Risk of Thromboembolic Events in Controlled Trials of rFVIIa in Spontaneous Intracerebral Hemorrhage

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Background and Purpose—Recombinant activated factor VII (rFVIIa) reduces hematoma expansion and improves outcome after intracerebral hemorrhage (ICH), with an apparent increase in nonfatal thromboembolic events (TEs) with higher doses. Despite low incidences of such events in rFVIIa-treated hemophiliacs, the frequency in older patients with more atherosclerosis and immobility has yet to be defined.

Methods—Data were pooled from 3 randomized placebo-controlled studies in patients diagnosed within 3 hours of spontaneous ICH who received a single dose of rFVIIa (5 to 160 μg/kg; n=371) or placebo (n=115). Clinical/laboratory evaluations, lower extremity Doppler studies, and 72-hour CT scans were used to monitor for TEs. Adverse events occurring while hospitalized and serious events occurring through day 90 were carefully reviewed.

Results—There was no overall increase in risk of total TEs in rFVIIa-treated patients; however, there were more arterial, but not venous, TEs in the high dose group (120 to 160 μg/kg) compared with placebo (5.4% versus 1.7%; P=0.13). Arterial events occurring within 7 days of drug administration classified as possibly or probably associated with study drug included myocardial ischemia (n=9, 8 were non–ST-segment elevation and non–Q-wave events; 2 of the 9 had sequelae) and ischemic stroke (n=9, 4 of which had likely causes other than rFVIIa). Regression analysis identified high doses (120 to 160 μg/kg) of rFVIIa as the only factor associated with arterial TEs (odds ratio=6.75; P=0.02).

Conclusions—There appears to be an increased risk of arterial TEs associated with higher doses of rFVIIa in ICH patients as compared with placebo. Further studies are underway to identify specific factors associated with these events and to define the dose that maximizes benefit and minimizes risk. (Stroke. 2008;39:850-856.)

Key Words: clinical trials ■ intracerebral hemorrhage ■ recombinant activated factor VII (rFVIIa) ■ thromboembolic events

Recombinant activated factor VII (rFVIIa) is currently approved in the United States for the control of spontaneous or surgical bleeding in patients with congenital hemophilia and inhibitors to factor VIII (FVIII) or factor IX (FIX), and in FVII-deficient patients. In this population, thromboembolic events are infrequently reported and occur primarily in high-risk patients with known predisposing factors. Recombinant activated factor VII (rFVIIa) provides a means by which rFVIIa is also the basis of the concern for thromboembolic events (TE) events. The hemostatic effect of FVIIa is, in part, exerted when it binds to tissue factor, which is exposed by endothelial injury and potentially on atherosclerotic plaques. The tissue factor-FVIIa complex converts factor X (FX) to Fxa and FIX to FIXa. FXa then converts factor II (II) to FIIa (prothrombin to thrombin)-activating platelets. With pharmacologic doses of rFVIIa this process may be augmented by tissue factor–independent binding of rFVIIa to activated platelets that aggregate at the site of blood vessel injury, producing a burst of thrombin producing a fibrin plug. Thus administration of rFVIIa to patients with atherosclerotic lesions may lead to thrombosis at unintended sites such as the coronary or cerebral vasculature.

Recently, considerable interest has developed in other uses of rFVIIa such as in trauma, surgery, and limiting hematoma expansion in intracerebral hemorrhage (ICH). We reported that rFVIIa administered within 4 hours of ICH symptom onset reduced hematoma growth, lowered mortality, and improved functional outcome despite a numerical increase in the number of thromboembolic events (7% versus 2% for rFVIIa and placebo-treated patients, respectively; P=0.12).

Controlled trials of rFVIIa use in patients with cirrhosis, or severe trauma have not demonstrated increased risk of throm-
boembolic events in patients receiving rFVIIa. In a recent review of the US Food and Drug Administration’s data, however, off-label use of rFVIIa was linked to a number of thromboembolic events. Because this system is based on spontaneous self-reports, it is not possible to determine frequency or risk factors associated with these thromboembolic events.

