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Safety and Efficacy of Recombinant Activated Factor VII

A Randomized Placebo-Controlled Trial in the Setting of Bleeding After Cardiac Surgery

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***Background*—**Blood loss is a common complication of cardiac surgery. Evidence suggests that recombinant activated factor VII (rFVIIa) can decrease intractable bleeding in patients after cardiac surgery. Our objective was to investigate the safety and possible benefits of rFVIIa in patients who bleed after cardiac surgery.

***Methods and Results*—**In this phase II dose-escalation study, patients who had undergone cardiac surgery and were bleeding were randomized to receive placebo (n=68), 40 μg/kg rFVIIa (n=35), or 80 μg/kg rFVIIa (n=69). The primary end points were the number of patients suffering critical serious adverse events. Secondary end points included rates of reoperation, amount of blood loss, and transfusion of allogeneic blood. There were more critical serious adverse events in the rFVIIa groups. These differences did not reach statistical significance (placebo, 7%; 40 μg/kg, 14%; P=0.25; 80 μg/kg, 12%; P=0.43). After randomization, significantly fewer patients in the rFVIIa group underwent a reoperation as a result of bleeding (P=0.03) or required allogeneic transfusions (P=0.01).

***Conclusions*—**On the basis of this preliminary evidence, rFVIIa may be beneficial for treating bleeding after cardiac surgery, but caution should be applied and further clinical trials are required because there is an increase in the number of critical serious adverse events, including stroke, in those patients randomized to receive rFVIIa. **(*Circulation*. 2009; 120:21-27.)**

Key Words: cardiac surgery ■ cardiopulmonary bypass ■ coagulation ■ factor VIIa ■ hemorrhage

Bleeding after cardiac surgery is a serious complication, and excessive blood loss frequently necessitates transfusion of allogeneic blood, blood products, and surgical re-exploration. Five percent to 7% of patients lose >2 L blood within the first 24 hours after surgery,[1] and up to 5% require reoperation for bleeding.[2] Both transfusion and re-exploration are associated with prolonged intensive care and hospital stays and reduced survival rates.[3]

Clinical Perspective on p 27

Recombinant factor VIIa (rFVIIa; NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark) is currently approved for the treatment of bleeding episodes and the prevention of bleeding in connection with surgical/invasive procedures in patients with hemophilia and inhibitors to coagulation factors VIII or IX, FVII deficiency, and acquired hemophilia. The mode of action of rFVIIa has been described and is localized predominantly to the site of vessel injury.[4,5]

Numerous reports have indicated a reduction in bleeding and transfusion requirements in patients given rFVIIa in the setting of severe uncontrolled hemorrhage outside hemophilia and other bleeding disorders despite the potential for thrombotic complications.[6–16] For patients bleeding after cardiac surgery, the risk, potential benefits, and optimal dose of rFVIIa have not been carefully assessed in a randomized, placebo-controlled trial.

Our objective was therefore to investigate the safety and possible benefits of different doses of rFVIIa in patients bleeding after cardiac surgery requiring cardiopulmonary bypass (CPB) in whom conventional transfusion therapy was

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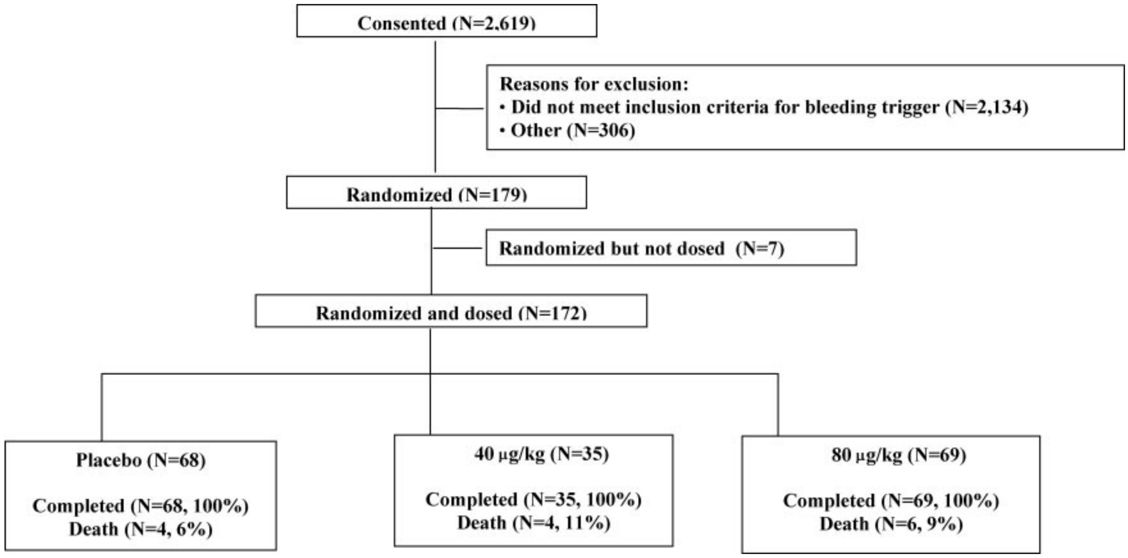

Figure 1. Numbers of patients who consented, were randomized, and completed the study. Of the 7 patients who were randomized but did not receive study drug, 3 were allocated to the placebo group, 3 to the 40 µg/kg group, and 1 to the 80 µg/kg group. In 4 of the 7 patients, the interactive voice response system (IVRS) was called prematurely and was the most common reason for lack of study drug administration. For the remaining 3 patients, there was 1 case each of IVRS called despite not meeting inclusion criterion for bleeding rate, IVRS called but the patient had to go back for reoperation, and IVRS not working.

indicated. We hypothesized that the use of rFVIIa to reduce bleeding in the postoperative setting after cardiac surgery requiring CPB was safe.

