Off-Label Use of Recombinant Factor VIIa in Pediatric Patients

**Abstract**

**Objective:** To examine off-label recombinant factor VIIa (rFVIIa) use in pediatric patients including clinical indications, dose, adverse events, and outcomes.

**Methods:** All pediatric patients entered into the Haemostasis Registry from 75 participating hospitals were analyzed.

**Results:** Three hundred and eighty-eight pediatric patients received off-label rFVIIa from 2003 to 2009. Median age was 12 months (interquartile range 1 month to 11 years). Clinical context included cardiac surgery (52.1%), medical (11.6%), other surgery (10.8%), hematology/oncology (10.3%), trauma (9.3%), intracranial hemorrhage (3.1%), and liver disease (2.8%). Twenty-six patients received extracorporeal membrane oxygenation at the time of rFVIIa administration. Median first dose was 114 mg/kg (interquartile range 90–181; range 7–2250). Thirty-four percent received 1 dose. There was a reduction in usage of red blood cells, platelets, fresh-frozen plasma, and cryoprecipitate in the 24 hours after the first dose for all patients (all P values <.001). Thromboembolic adverse events (TEAs) were reported in 5.4%. No association between TEA and size of first dose was found. Where data were available, 82% of patients were subjectively classified as responding to rFVIIa. Overall 28-day mortality was 27%. In multivariate analysis, pH values before administration and clinical context were independently associated with response to first dose and 28-day mortality.

**Conclusions:** There was a significant reduction in blood product administration after rFVIIa and a subjective response rate of 82%. Both pH and clinical context were associated with response to rFVIIa and mortality. Overall, 5.4% had a TEA reported. *Pediatrics* 2012;129:e1533–e1540

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**Key Words**

factor VIIa/administration and dosage, factor VIIa/adverse effects, hemorrhage/blood, infant, child, adolescent, transfusion

**Abbreviations**

APTT—activated partial thromboplastin time

ECMO—extracorporeal membrane oxygenation

FFP—fresh-frozen plasma

INR—international normalized ratio

IQR—interquartile range

rFVIIa—recombinant factor VIIa

TEA—thromboembolic adverse event

Drs McQuilten, Barnes, Zatta, and Phillips all participated in planning the study, analyzing the data, and drafting the manuscript. All authors approved the final manuscript.

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Recombinant factor VIIa (rFVIIa) is a hemostatic agent that at pharmacological doses enhances localized thrombin generation on thrombin-activated platelets at the site of injury, thereby enhancing platelet adhesion and aggregation, increasing availability of phospholipids, and resulting in formation of a stable fibrin plug resistant to premature lysis.\(^1\)

There has been an increasing number of reports of the use of rFVIIa to manage uncontrolled hemorrhage in clinical settings outside of these licensed indications, including cardiac surgery, trauma, and obstetrics.\(^2\)–\(^4\) Until recently, there have been few data on off-label use of rFVIIa in pediatric patients, and most have been limited to single case reports\(^5\)–\(^7\) and small or single-center case series,\(^8\)–\(^9\) including in cardiac surgery,\(^10\)–\(^12\) trauma,\(^13\) and neurosurgery.\(^14\)–\(^16\) There are important differences between pediatric and adult patients with regard to their coagulation system and risk of thromboembolism, susceptibility to bleeding after cardiopulmonary bypass,\(^17\) and the pharmacokinetics of rFVIIa.\(^18\)–\(^20\) Therefore, studies specific to pediatric patients are required to establish efficacy and safety of rFVIIa administration. However, with a few exceptions, there are practical and ethical issues that have impeded the conduct of interventional studies to address these issues in pediatric patients.\(^21\) In the absence of randomized controlled trials, registry data have a valuable role in describing current practice and may provide an opportunity to identify major trends in outcome or adverse events. We aimed to review the data on off-label use of rFVIIa in all pediatric patients entered onto the Haemostasis Registry with regard to patient demographics, indication for use, dose administered, adverse events, and patient outcome.

