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ORIGINAL ARTICLE

Efficacy and Safety of Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

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ABSTRACT

BACKGROUND

Intracerebral hemorrhage is the least treatable form of stroke. We performed this phase 3 trial to confirm a previous study in which recombinant activated factor VII (rFVIIa) reduced growth of the hematoma and improved survival and functional outcomes.

METHODS

We randomly assigned 841 patients with intracerebral hemorrhage to receive placebo (268 patients), 20 μ g of rFVIIa per kilogram of body weight (276 patients), or 80 μ g of rFVIIa per kilogram (297 patients) within 4 hours after the onset of stroke. The primary end point was poor outcome, defined as severe disability or death according to the modified Rankin scale 90 days after the stroke.

RESULTS

Treatment with 80 μ g of rFVIIa per kilogram resulted in a significant reduction in growth in volume of the hemorrhage. The mean estimated increase in volume of the intracerebral hemorrhage at 24 hours was 26% in the placebo group, as compared with 18% in the group receiving 20 μ g of rFVIIa per kilogram ($P=0.09$) and 11% in the group receiving 80 μ g ($P<0.001$). The growth in volume of intracerebral hemorrhage was reduced by 2.6 ml (95% confidence interval [CI], -0.3 to 5.5; $P=0.08$) in the group receiving 20 μ g of rFVIIa per kilogram and by 3.8 ml (95% CI, 0.9 to 6.7; $P=0.009$) in the group receiving 80 μ g, as compared with the placebo group. Despite this reduction in bleeding, there was no significant difference among the three groups in the proportion of patients with poor clinical outcome (24% in the placebo group, 26% in the group receiving 20 μ g of rFVIIa per kilogram, and 29% in the group receiving 80 μ g). The overall frequency of thromboembolic serious adverse events was similar in the three groups; however, arterial events were more frequent in the group receiving 80 μ g of rFVIIa than in the placebo group (9% vs. 4%, $P=0.04$).

CONCLUSIONS

Hemostatic therapy with rFVIIa reduced growth of the hematoma but did not improve survival or functional outcome after intracerebral hemorrhage. (ClinicalTrials.gov number, NCT00127283.)

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*The institutions participating in the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial are listed in the Appendix.

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INTRACEREBRAL HEMORRHAGE IS THE MOST devastating form of stroke. Approximately 40% of patients with intracerebral hemorrhage die within 30 days, and the majority of survivors are left with severe disability.^{1,2} Hematoma growth occurs in up to 70% of patients who have intracerebral hemorrhage documented by computed tomographic (CT) scanning performed within 3 hours after the onset of symptoms.^{3,4} Furthermore, hemorrhage expansion is an independent determinant of death and disability.⁴ In addition to intracerebral-hemorrhage growth, other predictors of poor outcome include age, baseline volume of the hemorrhage, Glasgow Coma Scale score, intraventricular hemorrhage, and infratentorial location.⁵

There is no proven treatment for intracerebral hemorrhage.⁶ Given its prognostic significance, hematoma expansion is an attractive therapeutic target.⁷ Factor VIIa acts locally at sites of tissue injury and vascular-wall disruption by binding to tissue factor and thus generating small amounts of thrombin sufficient to activate platelets. At pharmacologic doses, recombinant activated factor VII (rFVIIa) directly activates factor X on the surface of activated platelets, resulting in a thrombin burst and acceleration of coagulation.⁸

We previously found that rFVIIa reduced the growth of intracerebral hemorrhage when administered within 4 hours after the onset of symptoms.⁹ In addition, rFVIIa resulted in improved survival and functional outcome at 90 days. In the current study, we evaluated the effects of 20 μ g and 80 μ g of rFVIIa per kilogram of body weight on rates of death and severe disability after intracerebral hemorrhage.

METHODS

The Factor Seven for Acute Hemorrhagic Stroke (FAST) trial was a multicenter, randomized, double-blind, placebo-controlled trial conducted between May 2005 and February 2007 at 122 sites in 22 countries. Written informed consent was obtained from each patient or a legally acceptable surrogate, and the trial was approved by local institutional review boards and national regulatory authorities, as applicable. The authors designed the trial protocol, directed the data analysis, and wrote the manuscript, whereas the sponsor was responsible for trial operations, including data analysis. The principal investigator (Dr. Mayer)

assumes full responsibility for the veracity and completeness of the reported data.

PATIENTS

Patients 18 years of age or older with spontaneous intracerebral hemorrhage documented by CT scan within 3 hours after the onset of symptoms were eligible for enrollment. The exclusion criteria were a Glasgow Coma Scale score of 5 or less; surgical evacuation of hematoma planned within 24 hours; secondary intracerebral hemorrhage resulting from trauma, arteriovenous malformation, or other causes; known use of oral anticoagulant therapy, thrombocytopenia, or coagulopathy; acute sepsis, crush injury, or disseminated intravascular coagulation; pregnancy; previous disability (prestroke modified Rankin scale score >2); and known recent (<30 days before enrollment) thromboembolic disease (angina, claudication, deep-vein thrombosis, cerebral infarction, or myocardial infarction).