Methods

This phase II dose-escalation study was conducted at 30 sites in 13 countries between August 2004 and November 2007. The trial was approved by national, local, and institutional ethics committees and/or review boards as applicable. Written informed consent was obtained before surgery from each patient who met the inclusion criteria (Table I of the online-only Data Supplement).

Patients

Patients eligible for randomization had undergone cardiac surgery requiring CPB and had been admitted to a postoperative care environment (eg, intensive care unit) for at least 30 minutes (stabilization period). Patients were randomized on reaching a prespecified bleeding rate (Table I of the online-only Data Supplement) based on the blood volume obtained from mediastinal drains.

Randomization, Study Monitoring, and Masking

A randomized, double-blind, placebo-controlled trial design was used for each of the individual dose tiers (cohorts). Patients meeting the inclusion criteria were randomized to rFVIIa or placebo. Initially, patients were to be allocated sequentially to 3 cohorts of escalating rFVIIa doses (40, 80, and 160 µg/kg rFVIIa). Cohort 1 comprised 70 patients equally allocated to 40 µg/kg rFVIIa or placebo. Cohort 2 comprised 51 patients randomized 2:1 (80 µg/kg rFVIIa:placebo). Safety and efficacy data were evaluated by a Novo Nordisk Safety Committee and an independent external Data Monitoring Committee at the end of cohort 1, then after every 10 patients randomized in cohort 2a, and every month in cohort 2b. The Data Monitoring Committee had access to all data at the end of each cohort to evaluate the incidence of critical serious adverse events (cSAEs) and advised the sponsor and the Steering Committee if the trial should continue. After completion of the original cohort 2 (cohort 2a), the Data Monitoring Committee recommended duplication of cohort 2 to clarify concerns raised by the data available to the committee. The protocol was amended by including an additional cohort (cohort 2b) with 51 patients randomized 2:1 (80 µg/kg rFVIIa:placebo). At the recommendation of the Steering Committee (masked to treatment allocations), the study was terminated before initiation of cohort 3 (160 µg/kg rFVIIa versus placebo). The committee's advice was based on the data within the expanding cardiac literature in which doses of rFVIIa were in the range of 60 µg/kg.[6,9,10,15]

Patients were randomized through an interactive voice response system and were always assigned to the lowest available randomization number. After randomization, freeze-dried powdered (4.8 mg) rFVIIa or placebo was reconstituted with 8.5 mL sterile water and administered as a bolus injection. To maintain masking within each dose level, an equal volume per body weight of trial product was administered to all patients regardless of treatment group. Physical appearances of the placebo and rFVIIa, either in the freeze-dried form or on reconstitution, were identical. Masking of treatment allocations was maintained until all patient data had been entered and the database was locked.

Transfusion Protocol

No changes to standard practices (eg, anesthesia, surgical practice, CPB, or intensive care) were made until patients reached the prespecified rate of bleeding in a postoperative environment that allowed randomization. At this time, all transfusions except allogeneic red blood cells were discontinued. The transfusion protocol was applied from randomization to day 5 but suspended during reoperations. This protocol is presented as Figure I of the online-only Data Supplement.

End-Point Definitions

The primary end point for the study was the incidence of cSAEs from trial drug administration to day 30. The cSAEs as defined for this trial were death, acute myocardial infarction (ECG evidence of ≥1 new Q waves, left bundle-branch block, or new pathological R waves; troponin T >3.4 µg/L at 48 hours after surgery; or an increase in creatine kinase-MB >30 µg/L at 2 consecutive time points >24 hours after surgery, plus a clinical picture of hemodynamic instability that gives rise to the suspicion of myocardial infarction or graft occlusion), cerebral infarction (new focal neurological deficit, either transient but present >24 hours or permanent), clinically symptomatic pulmonary embolus (clinical signs or suspicion of pulmonary embolus further diagnosed by V/Q scan or postmortem examination; clinical examination is not sufficient for diagnosis), and other clinically symptomatic thrombotic events (signs or suspicion of clinically significant thromboembolic event

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Table 1. Baseline Characteristics of the Patients