**METHODS**

Data were extracted from the Haemostasis Registry on all pediatric patients (age 16 years and younger) who received off-label rFVIIa between February 2003 and December 2009.

**The Registry**

The Haemostasis Registry, established by the Department of Epidemiology and Preventive Medicine, Monash University, is a register designed to collect data on all off-label rFVIIa use in patients treated at participating hospitals. Seventy-five hospitals contribute data to the Haemostasis Registry across Australia and New Zealand, including all major pediatric services in the 2 countries. The Registry estimates 85% of all off-label use in Australia and New Zealand is covered by hospitals participating in the Registry. All nonhemophiliac patients treated at participating hospitals are recorded in the Registry. Local investigators identify eligible patients after treatment with rFVIIa, usually through pharmacy or hematology records. Trained data collectors enter the data onto the registry and an assessment of whether these events were linked to the administration of rFVIIa.

**Statistical Analysis**

Summary statistics are reported as median and interquartile range (IQR) for nonnormally distributed data. Laboratory values and blood product administration before and after administration of the first dose of rFVIIa were compared by using Wilcoxon matched-pairs signed-rank tests, because many of the variables were nonnormally distributed. The first dose of rFVIIa was used because all patients received at least 1 dose, but not all patients received subsequent doses. Hypothesis testing for categorical variables was performed by using \(\chi^2\) or Fisher exact test if the sample size was small. Linear regression analysis was used to assess the association between rFVIIa dose and patient age. Multivariate analyses modeled the association between covariates (age, gender, clinical context, temperature, pH, laboratory values before and after each dose of rFVIIa (prothrombin time, international normalized ratio [INR]) and laboratory values before first rFVIIa dose, and blood products transfused in 24 hours before first rFVIIa dose) and the outcomes of mortality and response to first dose of rFVIIa by using a backward stepwise approach. A P value < .05 was considered statistically significant. All analyses were performed by
using Stata v. 11.0 (Stata Corp, College Station, TX).

RESULTS

Patient Demographics

A total of 3446 cases from 75 hospitals were entered into the Haemostasis Registry during the study period. Of these, 388 patients from 27 hospitals were <16 years of age. The median age of the pediatric cohort was 12 months (IQR 1 month to 11 years; range 9 hours to 16 years) (Table 1) and there were more boys (60%) than girls. Age and the clinical context in which rFVIIa was administered are shown in Fig 1. The administration of rFVIIa was for active bleeding in 377 (60%) than girls. Age and the clinical context in which rFVIIa was administered (−10.4, P < .001), with younger patients receiving higher doses of rFVIIa (see Fig 2). The median dosing interval was 120 minutes (IQR 35–164).

Patients <12 months of age had a median dosing interval of 90 minutes (IQR 30–122). Eleven patients (from 5 hospitals) had a first dose >1000 μg/kg. All were <12 months of age and received rFVIIa in the context of cardiac or other surgery.

rFVIIa Dose Administered

The median first dose administered was 114 μg/kg (IQR 90–181.25; range 7–2250). The median total dose administered was 1.2 mg (IQR 0.54–4.8). With regard to the number of doses, 255 (66%) had 1, 78 (20%) had 2, 24 (6%) had 3, 5 (1%) had 4, and 26 (7%) had 5 or more doses (range, 1–84). By linear regression, there was a correlation between patient age and dose administered (P = .510). There was a higher rate of mortality when used after cardiac surgery (94%). The clinical context and pH were both associated with the subjective response to the first dose in multivariate analysis (Table 3 and Appendix), with lower pH or use in a nonsurgical clinical context less likely to respond.