Patients with ICH may have an inherently greater risk of thromboembolic events attributable to advanced age, high incidence of hypertension, and preexisting atherosclerotic disease and diabetes. Additionally, ICH-induced hemiplegia increases the potential for venous thrombosis and pulmonary embolism.

In this manuscript we review thromboembolic events from all 3 controlled clinical trials of rFVIIa in ICH7,12,13 to help define thromboembolic event frequency and identify risk factors. 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.

Materials and Methods

The details of the trials have been reported elsewhere.7,12,13 A total of 87 patients were enrolled in the 2 dose escalation safety trials. An additional 399 patients were enrolled in a multi-national, double-blind, placebo-controlled proof-of-concept trial, providing a total of 486 patients for this analysis. The protocols and safety assessments for each trial were similar, allowing the pooling of the data.

Patient Selection

Patients were eligible for enrolment in the 3 trials if they presented with symptoms attributable to a spontaneous ICH evident on CT scan, performed within 3 hours of onset. Exclusion criteria included: age under 18 years; Glasgow Coma Scale (GCS) score ≤5; planned early surgery; ICH secondary to coagulopathy (including oral anti-coagulant use); sepsis, crush injury, or disseminated coagulopathy (DIC); pregnancy, or preexisting disability.

In all 3 studies patients were also excluded if they had symptomatic thromboembolic or vasoocclusive disease (angina, claudication, deep vein thrombosis, and cerebral or myocardial infarction) within 30 days of ICH. However, midway through the proof-of-concept trial (after inclusion of 205 of the 399 patients), the exclusion criteria were modified to exclude patients with any history of thromboembolic events, as opposed to only patients with such a history within the preceding 30 days, based on a recommendation from the Data Safety and Monitoring Board (DSMB).

Study Intervention

In the 2 dose escalation trials patients were enrolled in dose tier blocks starting at 5 μg/kg and progressively increasing to 80 μg/kg rFVIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) in the US-based trial and to 160 μg/kg rFVIIa in the European/Australasia trial, in either an 8:2 (United States) or 6:2 (Europe/Australasia) allocation of patients to rFVIIa or placebo. In the proof-of-concept trial patients were randomly assigned to dose groups of 40, 80, or 160 μg/kg of rFVIIa or placebo. In all 3 trials 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.

Clinical Assessments

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

Safety Assessments

Adverse events were defined, based on regulatory criteria, as any clinical or laboratory occurrence that resulted in any undesirable event, whether or not it appeared to be related to trial drug administration. Any adverse event that resulted in death, a life-threatening experience, prolongation of hospitalization, a persistent or significant disability/incapacity, or was considered significant by a local investigator was considered a serious adverse event. The details of all adverse events until day 15 (or discharge) and all serious adverse events until day 90 were recorded. In the proof-of-concept trial the DSMB performed an interim analysis after every 40 patients were enrolled, comparing the proportion of dead or severely disabled (defined by an mRS score of 4 to 6 on day 15) patients in the combined rFVIIa-treatment group with that of the placebo group.

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 enrolment; and “recovered with sequelae,” as a result of the adverse event the subject suffered persistent and significant disability/incapacity. In addition, the following predefined adverse events were considered critical if they occurred within 7 days after trial drug administration: death; consumption coagulopathy (thrombocytopenia, reduction of fibrinogen levels and elevation of D-dimer levels; acute myocardial ischemia (ischemic ECG changes or a troponin-I >0.5 μg/L); ischemic stroke (defined by clinical signs and follow-up hour CT scan); pulmonary embolism (ventilation-perfusion scan or CT angiography); excessive perihematomal edema (ratio of edema/ICH volume ≥2.5); cerebral venous thrombosis (clinical signs and imaging studies). To monitor for these events, the following screening tests were routinely performed: coagulation parameters (fibrinogen, prothrombin fragment 1+2, platelet count, and INR) before and 1 and 24 hours after trial drug administration; cardiac-troponin-I before dosing and at 1 and 24 hours after trial drug administration for the dose escalation trials and prior to dosing and at 1 hour for the dose-ranging study, ECG on admission and at 24 hours; Doppler ultrasound of lower extremities on day 3 and head CT scan at 72 hours.