Characteristic and Treatment	Placebo (n=68)	rFVIIa 40 μg/kg (n=35)	rFVIIa 80 μg/kg (n=69)
Age, y			
Mean	62±16	68±12	63±16
Median	67	71	65
Range	28–84	30–83	22–84
Male sex, n (%)	55 (81)	24 (69)	49 (71)
Body surface area >1.9 m^2, n (%)	25 (37)	17 (49)	24 (35)
Body mass index, kg/m^2	25.1±4.5	26.9±3.9	25.5±4.4
Mean baseline creatinine ≥130 μmol/L, n (%)	3 (4)	3 (9)	7 (10)
Preoperative hemoglobin <12 g/dL female, 13g/dL male, n (%)	1 (1)	0	0
Antifibrinolytic treatment, n (%)	36 (53)	23 (66)	30 (43)
No prior cardiac surgery, n (%)	57 (84)	31 (89)	55 (80)
Surgery classification, n (%)			
Elective	56 (82)	24 (69)	60 (87)
Urgent/emergent	12 (18)	11 (31)	9 (13)
Surgery type, n (%)			
CABG only	8 (12)	5 (14)	8 (12)
Single-valve repair/replacement			
Aortic valve	7 (10)	4 (11)	11 (16)
Mitral valve	7 (10)	1 (3)	9 (13)
Double/triple procedures	54 (79)	28 (80)	52 (75)
CPB time, min			
Mean	122±47	122±52	115±47
Median	115	111	110
Range	30–255	68–359	37–315
Cross-clamp time, min			
Mean	89±39	85±35	84±38
Median	85	78	77
Range	23–205	34–202	30–242
Time from ICU admission to dosing, min			
Mean	166±75	165±77	176±80
Median	140	142	150
Range	73–390	40–385	77–422
Volume chest drains (ICU admission to dosing), mL			
Mean	597±403	616±264	657±448
Median	455	600	550
Range	150–2225	217–1445	125–2955
Predose allogeneic transfusion volumes, mL			
Red blood cells			
Mean	353±533	641±819	450±653
Median	282	320	329
Range	210–1600	230–2100	200–2100
Fresh frozen plasma			
Mean	223±381	405±633	230±440
Median	250	500	245
Range	150–830	210–1200	150–1000
Platelets			
Mean	89±199	125±222	160±355
Median	302	300	250
Range	50–500	216–655	50–2000

CABG indicates coronary artery bypass grafting; ICU, intensive care unit. There were no significant differences between treatment groups. Values are mean±SD when appropriate.

confirmed by positive finding in a follow-up investigation such as a lower-limb venogram or duplex Doppler studies).

Secondary end points evaluated efficacy and included the rates of reoperation within 30 days after rebleeding, transfusion of allogeneic blood and blood products within 5 days after trial drug administration, and drainage volumes from cardiothoracic cavity within 4 hours, 24 hours, and 5 days after trial drug administration.

Statistical Analyses

The data presented in this study are for the safety population (defined as all patients randomized who received either rFVIIa or placebo treatment). Sample size was based on the probability that uneven distribution of cSAEs between placebo and rFVIIa treatment groups would be minimized. That is, sample size was chosen to have ≤20% risk of seeing ≥14 (of 35) on active versus ≤7 (of 35) on placebo or ≤7 on active versus ≥14 on placebo in cohort 1 and ≤16.7% risk of ≥13 (of 34) on active versus ≤2 (of 17) on placebo or ≤7 on active versus ≥8 on placebo in cohorts 2a, 2b, and 3, all assuming no differences and 21 events in cohort 1 and 15 events in cohorts 2a, 2b, and 3. Additionally, the sample size was chosen to give adequate power to detect a 35% reduction in the need for any allogeneic transfusions. The power for the efficacy evaluation is based on a comparison of (all) placebo patients with the highest dose of rFVIIa (ie, cohort 3). This simple comparison between 2 groups (86 on placebo versus 34 on rFVIIa) then has 80% power assuming 80% transfusion rate on placebo and a 35% relative reduction [to 52%=80%×(100%−35%)].

All analyses presented, including covariates, were prespecified in the statistical analysis plan unless stated otherwise (eg, posthoc analysis). The frequency of cSAEs (primary end point) was analyzed by logistic regression adjusted for the prespecified variables of prior cardiac surgery, use of antifibrinolytic medication, and treatment.

Reoperation for bleeding was analyzed with χ^2 tests. Continuous efficacy end points (drainage rates, drainage volumes, transfusion volumes) were analyzed by ANCOVA with adjustment for the prespecified variables of prior cardiac surgery, CPB time, use of antifibrinolytic medication, country, and treatment. Analyses of drainage volumes and rates also were adjusted for predosing drainage rate or predosing transfusions volume as appropriate. Data were transformed to ranks because they were not normally distributed and were substantially skewed. This analysis was considered a nonparametric test adjusted for relevant covariates. Estimates are presented as medians.

Categorical efficacy outcomes (percentage of subjects having transfusion, combined and by type) were analyzed by logistic regression adjusted for prespecified variables of prior cardiac surgery, use of antifibrinolytic medication, and treatment.

The authors designed the trial protocol (Appendix A in the online-only Data Supplement), directed the statistical analysis plan,

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Table 2. Overview of cSAEs

		rFVIIa		
cSAEs	Placebo (n=68)	40 μg/kg (n=35)	80 μg/kg (n=69)	rFVIIa Combined
Death, n (%)*	4 (6)	4 (11)	6 (9)	
Cerebral infarction, n (%)	0	2 (6)	2 (3)	
Myocardial infarction, n (%)	1 (2)	0	0	
Pulmonary embolism, n	0	0	0	
Other TEs, n (%)	0	1 (3)	2 (3)	
Patients with cSAEs, n (%)	5 (7)	5 (14)	8 (12)	13 (12)
P	...	0.25	0.43	0.40
Odds ratio (95% CI)	...	2.16 (0.58–8.12)	1.61 (0.50–5.25)	1.67 (0.50–5.47)

Other thrombotic events (TEs) included gut infarction (1 event each in the 40 and 80 μg/kg groups) and 1 superficial venous thrombosis (80 μg/kg). Columns are not additive because some patients may have had multiple cSAEs. Probability values were adjusted for prior cardiac surgery and antifibrinolytics and compared with placebo. Percentages are based on the number of patients in each treatment group. There were more cSAEs in the rFVIIa treatment group than in the placebo treatment group; this difference did not reach statistical significance.