Mortality

Mortality data were available for all patients. In total, 106 (27%) were deceased at 28 days after administration of rFVIIa. Mortality data by clinical context and age group are shown in Table 1. Of the patients who were classified as responding to rFVIIa, 14% were deceased at 28 days compared with 67% of the patients classified as nonresponders (P < .001). Patients who received rFVIIa in a nonsurgical clinical context had a higher 28-day mortality (44% vs 21%, P < .001). Of the 23 patients who received ECMO, 12 (52%) were deceased at 28 days. The clinical context and pH before rFVIIa administration were associated with 28-day mortality in multivariate analysis (see Table 3 and Appendix).

Adverse Events

Of the entire cohort, 21 (5.4%) patients experienced a thromboembolic adverse event (TEA), which included 14 cerebrovascular accidents, 1 deep venous thrombosis, 1 pulmonary embolus, and 9 other thrombotic events. There was no increase in TEAs in patients who received a dose in excess of 200 μg/kg compared with those that received a dose lower than this (3 [6.0%] vs 17 [5.7%], P = .925) and there was no significant association between number of doses given and TEAs (P = .688). There was no significant difference in number of TEAs across the different age groups (P = .510). There was a higher rate of reported TEA in patients receiving ECMO.

TABLE 1 Patient Demographics

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. (%)</th>
<th>Median First Dose, μg/kg (IQR)</th>
<th>Median No. of Doses (IQR)</th>
<th>Mortality</th>
<th>TEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Premature</td>
<td>21 (5)</td>
<td>131 (98–184)</td>
<td>2 (1–2.5)</td>
<td>13 (62)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>&lt;4 wk</td>
<td>82 (21)</td>
<td>160 (86–207)</td>
<td>1 (1–2)</td>
<td>22 (27)</td>
<td>60 (73)</td>
</tr>
<tr>
<td>4 wk to 12 mo</td>
<td>107 (29)</td>
<td>150 (96–200)</td>
<td>1 (1–2)</td>
<td>17 (16)</td>
<td>90 (84)</td>
</tr>
<tr>
<td>1–5 y</td>
<td>49 (13)</td>
<td>100 (75–141)</td>
<td>1 (1–2)</td>
<td>14 (29)</td>
<td>35 (71)</td>
</tr>
<tr>
<td>6–10 y</td>
<td>26 (7)</td>
<td>91 (89–111)</td>
<td>1 (1–2)</td>
<td>11 (42)</td>
<td>15 (58)</td>
</tr>
<tr>
<td>11–16 y</td>
<td>103 (26)</td>
<td>92 (84–113)</td>
<td>1 (1–2)</td>
<td>29 (28)</td>
<td>74 (72)</td>
</tr>
</tbody>
</table>

Primary context

Cardiac surgery       | 202 (52) | 133 (80–193)                    | 1 (1–2)                   | 24 (12)   | 178 (88) | 16 (8)  | 186 (82) |

Medical               | 45 (12)  | 100 (80–144)                    | 2 (1–4.5)                 | 16 (36)   | 29 (64) | 1 (2)   | 44 (98) |

Other surgery         | 42 (11)  | 100 (63–180)                    | 1 (1–2)                   | 16 (38)   | 26 (62) | 1 (2)   | 41 (98) |

Hematology/oncology   | 40 (10)  | 97 (86–125)                     | 2 (1–5)                   | 20 (50)   | 20 (50) | 1 (5)   | 39 (87) |

Trauma                | 36 (9)   | 111 (86–120)                    | 1 (1–2)                   | 18 (50)   | 18 (50) | 1 (5)   | 35 (87) |

Intracranial hemorrhage| 12 (3)   | 92 (80–111)                     | 1 (1–2)                   | 6 (50)    | 6 (50)  | 0 (0)   | 12 (100) |

Liver disease         | 11 (3)   | 111 (86–179)                    | 1 (1–2)                   | 6 (55)    | 5 (45)  | 1 (9)   | 10 (91) |
compared with those patients who did not require ECMO support (5 [19%] vs 16 [4%], \(P = .009\)). The reported TEAs in patients on ECMO included 3 cerebrovascular accidents, 1 deep venous thrombosis, and 1 other arterial thrombosis.