TREATMENT

The patients underwent block randomization according to site to receive a single intravenous dose of placebo or of rFVIIa (NovoSeven, Novo Nordisk) at a dose of 20 μ g or 80 μ g per kilogram. Treatment was administered within 1 hour after the baseline CT scan and no later than 4 hours after the onset of symptoms. The study drug was supplied as a freeze-dried powder and was reconstituted in sterile water before being administered intravenously over a period of 2 minutes. Dosing was based on estimated body weight. It was recommended that medical management conform with the 1999 American Stroke Association guidelines for intracerebral hemorrhage.¹⁰

CT SCANNING

Follow-up CT scans were performed at target intervals of 24 hours (range, 21 to 27) and 72 hours (range, 66 to 78) after drug administration. When a 24-hour scan was not available within the specified time period, the first follow-up scan performed within 48 hours was analyzed. Digital CT data were analyzed with the use of Analyze software (Mayo Clinic) by two neuroradiologists who were unaware of the treatment assignment. The volumes of intracerebral hemorrhage, intraventricular hemorrhage, and edema were calculated with the use of computerized planimetric techniques and were evaluated as secondary end points.

We have previously shown that the interobserver reliability of this method is excellent.¹¹

CLINICAL ASSESSMENTS

Clinical assessments were performed at enrollment; at 1 hour and 24 hours after drug administration; on days 2, 3, and 15 of hospitalization (or at discharge if earlier); and on day 90 after the stroke. Neurologic deficit was assessed according to scores on the Glasgow Coma Scale, which range from 15 (normal) to 3 (deep coma),¹² and the National Institutes of Health Stroke Scale (NIHSS), which range from 0 (normal) to 42 (coma with quadriplegia).¹³ The primary outcome measure was the score on the modified Rankin scale at day 90.¹⁴ The modified Rankin scale evaluates global disability and handicap; scores range from 0 (no symptoms or disability) to 6 (death). Secondary end points at day 90 included the Barthel index (ranging from 100 [independent in all activities of daily living] to 0 [completely dependent]),¹⁵ the Extended Glasgow Outcome Scale,¹⁶ the NIHSS, the EuroQol scale,¹⁷ and the Revised Hamilton Rating Scale for Depression.¹⁸ At the 90-day follow-up, patients who had died were assigned a Barthel index score of 0, and the last recorded NIHSS score was carried forward.

SAFETY ASSESSMENTS

We recorded all adverse events until discharge and all serious adverse events until day 90. Medical events of special interest, defined as myocardial infarction, ischemic stroke, deep-vein thrombosis, and pulmonary embolism, were subject to detailed reporting and expedited review. All medical events of special interest and serious adverse events identified by local investigators were reported to an independent data and safety monitoring committee. In addition, all electrocardiograms, centrally analyzed cardiac troponin I values, and 72-hour CT scans were reviewed by the data and safety monitoring committee in order to identify unreported cases of myocardial or cerebral ischemia. The data and safety monitoring committee compared the results for death, serious adverse events, and medical events of special interest in the three treatment groups after the enrollment of every 75 patients.

STATISTICAL ANALYSIS

All analyses were based on the intention-to-treat principle. The primary efficacy end point was se-

vere disability or death, defined as a modified Rankin scale score of 5 or 6 at day 90. The study was powered to detect an odds ratio of poor outcome of 0.53 or less with active treatment as compared with placebo (on the assumption of a frequency of poor outcome of 45% in the placebo groups and 30% in the treatment groups) on the basis of a one-sided chi-square test, with a beta level of 0.10 and an alpha level of 0.025. After a planned sample-size review midway through the trial that evaluated the proportion with poor 90-day outcomes in the pooled group of patients receiving placebo and those receiving 80 μ g of rFVIIa per kilogram, the study population was increased by 123 patients to a new target of 816. The primary outcome measure was analyzed by logistic regression, with treatment, age, sex, baseline volume of intracerebral hemorrhage, pre-stroke modified Rankin scale score, and location (supratentorial or infratentorial) as covariates according to a prespecified statistical-analysis plan. For surviving patients with missing outcome data, the last observation was carried forward. The scores on the Barthel index and the NIHSS were analyzed with the use of an analysis-of-variance model with the same covariates, with the baseline score on the Glasgow Coma Scale used instead of the modified Rankin scale score.