Adjudication Process

At the conclusion of the proof-of-concept study, the DSMB performed a detailed review of medical records, imaging studies, and reports from the local investigators for all reported thromboembolic events. In addition, an external cardiologist provided an independent review of all cardiac events.

Statistical Analysis

The overall safety population of the pooled ICH studies comprised 486 patients of whom 371 received rFVIIa and 115 placebo. Allocation to individual dose groups was as follows: 5 μg/kg, 8 patients; 10 μg/kg, 6 patients; 20 μg/kg, 14 patients; 40 μg/kg, 122 patients; 80 μg/kg, 106 patients; 120 μg/kg, 6 patients; and 160 μg/kg, 109 patients. To provide a representative sample, patients who received 5, 10, 20, and 40 μg/kg were combined, as were patients who received 120 and 160 μg/kg.

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 rFVIIa patients combined was compared with the placebo group using a 2-sided Chi-square test. Because we found an increase in arterial but not venous events, a separate analysis was performed for arterial thromboembolic events.

Logistic regression analysis was performed to identify factors related to the occurrence of arterial thromboembolic events. 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; PT/INR; troponin-I; fibrinogen; platelet count; prothrombin fragment 1+2; and antiplatelet medications (eg, rofecoxib, aspirin, and other non-steroidal anti-inflammatory drugs). After screening with univariate analysis, vari-
ables with \(P<0.25\) were entered into the regression model. The model was then successively 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 4 dose groups were similar in terms of age, race, gender, disease severity (GCS score, ICH volume), and hemorrhage location (Table 1). Time to treatment also did not differ across groups.

**Adverse Events**

The proportion of patients with adverse events was similar across groups. The most common serious adverse events were attributable to the underlying condition. Adverse events deemed possibly or probably related to trial drug by the investigator or DSMB occurred with similar frequency in the placebo and rFVIIa treatment groups.

The overall 90-day mortality was 17%, 16%, and 19% in the 5 to 40 \(\mu\)g/kg, 80 \(\mu\)g/kg, and 120 to 160 \(\mu\)g/kg rFVIIa dose groups. Mortality in all rFVIIa patients combined was 18% compared with 27% in the placebo group (\(P=0.0264\); Table 2). The 6 deaths that were assessed by the investigator or DSMB as possibly or probably related to trial drug were evenly distributed among the groups.

**Thromboembolic Events**

The rate of thromboembolic events in patients receiving rFVIIa was similar to that in the placebo group (8% versus 5%; \(P=0.42\); Table 2). These events were considered serious in 6.5% of rFVIIa-treated patients and 3.5% of placebo-treated (\(P=0.36\)); however, the proportion in the highest dose

### Table 1. Patient Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=115)</th>
<th>5 to 40 (\mu)g/kg (n=150)</th>
<th>80 (\mu)g/kg (n=106)</th>
<th>120 to 160 (\mu)g/kg (n=115)</th>
<th>Combined (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±12</td>
<td>66±13</td>
<td>65±12</td>
<td>64±13</td>
<td>65±13</td>
</tr>
<tr>
<td>Male, %</td>
<td>55</td>
<td>59</td>
<td>62</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Race or ethnic group, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>77</td>
<td>69</td>
<td>79</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>Asian/Pacific islander</td>
<td>15</td>
<td>20</td>
<td>13</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hemorrhage location, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>56</td>
<td>49</td>
<td>41</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Thalamus</td>
<td>30</td>
<td>33</td>
<td>38</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Lobar hemisphere</td>
<td>20</td>
<td>15</td>
<td>25</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Brainstem</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>GCS score</td>
<td>14 (3.0–15.0)</td>
<td>15 (6.0–15.0)</td>
<td>14 (6.0–15.0)</td>
<td>15 (6.0–15.0)</td>
<td>14 (6.0–15.0)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>14.9±6.3</td>
<td>13.9±6.6</td>
<td>12±5.4</td>
<td>13.8±6.3</td>
<td>13.3±6.2</td>
</tr>
<tr>
<td>Onset-to-treatment time, min</td>
<td>166.3±32.4</td>
<td>174.3±34.7</td>
<td>169.4±34.2</td>
<td>166.8±33.7</td>
<td>170.6±34.3</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>24±23</td>
<td>21±22</td>
<td>22±24</td>
<td>27±32</td>
<td>23±26</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale. Values are mean±SD, median (range), or percent. Values may not add up to 100% because of rounding.