*One patient in the 80 μg/kg group died outside the 30-day study window (day 32).

and wrote the manuscript. The sponsor was responsible for trial operations and the statistical analyses. The principal investigator (R.G.) assumes full responsibility for the veracity and completeness of the reported data.

Results

Baseline Characteristics

A total of 2619 patients gave informed consent before surgery; of these, 179 patients met the postoperative inclusion criteria and were randomized, and 172 patients were dosed (Figure 1). Overall, 158 patients (92%) survived the trial and 14 patients (8%) died. The distribution of age, gender, body surface area, types of surgery, rates of previous cardiac surgery, and surgery details are provided in Table 1. There were no statistically significant differences between treatment groups. Randomization and trial drug dosing occurred on average 2.8 hours after admission to the postoperative care unit.

Safety End Points

There were more cSAEs in the rFVIIa treatment group than in the placebo treatment group (Table 2); this difference did not reach statistical significance. Because only 1 myocardial infarction was identified in the study, an external adjudication committee was asked to evaluate all patients with elevated cardiac biomarkers. The findings of the committee did not alter the original results reported (Table II of the online-only Data Supplement). The only myocardial infarction in the study (placebo group) was originally reported as a nonserious adverse event. This was changed to a cSAE by the sponsor to comply with the trial protocol. It does not alter the statistical findings in this trial.

The statistical analysis plan specified that analyses of cSAEs should be adjusted for treatment, country or center, prior cardiac operation, and administration of antifibrinolytics. Because there were only 18 events, this could not occur. There were a total of 14 deaths (placebo, 4 deaths [6%]; combined rFVIIa dose groups, 10 deaths [10%]) in this study (Table 2). A representation of the time to cSAE and/or death for each patient is provided in Figure 2.

Efficacy End Points

After trial drug administration, significantly more patients in the placebo group underwent a reoperation for bleeding than in either of the rFVIIa treatment groups (placebo, 25%; 40 μg/kg rFVIIa, 14% [$P=0.21$]; 80 μg/kg rFVIIa, 12% [$P=0.04$]; Figure 3A).

After dosing, patients in the rFVIIa treatment groups received significantly less allogeneic blood transfusion volumes than placebo-treated patients (placebo, 825 mL [25% to 75% interquartile range (IQR), 326.5 to 1893 mL]; 40 μg/kg rFVIIa, 640 mL [25% to 75% IQR, 0 to 1920 mL], $P=0.047$; 80 μg/kg rFVIIa, 500 mL [25% to 75% IQR, 0 to 1750 mL], $P=0.042$) respectively. The proportion of patients avoiding transfusions was significantly higher in both rFVIIa treatment groups compared with placebo treatment (Figure 3B).

Four hours after randomization and drug administration, the median drainage rate in the 80 μg/kg rFVIIa group was significantly slower (24 mL/h; 25% to 75% IQR, 13.3 to 32.0 mL/h; $P=0.018$) than in the placebo (51 mL/h; 25% to 75% IQR, 21.3 to 82.7 mL/h) and 40 μg/kg rFVIIa (35 mL/h; 25% to 75% IQR, 26.7 to 85.3 mL/h; $P=0.763$) groups. Consequently, there was an ≈50% reduction in the drainage volume within 4 hours after treatment with 80 μg/kg rFVIIa ($P<0.001$) compared with placebo (Figure IIA of the online-only Data Supplement). Evaluation of the cumulative drainage volumes at 24 hours and 5 days after dose indicated that this difference was maintained for the 80 μg/kg rFVIIa treatment group compared with placebo treatment (Figure IIB and IIC of the online-only Data Supplement). No such difference was observed between placebo and 40 μg/kg rFVIIa.

Discussion

In this trial, we observed a numerical increase in cSAEs in patients randomized to rFVIIa compared with placebo. However, this difference was not statistically significant. In our results, the unadjusted and adjusted log odds ratios for the incidence of adverse events are similar to placebo. Our results show that patients receiving rFVIIa had significantly fewer