Lesion volumes on CT were analyzed with the use of linear mixed models to yield estimated mean values. The patient and the two scan readers were included as random effects, and treatment, baseline volume of intracerebral hemorrhage, time from onset of symptoms to baseline CT scan, and time from baseline CT scan to treatment were included as fixed-effect covariates. Percentage increases were log-transformed to obtain normality after the addition of 100 to eliminate negative values. The chi-square test was used to compare the frequencies of arterial, venous, and all thromboembolic serious adverse events in the three treatment groups at day 90. Exploratory post hoc analyses were performed to determine how the timing of treatment influenced the hemostatic effect of rFVIIa; whether stratification according to age, baseline volume of the hemorrhage, or timing of treatment influenced the clinical response to rFVIIa treatment; and whether baseline predictors of thromboembolic serious adverse events could be identified. All analyses were performed with SAS software, version 8.2, on a UNIX platform.

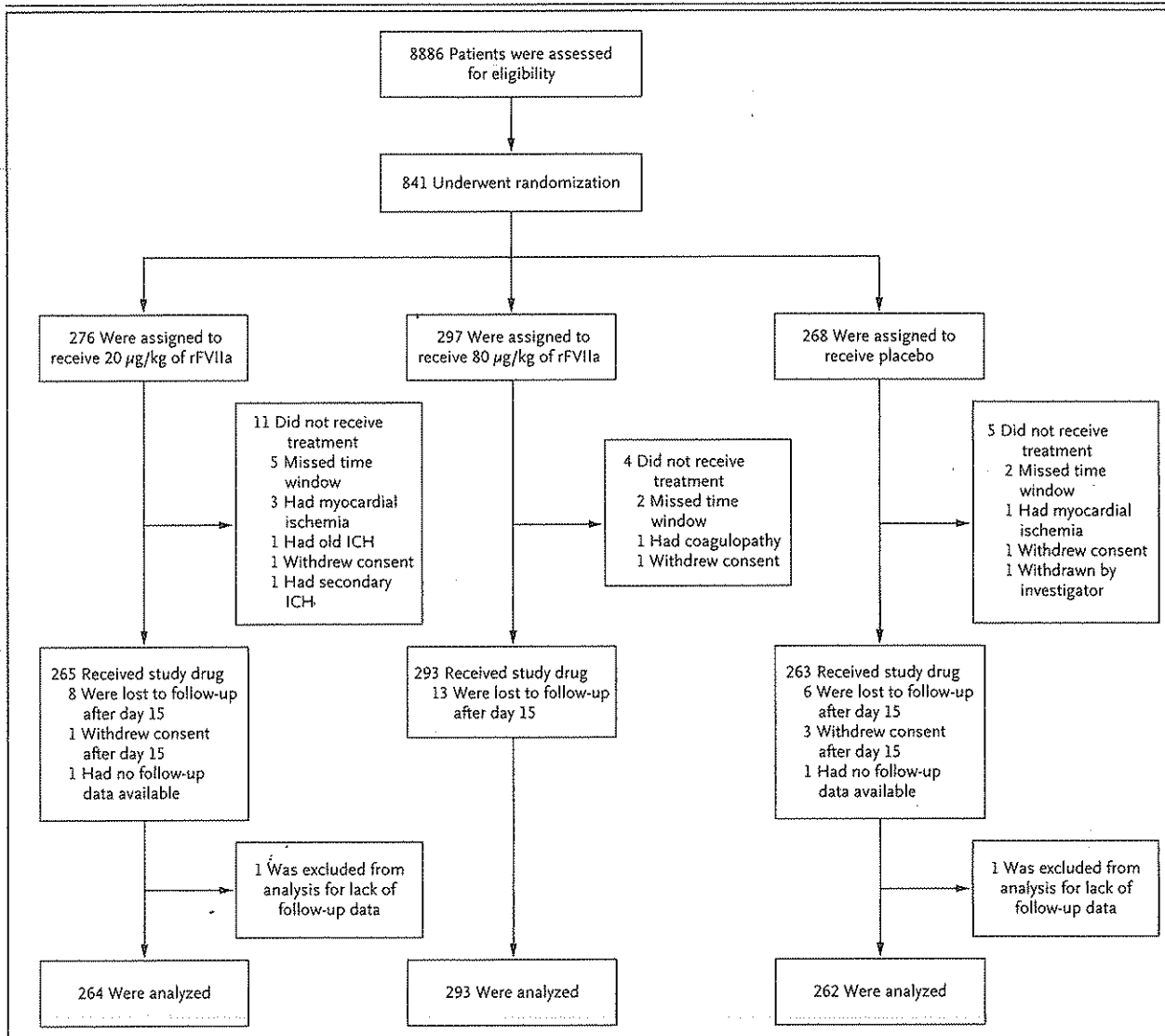


Figure 1. Enrollment and Follow-up.

ICH denotes intracerebral hemorrhage, and rFVIIa recombinant activated factor VII.