**Cardiac Surgery**

Approximately half of all patients received rFVIIa after cardiac surgery (see Table 1). Cardiac surgery was performed predominantly for correction of congenital heart defects, including transposition of the great arteries (28%), tetralogy of Fallot (10%), hypoplastic left heart syndrome (10%), ventricular septal defect (9%), truncus arteriosus (4%), and atrial septal defect (4%). Seven (3%) cases received rFVIIa prophylactically and 195 (97%) received rFVIIa for active bleeding. There was a significant reduction in volume of transfused red blood cells, platelets, FFP, and cryoprecipitate (all \(n = 101\), \(P < .001\)) administered before and after rFVIIa use in infants <12 months of age. For those >12 months of age, there was a significant reduction in number of units of red blood cells, platelets, and cryoprecipitate administered before and after rFVIIa use in infants <12 months of age. For those >12 months of age, there was a significant reduction in volume of transfused red blood cells, platelets, FFP, and cryoprecipitate (all \(n = 101\), \(P < .001\)) administered before and after rFVIIa use in infants <12 months of age. For those >12 months of age, there was a significant reduction in number of units of red blood cells, platelets, and cryoprecipitate administered before and after rFVIIa use in infants <12 months of age.

**DISCUSSION**

This study describes the largest case series of off-label use of rFVIIa in pediatric patients that has been reported to date, from a well-designed, representative, and rigorously audited registry. The main finding of the study was a significant reduction in blood product administration in the 24 hours after rFVIIa administration. The most frequent indication for rFVIIa use in our series was to control hemorrhage after cardiac and other surgical procedures. The occurrence of TEAs was not associated with the dose or number of doses of rFVIIa.

The reduction in blood product administration is consistent with reports from observational studies that have demonstrated reduction in blood product requirements in pediatric patients treated with rFVIIa for uncontrolled hemorrhage \(^8,16,17\) and studies in surgical patients that have demonstrated reductions in blood loss after rFVIIa administration. \(^11,12,17\) Despite the observed reduction in transfusion requirements, it is difficult to make conclusions regarding the efficacy of rFVIIa from our data. Other interventions used at the same time as rFVIIa administration may account for the reduction in blood product usage and subjective bleeding assessment, and no control group is available for comparison. This applies to similar studies that have used reduction in transfusion and blood loss to assess efficacy. Changes in APTT and prothrombin time after rFVIIa administration have been reported, but these differences may also be accounted for by other interventions (including blood product administration). Furthermore, shortening of these laboratory tests does not necessarily correlate with clinical efficacy. \(^22,23\)

In multivariate analysis, the pH at the time of administration was strongly associated with subjective response to rFVIIa, consistent with other studies in critically ill adults. \(^2\) Patients who were
Table 2: Blood Products Administered in the 24 Hours Before and the 24 Hours After Administration of First Dose of rFVIIa

<table>
<thead>
<tr>
<th>Blood Product</th>
<th>No.</th>
<th>Before rFVIIa Median (IQR)</th>
<th>After rFVIIa Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed red blood cells</td>
<td>178</td>
<td>2.5 (0.7–6)</td>
<td>1 (0–2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>19 (6–60)</td>
<td>10 (0–20)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Platelets</td>
<td>176</td>
<td>1 (0–3)</td>
<td>0.05 (0–2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>20 (9–33)</td>
<td>0 (0–11)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FFP</td>
<td>177</td>
<td>1 (0–4)</td>
<td>0 (0–2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>13 (0–38)</td>
<td>0 (0–16)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>175</td>
<td>0 (0–4)</td>
<td>0 (0–1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>8 (3–19)</td>
<td>0 (0–3)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Blood products reported in milliliters per kilogram for infants <12 months of age and in units for those >12 months of age.