### Table 2. Effect of Thromboembolic Events on 90-Day Mortality

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=115)</th>
<th>5 to 40 (\mu)g/kg (n=150)</th>
<th>80 (\mu)g/kg (n=106)</th>
<th>120 to 160 (\mu)g/kg (n=115)</th>
<th>Combined (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic event rate, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>11</td>
<td>8 (P=0.4150)</td>
</tr>
<tr>
<td>Venous</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3 (P=0.99)</td>
</tr>
<tr>
<td>Arterial</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>5 (P=0.1251)</td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly related to thromboembolic events</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1 (P=0.99)</td>
</tr>
<tr>
<td>All causes</td>
<td>27</td>
<td>17</td>
<td>16</td>
<td>19</td>
<td>18 (P=0.0264)</td>
</tr>
</tbody>
</table>

\(P\) values are based on Fisher exact test except for all cause mortality, which is a 2-sided \(\chi^2\) test.
group was double that of the next highest group. Thromboembolic events considered possibly or probably treatment-related by the investigator or DSMB occurred in 5% of those receiving rFVIIa and 4% of patients receiving placebo.

The incidence of venous thromboembolic events did not differ in patients receiving rFVIIa compared with placebo-treated patients; however, there was a increased risk of arterial thromboembolic events associated with higher doses of rFVIIa. Based on investigator reports and DSMB review, myocardial ischemia or ischemic stroke occurred in 20 of the 371 (5.4%) rFVIIa-treated patients compared with 2 of the 115 (1.7%) patients who received placebo ($P=0.13; \text{Table 2}$).

The logistic regression analysis of arterial thromboembolic events identified an increased risk in those patients who received 120 to 160 $\mu g/kg$ of rFVIIa (odds ratio [OR], 6.75; 95% confidence interval [CI], 1.44 to 31.63; $P=0.02$).

**Myocardial Ischemia and Infarction**

Eleven episodes of myocardial ischemia or infarction were identified among the 486 randomized patients; 9 were classified by the investigator or DSMB as being probably/possibly related to the study drug. Three of the events occurred in the 5 to 40 $\mu g/kg$-dose group, and 6 in the 120 to 160 $\mu g/kg$, and none in the placebo group (Table 3). The number of myocardial events tended to be higher in the combined rFVIIa treatment groups compared with placebo (3.0% versus 0.0%, respectively; $P=0.075$).

The 9 total myocardial events were classified using both the Q-wave and STEMI (ST elevation) criteria. Eight were non–ST-segment elevation and non–Q-wave events, of which 1 had sequelae. One patient had a Q-wave myocardial infarction that was also classified as a STEMI and had residual effects of the cardiac event.

**Ischemic Strokes**

Thirteen ischemic strokes were reported among the 486 patients included in the study, 2 (2%) among the 115 placebo patients, and 11 (3%) among the 371 rFVIIa-treated patients (Fisher exact test; $P=0.74$). Either the investigator or the DSMB indicated that 9 were possibly or probably related to the study drug (Table 4). Of those 2 appear to represent hemorrhage into an ischemic infarct (Figure 1A and 1B), 1 occurred after emergency craniotomy for hematoma evacuation (Figure 1C), 1 was likely attributable to internal carotid