RESULTS

BASELINE CHARACTERISTICS

A total of 8886 patients with intracerebral hemorrhage were screened; 841 were enrolled and underwent randomization, and 821 received the study drug (Fig. 1). Baseline data from 20 patients who did not receive the study drug were included in the intention-to-treat analysis; no data for 90 days after the stroke were available for these patients. The mean age was 65 years (range, 23 to 97), and 62% of the patients were male, 69% were white, 19% were Asian, and 9% were

black. The median Glasgow Coma Scale score was 14 (range, 6 to 15), and the mean NIHSS score was 13 (range, 0 to 38). The deep gray matter was involved in 78% of cases, and the lobar regions were involved in 22%. The baseline characteristics of the three treatment groups were similar, except that intraventricular hemorrhage and, to a lesser extent, left ventricular hypertrophy (according to electrocardiographic criteria) and coma (Glasgow Coma Scale score, 6 to 8) occurred more frequently in the two groups receiving rFVIIa (Table 1). The mean volume of the intracerebral hemorrhage at baseline for all pa-

tients was 23.2 ml (range, 0.3 to 153.4) and was similar in the three groups (Table 2).

The mean time from onset of symptoms to baseline CT scan was 109±39 minutes, the mean time from baseline CT scan to treatment was 51±17 minutes, and the mean time from onset of symptoms to treatment was 160±37 minutes. Seventeen percent of patients were treated within 2 hours after the onset of symptoms and 72% within 3 hours; only one patient was treated outside the 4-hour time window. The timing of treatment was similar in the three groups (Table 1).

RADIOGRAPHIC OUTCOMES

A total of 819 CT scans performed at baseline and 794 performed at 24 hours were available for

analysis. The estimated mean increase in the volume of intracerebral hemorrhage was 26% in the placebo group and 11% in the group receiving 80 µg of rFVIIa per kilogram; the increase in the volume of hematoma was 3.8 ml less in the group receiving 80 µg of rFVIIa than in the placebo group (95% confidence interval [CI], 6.7 to 0.9; P=0.009) (Table 2). The increase in the volume of intracerebral hemorrhage in patients receiving 20 µg of rFVIIa per kilogram was 2.6 ml less than that in patients receiving placebo (95% CI, 5.5 to -0.3; P=0.08). In a post hoc analysis, the absolute reduction in the growth of intracerebral-hemorrhage volume in patients receiving 80 µg of rFVIIa per kilogram as compared with those receiving placebo was even greater among patients

Table 1. Baseline Characteristics and Timing of Treatment.*

Variable	rFVIIa, 20 µg/kg (N=276)	rFVIIa, 80 µg/kg (N=297)	Placebo (N=268)
Age (yr)	65±14	65±13	65±14
Male sex (%)	61	61	63
Race or ethnic group (%)†			
White	72	69	67
Black	9	9	9
Asian	16	18	21
Unknown or other	3	3	3
Location of hemorrhage (%)‡			
Deep gray matter	77	80	78
Lobar regions	23	20	20
Cerebellum	2	2	4
Brain stem	3	2	3
Intraventricular hemorrhage (%)	35	41	29
Glasgow Coma Scale score§			
Median	14	14	15
Range	6–15	6–15	6–15
Glasgow Coma Scale score of 6–8 (%)	6	6	3
NIHSS score¶	13±7	13±7	13±6
Systolic blood pressure at treatment (mm Hg)	179±30	182±32	180±28
Left ventricular hypertrophy on baseline ECG (%)	31	30	23
Time from onset of symptoms to treatment (min)	161±37	160±36	160±38
Treated ≤3 hr after onset of symptoms (%)	72	74	72

* Plus-minus values are means ±SD. Percentages may not add to 100 because of rounding. ECG denotes electrocardiogram, NIHSS National Institutes of Health Stroke Scale, and rFVIIa recombinant activated factor VII.

† Race or ethnic group was reported by the patient or a family member.

‡ More than one region could be involved in a given patient.

§ Scores range from 15 (normal) to 3 (deep coma).

¶ Scores range from 0 (normal) to 42 (coma with quadriplegia).

Table 2. Hemorrhage Volumes at Baseline and Follow-up.*

Variable	rFVIIa, 20 µg/kg (N=276)	rFVIIa, 80 µg/kg (N=297)	Placebo (N=268)
Volume of intracerebral hemorrhage			
At baseline — ml	24±26	23±26	22±24
At 24 hr — ml	28±30	25±28	28±31
Estimated percent increase from baseline — mean (95% CI)	18 (13 to 24)	11 (6 to 17)	26 (20 to 32)
P value vs. placebo	0.09	<0.001	—
Estimated milliliters of increase from baseline — mean (95% CI)	4.9 (2.9 to 7.0)	3.7 (1.7 to 5.7)	7.5 (5.4 to 9.6)
P value vs. placebo	0.08	0.009	—
Volume of intraventricular hemorrhage			
At baseline — ml	3.6±8.0	5.3±11.7	2.7±7.5
At 24 hr — ml	5.8±17.2	5.4±10.8	4.6±10.3
Estimated milliliters of increase from baseline — mean (95% CI)	2.0 (0.6 to 3.3)	1.0 (−0.2 to 2.3)	1.6 (0.3 to 3.0)
P value vs. placebo	0.74	0.51	—
Volume of intracerebral hemorrhage plus intraventricular hemorrhage plus edema			
At baseline — ml	46±45	46±49	42±47
At 72 hr — ml	71±69	65±66	68±67
Estimated milliliters of increase from baseline — mean (95% CI)	26 (21 to 31)	22 (17 to 27)	29 (23 to 34)
P value vs. placebo	0.53	0.06	—