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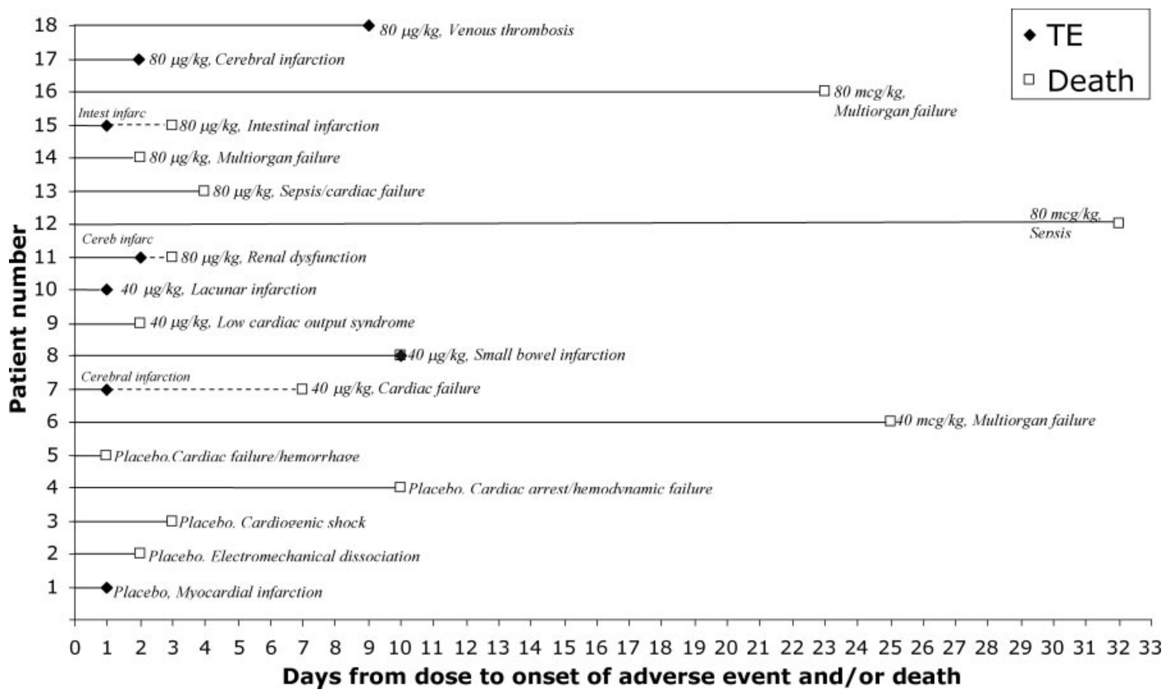

Figure 2. Time to adverse event and/or death. Data are shown to indicate adverse event, day of onset of adverse event, and day and cause of death after administration of study drug. Solid line denotes the interval from dose to first event; dashed line, the interval between the day of thrombotic event (TE) onset and day of death. Patient 8 had a small bowel infarction and died on the same day (postdose day 10).

reoperations and significantly less transfusion of allogeneic blood and blood products after randomization.

Safety of rFVIIa

Bleeding after cardiac surgery may lead to transfusion of allogeneic blood and blood products and/or reoperation. Transfusion of blood at the time of cardiac surgery is associated with a decreased long-term survival.[17–21] Receipt of 5 U allogeneic red blood cells is associated with an 8-fold increase in the chance of death.[22] Moreover, if bleeding does not stop, the patient will require reoperation, which may lead to a prolonged intensive care and hospital stay, increasing the risk of wound infections and marked reductions in the 3-year survival rates.[3]

Recent reviews have identified 415 patients who received rFVIIa for life-threatening bleeding after cardiac surgery.[15,23] In these reviews, only a few suffered thromboembolic complications after the administration of rFVIIa, but the tendency for clinicians to report only those successful cases cannot be excluded. On the other hand, a review of the Food and Drug Administration's adverse event reporting system suggests that 1 in 50 patients (from many medical disciplines) receiving rFVIIa for an unapproved indication developed a thromboembolic complication, with 1 in 200 patients dying.[11]

In cardiac surgery, mortality and complication rates of patients who have failed to respond to standard transfusion therapy and then received rFVIIa are in range of 19% to 40%.[10,14,24,25] The lack of control patients in most of these case series makes it difficult to determine whether the reported adverse events are related to the administration of rFVIIa or the critical unstable condition of patients when they received rFVIIa. When rFVIIa was used on a compassionate basis to reduce uncontrolled bleeding in 51 patients after cardiac surgery, propensity matching techniques to adjust for baseline risks demonstrated that the rates of cSAEs were equivalent.[26] In a group of patients with very high risk of stroke, a matched analysis of patients receiving rFVIIa after major ascending and aortic arch reconstructive surgery suggested that the stroke rates were equal.[27] Although our study is underpowered to make a definitive statement about cSAEs, in this study, we see a numerical increase in cSAEs in rFVIIa-treated patients. This finding is consistent with the absolute rate of cSAEs reported in observational data.

This is the first randomized trial attempting to examine the risks of rFVIIa in patients bleeding enough to justify the administration of blood products after cardiac surgery. Our results show a numerical but statistically insignificant increase in cSAEs compared with placebo. The findings suggest the need for a cautious approach and additional trials.

Efficacy of rFVIIa

There is a clinical sentiment that rFVIIa decreases bleeding.[9,10,13,15,23,25,28] This is illustrated by an increase in the off-label use of rFVIIa from 300 doses in 1999 to 4500 doses in 2004[11] and numerous case reports and case series reporting its efficacy in reducing bleeding and transfusion requirements. Recombinant FVIIa also has been shown to significantly reduce transfusion in a small randomized pilot study of patients undergoing major cardiac reconstructive surgery.[29] The results of this randomized controlled trial support these observations, and for the first time, a hemostatic agent has the possibility of being an effective alternative to allogeneic transfusion in cardiac surgery patients with uncontrolled postoperative bleeding.