### Table 3. Episodes of Myocardial Ischemia/Infarction Possibly or Probably Related to Study Drug

<table>
<thead>
<tr>
<th>Dose, $\mu g/kg$</th>
<th>Q-wave MI</th>
<th>STEMI</th>
<th>Troponin I</th>
<th>Troponin T</th>
<th>Latency, days</th>
<th>Age, y</th>
<th>Sex</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>No</td>
<td>No</td>
<td>20</td>
<td></td>
<td>4</td>
<td>84</td>
<td>F</td>
<td>Recovered</td>
</tr>
<tr>
<td>40</td>
<td>No</td>
<td>No</td>
<td>1.7</td>
<td>0.53</td>
<td>2</td>
<td>52</td>
<td>F</td>
<td>Recovered</td>
</tr>
<tr>
<td>40</td>
<td>No</td>
<td>No</td>
<td>11.4</td>
<td></td>
<td>1</td>
<td>86</td>
<td>F</td>
<td>Recovered</td>
</tr>
<tr>
<td>160</td>
<td>No</td>
<td>No</td>
<td>1.41</td>
<td></td>
<td>4</td>
<td>78</td>
<td>M</td>
<td>Recovered</td>
</tr>
<tr>
<td>160</td>
<td>Yes</td>
<td>Yes</td>
<td>6.2</td>
<td></td>
<td>2</td>
<td>69</td>
<td>M</td>
<td>Recovered with sequelae</td>
</tr>
<tr>
<td>160</td>
<td>No</td>
<td>No</td>
<td>22.6</td>
<td>0.66</td>
<td>1</td>
<td>58</td>
<td>M</td>
<td>Recovered</td>
</tr>
<tr>
<td>160</td>
<td>No</td>
<td>No</td>
<td>20.8</td>
<td></td>
<td>1</td>
<td>76</td>
<td>M</td>
<td>Recovered</td>
</tr>
<tr>
<td>160</td>
<td>No</td>
<td>No</td>
<td>0.12</td>
<td></td>
<td>2</td>
<td>56</td>
<td>M</td>
<td>Recovered with sequelae</td>
</tr>
<tr>
<td>160</td>
<td>No</td>
<td>No</td>
<td>3.19</td>
<td></td>
<td>2</td>
<td>65</td>
<td>F</td>
<td>No clinical event reported</td>
</tr>
</tbody>
</table>

F indicates female; M, male; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction. “Recovered,” fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent. “Recovered with sequelae,” as a result of the adverse event the subject suffered persistent and significant disability/incapacity.

### Table 4. Episodes of Cerebral Infarction Possibly or Probably Related to Study Drug

<table>
<thead>
<tr>
<th>Dose, $\mu g/kg$</th>
<th>Age, y</th>
<th>Sex</th>
<th>Latency, days</th>
<th>Investigator/AIDSMB Rating</th>
<th>Findings</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>77</td>
<td>F</td>
<td>4</td>
<td>Possibly</td>
<td>Investigator reported new ischemic event due to mass effect of ICH</td>
<td>E</td>
</tr>
<tr>
<td>40</td>
<td>67</td>
<td>F</td>
<td>2</td>
<td>Possibly</td>
<td>Investigator reported as asymptomatic</td>
<td>F</td>
</tr>
<tr>
<td>40</td>
<td>58</td>
<td>M</td>
<td>6</td>
<td>Possibly</td>
<td>Left ICA occlusion on U/S 3 days prior to ICH (unknown on enrolment), large, distant from ICH</td>
<td>D</td>
</tr>
<tr>
<td>80</td>
<td>65</td>
<td>M</td>
<td>2</td>
<td>Possibly</td>
<td>Occurred after emergent clot evacuation,? due to surgery</td>
<td>C</td>
</tr>
<tr>
<td>160</td>
<td>68</td>
<td>F</td>
<td>4</td>
<td>Possibly</td>
<td>Possible new parietal infarct adjacent to ICH</td>
<td>H</td>
</tr>
<tr>
<td>160</td>
<td>71</td>
<td>F</td>
<td>2</td>
<td>Possibly</td>
<td>Hemorrhage into infarction</td>
<td>A</td>
</tr>
<tr>
<td>160</td>
<td>50</td>
<td>M</td>
<td>2</td>
<td>Probably</td>
<td>Large, contralateral</td>
<td>I</td>
</tr>
<tr>
<td>160</td>
<td>90</td>
<td>M</td>
<td>2</td>
<td>Possibly</td>
<td>Hemorrhage into infarction</td>
<td>B</td>
</tr>
<tr>
<td>160</td>
<td>68</td>
<td>M</td>
<td>4</td>
<td>Possibly</td>
<td>DSMB review of CT indicated new small right parietal ischemic lesion</td>
<td>G*</td>
</tr>
</tbody>
</table>