* Plus-minus values are means ±SD. For estimated mean increases, 95% confidence intervals (CIs) are derived from a linear mixed model with the patient and the reader as random effects and baseline volume of the hemorrhage, time from onset of symptoms to baseline CT scan, and time from baseline CT scan to treatment as fixed effects. CT scans at 24 hours were missing for 12 patients receiving placebo, 17 receiving 20 µg of rFVIIa (recombined activated factor VII) per kilogram, and 12 receiving 80 µg of rFVIIa per kilogram.

treated within 3 hours after the onset of symptoms (−4.5 ml; 95% CI, −8.0 to −1.0) and was greater still among those treated within 2 hours after onset (−5.6 ml; 95% CI, −13.1 to −2.0). However, there was no significant interaction between treatment effect and the time from onset of symptoms to treatment.

Although the intraventricular-hemorrhage volume at 24 hours doubled in the placebo group and was essentially unchanged in the group receiving 80 µg of rFVIIa per kilogram, the difference between the groups was not statistically significant. Growth in volume of the total lesion (intracerebral hemorrhage, intraventricular hemorrhage, and edema) was 7 ml less in the group receiving 80 µg of rFVIIa per kilogram than in the placebo group ($P=0.06$). However, the final total lesion volumes at 72 hours were similar in the three groups (Table 2). There were no significant differences among the three groups in edema volume at 72 hours.

CLINICAL OUTCOMES

Mortality at 3 months was approximately 20% in the three groups (Table 3 and Fig. 2). The primary outcome measure (the proportion of patients who died or were severely disabled) did not differ significantly among the three groups (Table 3). Similarly, the distribution of outcomes on the modified Rankin scale (Fig. 3) and the median scores on the Barthel index were similar among the three groups. The NIHSS scores were significantly lower in the group receiving 80 µg of rFVIIa per kilogram than in the placebo group, but the magnitude of this difference was small (Table 3).

In a series of exploratory post hoc analyses, we tested the hypothesis that rFVIIa at a dose of 80 µg per kilogram may have benefited a subgroup of younger patients with smaller hemorrhages treated within an earlier time window. The cutoff points for age (65, 70, 75, and 80 years), volume of intracerebral hemorrhage (60 ml), intra-

Table 3. Clinical Outcome and Thromboembolic Serious Adverse Events at 90 Days.*

Variable	rFVIIa, 20 µg/kg (N=276)	rFVIIa, 80 µg/kg (N=297)	Placebo (N=268)
Death — no. of patients (%)	50 (18)	62 (21)	51 (19)
Odds ratio for survival (95% CI)	0.8 (0.5–1.4)	1.1 (0.7–31.8)	
P value vs. placebo	0.38	0.75	
Modified Rankin scale score†			
Poor outcome (score 5 or 6) — no. of patients (%)	69 (26)	84 (30)	62 (24)
Odds ratio for poor outcome (95% CI)‡	1.0 (0.6–1.6)	1.4 (0.9–2.2)	—
Barthel index score§			
Median	72.5	70.0	70.0
P value vs. placebo	0.54	0.91	—
NIHSS score¶			
Median	5.0	4.0	5.0
P value vs. placebo	0.20	0.02	—
Thromboembolic serious adverse events — no. of patients affected (%)			
Total	24 (9)	31 (10)	21 (8)
Arterial**	14 (5)	25 (8)	11 (4)
Myocardial infarction	11 (4)	14 (5)	8 (3)
Cerebral infarction	4 (1)	10 (3)	4 (1)
Venous	10 (4)	7 (2)	11 (4)
Deep-vein thrombosis	7 (3)	7 (2)	9 (3)
Pulmonary embolism	4 (1)	3 (1)	2 (1)