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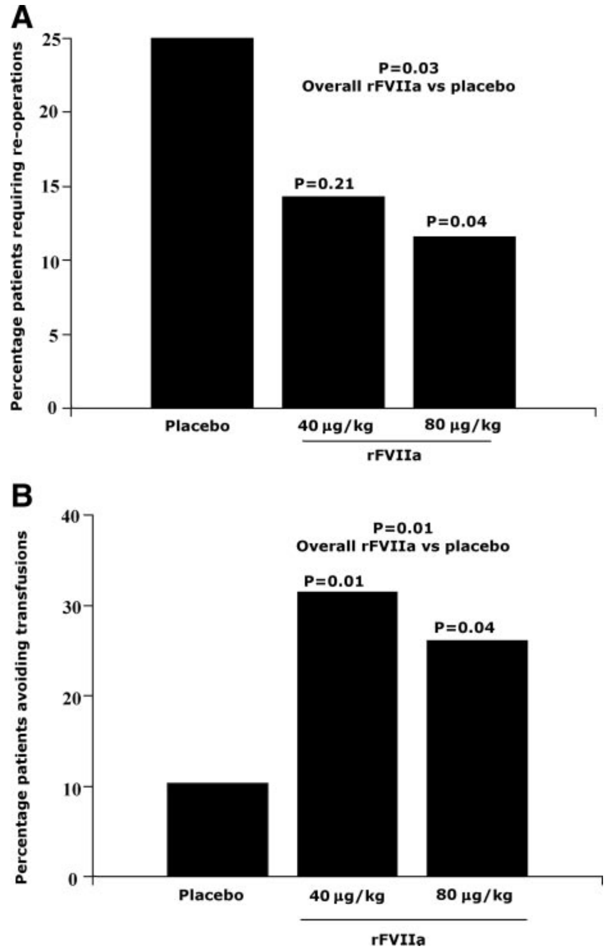

Figure 3. A, Percentage of patients requiring reoperations because of bleeding. Percentages are based on the number of patients randomized and dosed (placebo, n=68 patients; 40 μg/kg rFVIIa, n=35 patients; 80 μg/kg rFVIIa, n=69 patients). *P* values were determined in comparison to placebo treatment values with χ^2 tests. B, Percentage of patients avoiding transfusions after administration of trial drug. Percentages are based on the number of patients randomized and dosed (placebo, n=68 patients; 40 μg/kg rFVIIa, n=35 patients; 80 μg/kg rFVIIa, n=69 patients).

Limitations

The major limitation of this study is its small sample size. Consequently, some of the patients who received rFVIIa were older, were on CPB longer, and received more transfusions before randomization. These factors are all recognized as being strong predictors of cSAEs and mortality and may partially account for the numerical difference observed between groups. Other factors that may have contributed to group imbalance were the time taken to complete the study (4 years) and the 2:1 (rFVIIa: placebo) randomization ratio in cohorts 2a and 2b. Although more patients were exposed to rFVIIa in the later phase, all placebo patients were counted as 1 cohort. It is, however, a pragmatic study in that rFVIIa administration mirrored clinical practice, although at a lower rate of bleeding than salvage compassionate use.

Conclusions

The results of this trial should be interpreted with caution, and we cannot say at this time that using rFVIIa is safe in this population. The study is underpowered, and our findings could be the result of a type II error. The numerical increase in the number of cSAEs with rFVIIa could be a true finding or the result of chance. The possible efficacy of rFVIIa can be interpreted and applied only within this population. We conclude that using rFVIIa in patients bleeding after cardiac surgery may be beneficial, but caution should be applied and further clinical trials are required.

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Disclosures

All the authors were members of the Steering Committee; they were compensated by Novo Nordisk for their time. In addition, Drs Gill and von Heymann have received lecturer fees from the sponsor. Neither of the 2 Novo Nordisk employees listed as authors (Drs Booth and Schmidt) hold equity or stock options in Novo Nordisk.

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CLINICAL PERSPECTIVE

Activated recombinant factor VII (rFVIIa) has been widely reported in the management of patients bleeding after cardiac surgery. Given its widespread off-label use, physicians must be comfortable with its efficacy in stopping bleeding and reducing transfusion. However, no prospective information has been collected on the safety profile of this agent in patients undergoing cardiac surgical operations. We have looked at the potential risks and possible benefits of rFVIIa in patients who bleed after cardiac surgery. We randomized patients actively bleeding after cardiac surgery in an intensive care unit to either placebo or rFVIIa. Our results show a small numerical non–dose-dependent increase in the number of critical serious adverse events suffered by patients receiving rFVIIa. In an underpowered study, this was not statistically significant. Fifty percent fewer patients underwent reoperation for bleeding when treated with rFVIIa. Those patients who received 80 μg/kg received considerably fewer transfusions of allogeneic blood or blood products. Our results imply that caution must be used if rFVIIa is given to patients without congenital coagulopathic disorders in whom its use is licensed.

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Supplementary Tables and Figures

Supplementary Table 1. Key Inclusion and Exclusion Criteria

Supplementary Table 2. Overview of Myocardial Infarctions

Only 1 MI was seen in the current study. To evaluate this finding, clinical data from a total of 43 randomized patients found to have elevated cardiac biomarkers were therefore additionally assessed by an expert adjudication committee (3 authors of the novel "universal" definition of myocardial infarction[1] that was masked to drug allocation). This Myocardial Event Adjudication Committee (MEAC) assessed that there had been 6 MIs among the randomized and dosed patients. The MEAC assessed 1 MI per study protocol but not per universal definition. The MEAC assessed 2 MIs per study protocol and per universal definition, and assessed 3 MIs per novel definition only. Specific inquiries were then made of the investigators at the sites where these five additional patients had been dosed. In every case the local investigators stated that despite the findings of the adjudication committee, it was their opinion that the patient had not experienced an MI. MI denotes myocardial infarction, AVR denotes aortic valve repair/replacement, CABG denotes coronary artery bypass graft, MVR denotes mitral valve repair/replacement

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Supplementary Figures

Supplementary Figure 1. Transfusion Protocol

* part thereof is defined by any 30 minute period following trial product administration.