*No baseline CT, only at 24 and 72 hours. F indicates female; ICA, internal carotid artery; M, male; U/S, ultrasound.
artery occlusion (discovered after enrollment to have been identified shortly before the ICH; Figure 1D), and 5 were new ischemic events unrelated to the hemorrhage (Figure 1E through 1I).

Deep Vein Thrombosis and Pulmonary Embolism
There was no significant difference in the frequency of deep vein thrombosis (n = 10) or pulmonary emboli (n = 8) between groups. Deep vein thrombosis was reported in 2%, 1%, 3%, and 3% of patients receiving placebo, 5 to 40 µg/kg, 80 µg/kg, and 120 to 160 µg/kg rFVIIa, respectively. Corresponding values for pulmonary embolism were 2%, 2%, 1%, and 2% (Figure 2).

Coagulation Parameters
At 1-hour after drug administration, fibrinogen levels fell from 4.0±1.2 to 3.6±1.2 g/L in patients receiving rFVIIa. There were no differences D-dimer levels. At 24 hours, mean fibrinogen levels and INR had returned to normal. There was no evidence of disseminated intravascular coagulation.

Risk Factors for Arterial Thromboembolic Events
The multiple regression analysis for risk of arterial thromboembolic events indicated that age (OR, 1.03; 95% CI, 1.00 to 1.07; P = 0.08) and race (African decent; OR, 4.75; 95% CI, 0.67 to 21.46; P = 0.11) had no influence. Similarly, lower doses of rFVIIa were not associated with a risk of such events (rFVIIa 5 to 40 µg/kg: OR, 2.21; 95% CI, 0.43 to 11.38; 854 Stroke March 2008

![Figure 1. Baseline and follow-up CT images of patients with new ischemic lesions considered possibly or probably related to study drug (see Table 4 for patient details). Two appear to represent hemorrhage into an ischemic infarct (A and B), 1 was likely attributable to recent internal carotid artery occlusion (D), and 5 were new ischemic events unrelated to the hemorrhage (E through I).](http://stroke.ahajournals.org/)

![Figure 2. Thromboembolic events by dose group. The number above the bars indicates the total number of events.](http://stroke.ahajournals.org/)
P=0.34; and rFVIIa 80 μg/kg: OR, 1.73; 95% CI, 0.28 to 10.72; P=0.56). The only factor independently associated with arterial thromboembolic events was receiving rFVIIa in the highest dose range (120 to 160 μg/kg), as described above.

Discussion

Until recently, rFVIIa has been administered predominantly to a subset of hemophilia patients who, in general, are considered to be at low risk of thromboembolic complications. They are typically under 60 years of age with few cardiovascular risk factors.1,13 With the potential for more widespread use of rFVIIa, however, it is important to reassess safety in older patients with intact coagulation systems and more risk factors for thromboembolic events.

In this article we report the incidence of thromboembolic complications in all patients with acute ICH and intact coagulation systems who received rFVIIa in 3 controlled trials. Although the risk of disabling or fatal adverse events was no higher in the rFVIIa-treated patients compared with placebo, we found that in these studies administration of higher doses (120 to 160 μg/kg) was associated with an increased risk of arterial thromboembolic events. These episodes consisted of myocardial and cerebral ischemia. Of note, there was no increased incidence of venous thromboembolic events which overall was quite low. We believe that the relatively low rate of venous TEs may reflect the fact that the population enrolled in these studies excluded those patients who are at the highest risk (GCS 3 to 5) and who had recent (or later in the trial any) history of thromboembolic events. In addition it may be a result of our strong emphasis providing a better definition of the risks for thromboembolic events.