- * The numbers of patients at the top of the columns represent the intention-to-treat population. Percentages of patients with a poor outcome (modified Rankin scale score of 5 or 6) were calculated on the basis of the number of patients with nonmissing day 90 values (264 in the 20-µg/kg group, 293 in the 80-µg/kg group, and 262 in the placebo group). Percentages of patients with one or more thromboembolic serious adverse events are based on the safety population (patients exposed to a study agent): 265 patients in the 20-µg/kg group, 293 in the 80-µg/kg group, and 263 in the placebo group. NIHSS denotes National Institutes of Health Stroke Scale, and rFVIIa recombinant activated factor VII.
- † The modified Rankin scale evaluates global disability and handicap; scores range from 0 to 6. A score of 0 indicates no symptoms or disability, a score of 5 indicates bed-bound and incontinent, and a score of 6 indicates death. Outcome scores at day 15 were used according to the principle of the last observation carried forward for 9 patients receiving placebo, 9 patients receiving 20 µg of rFVIIa per kilogram, and 13 patients receiving 80 µg of rFVIIa per kilogram (3.7% of patients overall) for whom scores at day 90 were missing. Modified Rankin scale scores were not available for one patient receiving placebo and one patient receiving 20 µg of rFVIIa per kilogram.
- ‡ Odds ratios were adjusted for prestroke modified Rankin scale score, baseline volume of intracerebral hemorrhage, location of intracerebral hemorrhage (infratentorial or supratentorial), age, and sex. The primary analysis used a one-sided chi-square test, under the hypothesis that rFVIIa was superior to placebo. Since the estimated effect of rFVIIa went in the opposite direction, the one-sided P value was greater than 0.50 and could not be determined exactly in the logistic-regression analysis because of the nonsymmetry of the chi-square distribution.
- § A score of 100 indicates complete independence in activities of daily living, and 0 indicates total dependence; patients who died before day 90 were assigned a score of 0. The treatment groups were compared with the placebo group by an analysis of variance on the ranks. Scores for day 15 were analyzed when scores for day 90 were missing (3.9% of patients overall).
- ¶ A score of 0 indicates no neurologic deficit, and a score of 42 indicates coma with quadriplegia. Treatment groups were compared with the placebo group by an analysis of variance on the ranks. For patients who died before day 90 (24.3% of patients overall), the last recorded NIHSS score was carried forward.
- || A patient could have more than one event.
- ** Arterial events include one case each of renal-artery thrombosis, intracardiac thrombus, and retinal-artery occlusion, all in the group receiving 80 µg of rFVIIa per kilogram. The frequency of arterial events was significantly increased in the group receiving 80 µg of rFVIIa per kilogram as compared with the placebo group (P=0.04 by the chi-square test).

ventricular-hemorrhage volume (5 ml), and time from onset of symptoms to treatment (2.0, 2.5, and 3.0 hours) were tested alone and in combination. Among subjects 70 years of age or younger

with a baseline volume of intracerebral hemorrhage of 60 ml or less, an intraventricular-hemorrhage volume of 5 ml or less, and a time from onset of symptoms to treatment of 2.5 hours or

DISCUSSION

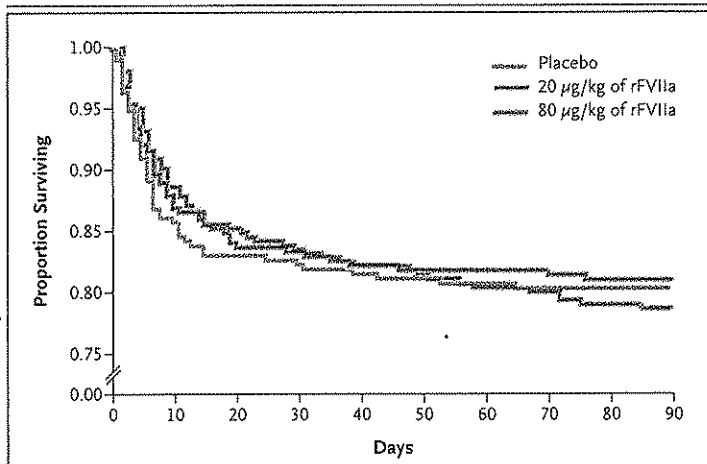


Figure 2. Kaplan-Meier Survival Curves.

A possible small benefit of early treatment with recombinant activated factor VII (rFVIIa) was evident at 15 days. This benefit disappeared beyond 1 month after treatment.

less (19% of the original study population), the adjusted odds ratio for poor 90-day outcome with rFVIIa was 0.28 (95% CI, 0.08 to 1.06; $P=0.03$).

ADVERSE EVENTS

The frequency of thromboembolic serious adverse events reported by the investigators was similar in the three groups (Table 3). There was no increase in the frequency of venous complications with rFVIIa treatment; there was an absolute increase of 5% in the frequency of arterial thromboembolic serious adverse events in the group receiving 80 μg of rFVIIa per kilogram as compared with the placebo group ($P=0.04$) (Table 3). The frequency of elevated troponin I values was 15%, 13%, and 22%, and the frequency of ST-segment elevation myocardial infarction was 1.5%, 0.4%, and 2.0% in the placebo group and the groups receiving 20 μg and 80 μg of rFVIIa per kilogram, respectively. CT evidence of acute cerebral infarction was identified by the data and safety monitoring committee in 2.2%, 3.3%, and 4.7% of patients in the placebo group and the groups receiving 20 μg and 80 μg of rFVIIa per kilogram, respectively. Also identified as risk factors for thromboembolic serious adverse events in a post hoc analysis were age (odds ratio per 5-year increase, 1.1; 95% CI, 1.0 to 1.2; $P=0.02$) and previous use of an antiplatelet agent (odds ratio, 1.9; 95% CI, 1.1 to 3.0; $P=0.01$), but not rFVIIa treatment.