APTT denotes activated partial thromboplastin time, FFP denotes fresh frozen plasma, INR denotes International Normalized Ratio, RBC denotes red blood cells, Hb denotes hemoglobin.

Supplementary Figure 2. Drainage Volume from Cardio-thoracic Cavity from (A) 15 minutes to 4 hours post-dose, (B) 15 minutes to 24 hours post-dose, (C) 15 minutes to 5 days post-dose

Percentages are based on the number of patients randomized and dosed (placebo=68 patients, 40 mcg/kg rFVIIa=35 patients, 80 mcg/kg rFVIIa=69 patients). P values compared to placebo

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Supplementary Table 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria: At screening	**Just before dose**
1. Informed consent obtained before any trial-related activities. (A trial-related activity is any procedure that would not have been performed during normal management of the subject.)	1. Patient has been admitted to post-operative care environm at least 30 minutes (stabilization period).
2. Age ≥ 18 years.	2. Post-operative bleeding into drains placed in the cardio-th minimum of a 30 minutes period following completion o defined as **at least one of the following criteria:** – ≥ 200 ml/hr in any one hour or part thereof; – ≥ 2 ml/kg/hr for 2 consecutive hours (part thereof is defin following stabilization period).
3. Subject is scheduled to undergo cardiac surgery requiring cardiopulmonary bypass.	3. The subject does not require urgent re-operation at the tim criterion #2 above, as per the investigator's judgment.

Exclusion Criteria: At screening	**Just before dose**
1. Pregnant or breast-feeding (if applicable).	1. Administration of Activated Prothrombin Complex Conce and/or any time just before dose.
2. The participation in another clinical or device trial after Randomization.	2. Administration of rFVIIa during current surgery and/or ar
3. First time coronary artery bypass grafting with none or only one antiplatelet medication within 5 days of surgery*, or with normal preoperative coagulation (normal coagulation as defined by either INR < 1.2, aPTT within normal local range, or platelets > 150,000x10^6/L).One antiplatelet medication can be replaced by low molecular weight heparin within 12 hours of surgery to comply with the above.	3. First admission to post-operative care environment (e.g. I randomisation.
4. Cardiac or cardiopulmonary transplantation procedure.	4. Any changes to the planned surgery, during surgery, whic requiring CPB or meeting exclusion criteria 4,7 and 10.
5. Refusal to receive blood or blood products due to religious or any other reasons.	
6. Any history of stroke and/or non-coronary thrombotic disorders (including DVT and PE).	
7. Clinical signs consistent with non-coronary thrombotic disease.	
8. Known congenital deficiency of Protein C, Protein S, Antithrombin and homozygous FV Leiden, or congenital bleeding disorder	
9. Patient having an unacceptable thrombotic risk, as per the investigator judgment.	
10. Current surgery including any implantable ventricular assist device requiring CPB including extracorporal membrane oxygenation, aortic arch and/or descending thoracic aorta.	

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Supplementary Table 2. Overview of Myocardial Infarctions

Patient Age (yr) and Gender	Surgery type	MI per protocol definition	MI per universal definition[1]	MI per investigator evaluation	Treatment group
54, Male	CABG	Yes	Yes	Yes	Placebo
77, Female	AVR + CABG	Yes	No	No	40 mcg/kg rFVIIa
78, Female	MVR + CABG	Yes	Yes	No	40 mcg/kg rFVIIa
62, Male	CABG	No	Yes	No	40 mcg/kg rFVIIa
80, Male	AVR + CABG	No	Yes	No	40 mcg/kg rFVIIa
76, Female	AVR + MVR	No	Yes	No	80 mcg/kg rFVIIa