The differential effect of rFVIIa on arterial and venous thromboembolic events is of interest. We speculate that the increased incidence of arterial thromboembolic events is related to exposure of endothelial tissue factor attributable to rupture or ulceration of atheromatous plaques.16 The rFVIIa may bind to such sites and initiate thrombosis which can result in myocardial or cerebral ischemia. Such plaques are common in patients at risk for ICH, and they are associated with an increased risk of thromboses forming in myocardial and cerebral vessels.16,17 On the other hand, venous thromboses develop as a result of stasis and thus may not be caused by rFVIIa-initiated thrombosis.

Of the 371 patients receiving rFVIIa, myocardial ischemia or infarction was identified as possibly or probably related to drug administration in 9. Eight of the 9 events were characterized as mild elevation of troponin levels and non-STEMI events that did not result in Q-waves of which 1 had sequelae. The ninth event was associated with ST elevation, Q-waves, and impaired cardiac function.

Elevated troponin levels are common after ICH.18 Their significance is uncertain and in some cases may represent a neurocardiac phenomenon, as is seen in subarachnoid hemorrhage19,20 and ischemic stroke.21 This neurocardiac phenomenon, best described in subarachnoid hemorrhage patients, is thought to occur through intense sympathetic activation producing myocardial coagulation band necrosis, which results in arrhythmias, electrocardiographic wall motion abnormalities, and in rare cases markedly depressed contractility and cardiac output referred to as “stunned myocardium.”22 Thus the exact meaning of the elevated troponin levels reported here and their relationship to rFVIIa is not certain. The absence of these events in patients receiving placebo suggests they may be drug related; however, the numbers are too small to draw any conclusions. Data from the subsequent trial will help clarify this question.

The occurrence of ischemic strokes immediately after a spontaneous ICH represents a phenomenon about which very little is known and which has not been previously reported. In the present study, 5 patients, 1 of whom received placebo, had new areas of infarction that was distant from the hematoma. Similarly, it is not clear how many “spontaneous” intracerebral hematomas are attributable to very rapid hemorrhage into acutely ischemic brain after rupture of a damaged supplying artery or arteriole. In the NINDS rt-PA Stroke Trial,23 there were 2 (0.6%) symptomatic ICH in placebo-treated patients who had normal baseline scans and subsequent development of large intracerebral hematomas. Based on retrospective review of the serial CT scans, in the present study, 3 of the ischemic strokes occurred in similar patients who suffered ischemic stroke with secondary hyperacute hemorrhage rather than ICH followed by an ischemic stroke.

The clinical impact of the ischemic events is very difficult to judge in this population. Several were only identified as incidental findings on the 72-hour CT scan. In patients who have a depressed level of consciousness attributable to the initial hemorrhage, however, comprehensive assessment of neurologic status is difficult. Thus it is possible that the clinical signs of a new ischemic stroke that would have been clearly evident in a previously intact patient would be missed in one shortly after an ICH.

The acute nature of the study intervention did not allow for very sensitive assessment of thromboembolic risk and the classification of risk in this study was based entirely on historical data. No specific biochemical risk factors were measured, nor was imaging of carotid or coronary arteries performed. Had such data been available for analysis, the results might have been more revealing.

It is important to emphasize the change in exclusion criteria that occurred midway through the proof-of-concept trial. Initially, patients with a history of ischemic events within 30 days were excluded and after the protocol change those with any history of such events were excluded. It is reassuring to note that the frequency of thromboembolic events was not higher in the first half of the trial, yet, because we had limited success in identifying risks factors for such events, the question of who is at risk remains unanswered.

The next steps in more precisely defining the risk of thromboembolic events include: (1) studying patients with risk factors for thromboembolic events by testing rFVIIa in a broader ICH patient population; (2) further determining the risk/benefit of lower doses in rFVIIa in ICH; and (3) providing a better definition of the risks for thromboembolic events, their characteristics, and consequences. All of these
factors have been incorporated into the ongoing phase III trial of rFVIIa in acute ICH (FAST Trial).

Disclosures
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References
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