In this study, rFVIIa given within 4 hours after the onset of symptoms of intracerebral hemorrhage significantly reduced growth of the hematoma but failed to improve survival or functional outcome at 90 days. This result contrasts with the clinical benefit demonstrated in our phase 2b trial, in which rFVIIa treatment produced a relative reduction in mortality of 38%.⁹ Possible explanations for these discrepant findings include randomization imbalances, an increase in arterial thromboembolic events with rFVIIa treatment, the inclusion of very elderly patients at high risk for non-neurologic causes of death, and substantially better outcomes in the placebo group as compared with our previous trial.

Our phase 2b trial compared doses of 40, 80, and 160 μg of rFVIIa per kilogram with placebo in 399 patients.⁹ All three rFVIIa doses produced a reduction in intracerebral-hemorrhage growth at 24 hours, from 29% in the placebo group to 14% in patients who received rFVIIa. We found a similar hemostatic effect with the 80 μg per kilogram dose in the present trial, with a reduction in the mean estimated increase in the volume of intracerebral hemorrhage from 26% to 11%. The dose of 20 μg per kilogram was associated with an 18% increase in the volume of bleeding, a result consistent with the dose-related hemostatic effect observed in the phase 2b study. Earlier treatment with 80 μg of rFVIIa per kilogram was associated with larger reductions in the growth of intracerebral-hemorrhage volume, which probably reflects the diminishing proportion of patients with active bleeding as time elapses after the onset of symptoms. This finding suggests that rFVIIa might be more likely to have clinical benefits if it were given earlier.

Patients with intracerebral hemorrhage who are treated with rFVIIa are at increased risk for arterial thromboembolic complications, most commonly cerebral infarction and myocardial ischemia, as indicated by elevated troponin I concentrations.¹⁹ In our phase 2b trial, 5% of the patients who were treated with rFVIIa had an arterial thromboembolic serious adverse event, as compared with none of those who received placebo, and there was no increase in venous thromboembolic events. In the FAST trial, we found an identical absolute increase of 5% in arterial throm-

boembolic serious adverse events in the group receiving 80 μg of rFVIIa per kilogram as compared with the placebo group (9% vs. 4%), with a higher overall frequency of events that was most likely due to centralized screening of cardiac troponin levels. In a pooled analysis of 371 patients with intracerebral hemorrhage treated with rFVIIa at doses ranging from 5 to 160 μg per kilogram, doses of 120 μg per kilogram or more were associated with a greater risk of arterial thromboembolic events.¹⁹ This finding had an important role in our decision in the FAST trial to select 80 μg per kilogram as the optimal dose for balancing the hemostatic effect of rFVIIa against the risk of thromboembolic complications. We included patients with a history (>30 days previously) of thromboembolic disease; this group was excluded midway through our phase 2b trial. In the present study, a post hoc analysis identified age and previous use of antiplatelet agents, but not rFVIIa treatment or a history of thromboembolic disease, as risk factors for a thromboembolic serious adverse event. Since the safety profile of rFVIIa in the present trial is similar to that in our phase 2b trial, it seems unlikely that rFVIIa-related complications can explain the lack of a beneficial treatment effect.

The patients enrolled in our two trials were similar and were typical of patients with spontaneous intracerebral hemorrhage. In the present trial, however, potentially important randomization imbalances were present. The most conspicuous of these is the proportion of patients with intraventricular hemorrhage at baseline, which varied from 29% in the placebo group to 41% in the group receiving 80 μg of rFVIIa per kilogram. Intraventricular hemorrhage is a well-established determinant of poor outcome after intracerebral hemorrhage,^{20,21} and we previously found that intraventricular hemorrhage blunts the clinical benefits of rFVIIa treatment.²¹ Other imbalances include the greater frequency of coma, the greater frequency of left ventricular hypertrophy according to baseline electrocardiography (Table 1), and the greater total lesion volume (intracerebral hemorrhage, intraventricular hemorrhage, and edema) at baseline (Table 2) in the group receiving 80 μg of rFVIIa per kilogram as compared with the placebo group. The imbalance in total lesion volume may explain in part why the present trial did not reproduce the significant

