lower specificity). Second, the sensitivity of the troponin I assays is so high that it often identifies events that have little if any clinical impact.

Summary

These data indicate that higher doses of rFVIIa in a population at high risk for TEs are associated with a small increased risk of arterial TEs, primarily minor cardiac events. Demonstration of the ability of rFVIIa to improve outcome in future studies should be driven by its effectiveness in slowing bleeding overshadowing the risk of a small increase in arterial TEs.

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