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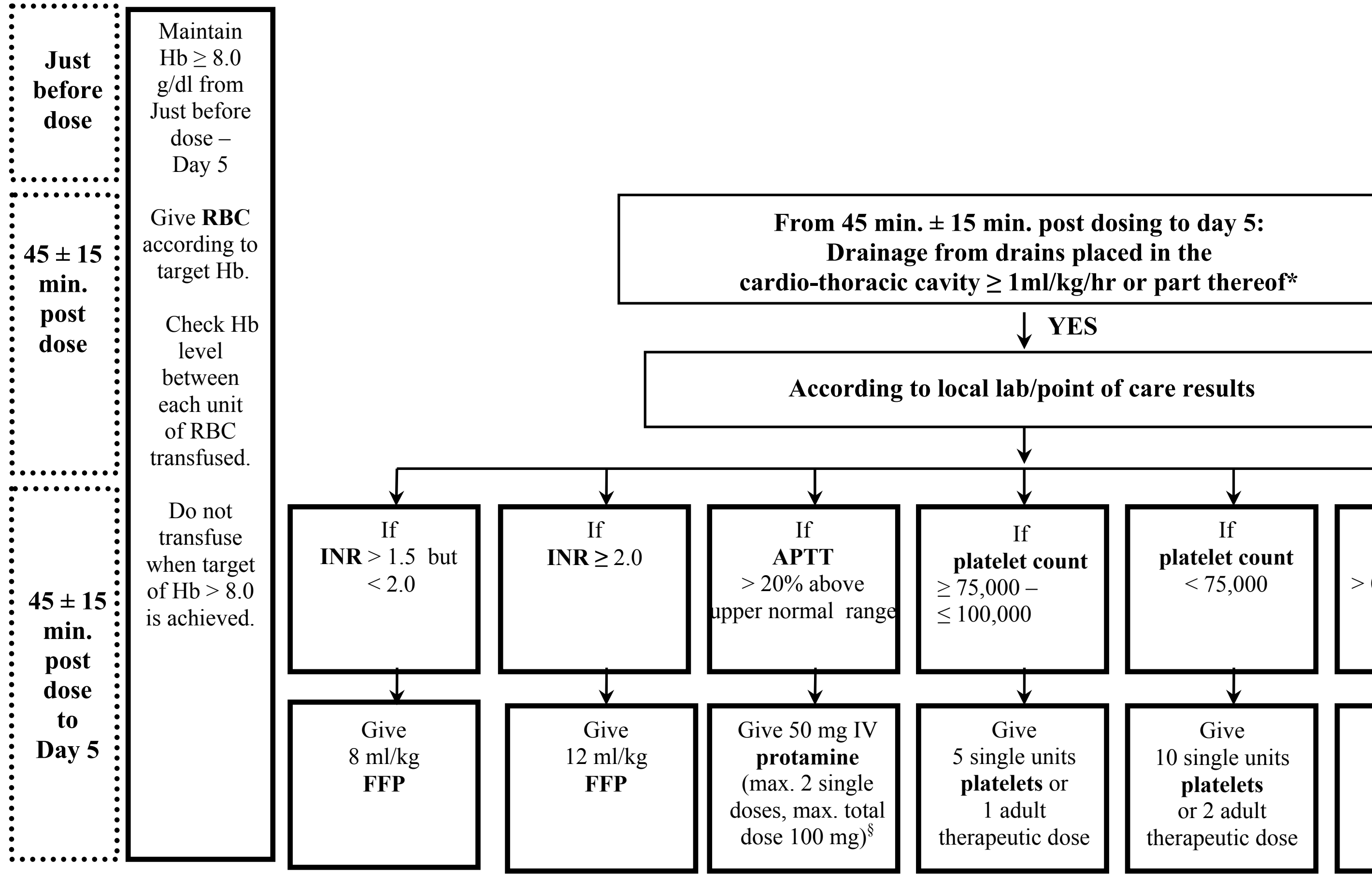
Supplementary Figure 1.



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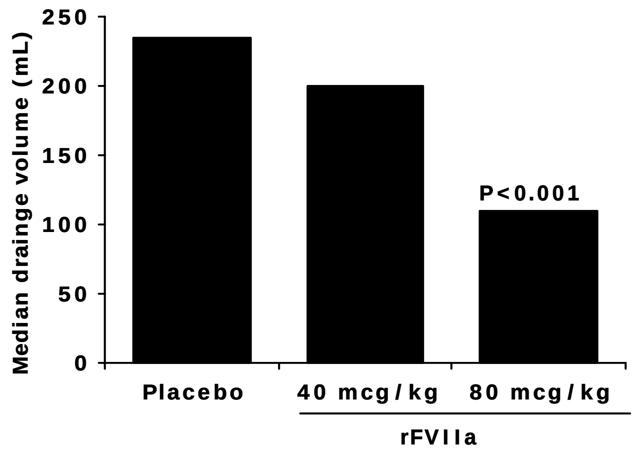
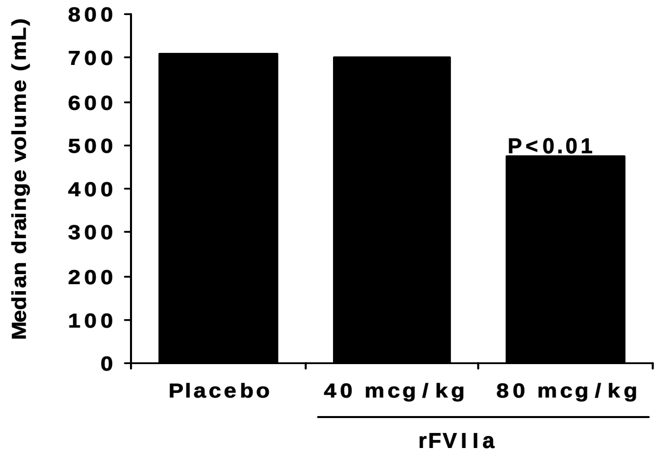
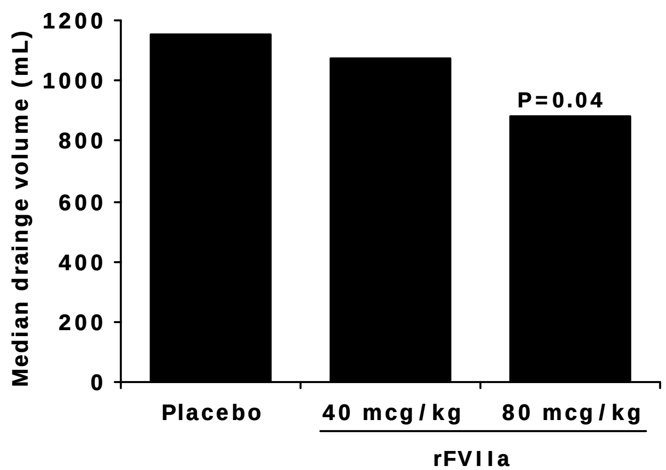
Supplementary Figure 2A.



Supplementary Figure 2B.



Supplementary Figure 2C.



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