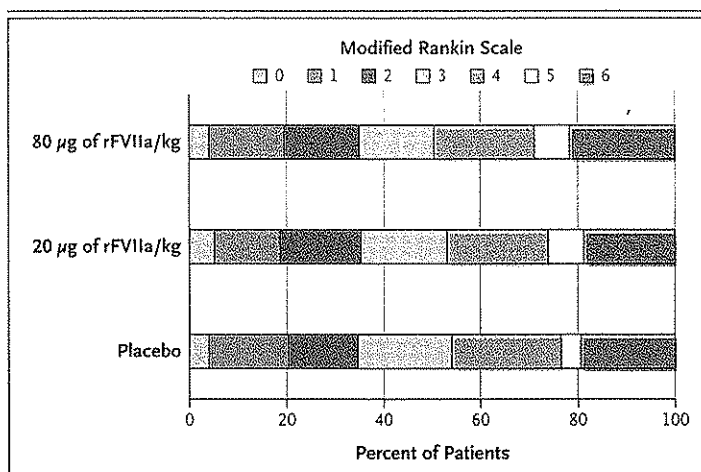


Figure 3. Clinical Outcome at 90 Days According to the Modified Rankin Scale. The modified Rankin scale evaluates global disability and handicap; scores range from 0 (no symptoms or disability) to 6 (death). There was no significant difference between the groups receiving recombinant activated factor VII (rFVIIa) and the placebo group.

reduction in 72-hour total lesion volume demonstrated in our phase 2b study (53 ml for all rFVIIa groups combined vs. 69 ml in the placebo group). Although these randomization imbalances may have contributed to the lack of clinical benefit with rFVIIa treatment that we observed in this trial, they are most likely only a minor part of the explanation.

The placebo group in the FAST trial had much more favorable outcomes than the placebo group in the phase 2b trial. In the placebo group of the FAST trial, the mortality rate was 19% and the frequency of severe disability or death (modified Rankin scale score of 5 or 6) was 24%, as compared with a 29% mortality rate and a 45% frequency of severe disability or death in the phase 2b trial.⁹ This discrepancy may reflect the higher proportion of patients receiving placebo who had intraventricular hemorrhage in the phase 2b trial as compared with the FAST trial (44% vs. 29%). Other possible explanations include practice variations in the phase 3 trial resulting from expansion to more sites, improvements in neurointensive care, or greater reluctance to withdraw support from severely injured patients. The poor outcome of the placebo group in the phase 2b study may have also been a chance result, a possibility supported by the 20% overall mortality rate in two trials of neuroprotective treatment for intracerebral hemorrhage with study popu-

lations similar to ours that yielded negative results.^{22,23} As the outcome of intracerebral hemorrhage continues to improve, trial end points may need to evaluate the full range of functional outcome, rather than focus specifically on mortality and severe disability.

In summary, rFVIIa reduced hematoma growth but did not reduce the rate of death or severe disability after intracerebral hemorrhage. Whether this hemostatic effect can translate to clinical benefit in a subgroup of patients at high risk for active bleeding, either by treatment within an earlier time window or by demonstration of intrahematoma contrast extravasation after CT angiography,^{24,25} deserves further study.

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Dr. Brun and Ms. Begtrup report being former employees of Novo Nordisk (Dr. Brun is now employed by Genzyme, and Ms. Begtrup by Genmab) and holding stock in Novo Nordisk; Dr. Skolnick reports being an employee of Novo Nordisk and holding stock in the company; Dr. Mayer reports receiving research support from Novo Nordisk; Dr. Broderick, consulting fees from Novo Nordisk; and Drs. Mayer, Davis, Diring, and Steiner, consulting and lecture fees from Novo Nordisk. Dr. Diring reports receiving lecture fees and consulting fees from Astellas Pharma. Dr. Mayer reports receiving lecture fees and consulting fees from Astellas Pharma and PDL BioPharma and receiving lecture fees from and holding stock options in Medivance. Dr. Davis reports receiving consulting fees and lecture fees from Sanofi Aventis, Servier, Boehringer Ingelheim, and Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The participants in the FAST trial were as follows: **Steering Committee** — S.A. Mayer, New York (chair); J. Broderick, Cincinnati; N.C. Brun, Bagsvaerd, Denmark (nonvoting); S. Davis, Melbourne, Australia; M.N. Diring, St. Louis; B.E. Skolnick, Princeton, NJ (nonvoting); Thorsten Steiner, Heidelberg, Germany. **Statistician** — K. Begtrup, Bagsvaerd, Denmark. **Data and Safety Monitoring Committee** — T.G. Brott, Jacksonville, FL (chair); Per Grande, Copenhagen; T.P. Bleck, Charlottesville, VA; M. Escobar, Houston; P. Wester, Umeå, Sweden; J. Verter, Rockville, MD. **Neuroradiologists** — J. Tsiouis, New York; J. Maldjian, Winston-Salem, NC; R. von Kummer, Dresden, Germany; **Clinical Centers** (with numbers of patients in parentheses; centers for which the number of patients is zero are listed in the Supplementary Appendix [available with the full text of this article at www.nejm.org]) — Y. Wang, Beijing Tiantan Hospital, Beijing (73); D. 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