Table 3: Variables Associated With Response to First Dose of rFVIIa and 28-Day Mortality in Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response to rFVIIa Administration</th>
<th>28 d Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>SE</td>
</tr>
<tr>
<td>Clinical context: nonsurgical</td>
<td>0.15</td>
<td>0.078</td>
</tr>
<tr>
<td>pH</td>
<td>2.32</td>
<td>0.389</td>
</tr>
</tbody>
</table>

n = 177 for response to rFVIIa administration and n = 197 for 28-day mortality. CI, confidence interval; OR, odds ratio.

Receiving rFVIIa for a nonsurgical indication (including medical patients and hematology/oncology patients) were also less likely to respond, which may reflect the type of bleeding and other comorbidities present. A recent single-center case series of off-label rFVIIa reported a poor response in pediatric patients with multiorgan dysfunction syndrome and disseminated intravascular coagulation, suggesting that the use of rFVIIa in these patients may be futile. Overall, the mortality rate of 27% at 28 days in our patient cohort was higher than the largest published case series to date (14.7%) and less than another smaller case series. In multivariate analysis, again the pH value before administration of rFVIIa and the clinical context were both independently associated with 28-day mortality.

There have been few studies on the use of rFVIIa in pediatric patients undergoing cardiac surgery. One double-blinded randomized controlled trial administered 40 μg/kg of rFVIIa electively before cardiopulmonary bypass surgery for congenital heart disease. This study did not find a reduction in the time to chest closure, intraoperative blood loss, or transfusion requirements between the rFVIIa treatment and standard treatment groups. However, there has not been a randomized controlled trial of the use of rFVIIa in cardiac surgery for patients with uncontrolled hemorrhage. A systematic review of rFVIIa use in pediatric cardiac surgery demonstrated a significant reduction in blood loss after rFVIIa administration, although it noted that the published literature was small and mostly based upon retrospective and noncomparative reports. A recently published retrospective study of 90 pediatric patients who received rFVIIa for uncontrolled postoperative hemorrhage after cardiac surgery for congenital heart disease also demonstrated a reduction in blood loss and transfusion requirements after rFVIIa and found that reexploration for bleeding was avoided in ~80% of cases. All patients in this study underwent transthoracic echocardiogram and clinical examination, and no cases of thrombosis were detected.

Thrombosis, a potential complication arising from rFVIIa administration, can lead to significant morbidity and possible mortality. The rate of TEAs in this cohort study (5.4%) is similar to published rates in adults and some pediatric case series, although it is higher than a case series of 265 children, in which <1% of patients had a reported TE, and the pediatric cardiac surgery case series discussed earlier. It should also be noted that our registry collected data on symptomatic thrombotic complications and, therefore, may not have captured asymptomatic and unrecognized TEAs. In our study, there did not appear to be a relationship between the dosing strategy of rFVIIa and risk of TEA. Patients who were receiving ECMO had a higher rate of TEAs (19%), and this was comparable to other reports of rFVIIa use in pediatric patients during ECMO support. However, this is similar to the rate of venous thrombosis found through Doppler surveillance in a cohort of neonates and young children not treated with rFVIIa. In a retrospective series of 17 patients, the number of TEAs (24%) was found to be no higher when compared with a historical control group (39%).

The dose of rFVIIa administered (median dose and upper range) in our study cohort (including cardiac surgery and infants <12 months) is high compared with previous reports in the literature. All 11 patients who received a first rFVIIa dose of >1000 μg/kg were <12 months. These patients were from 5 different institutions, suggesting these high doses were not accounted for by a local practice or protocol at a single institution. Overall, the dosing was higher in our study cohort than the 90 μg/kg.
dose recommended for the treatment of hemophilia A or B. There is evidence that rFVIIa has a shorter half-life and more rapid clearance in children compared with adults, and this may partly explain the use of higher doses by treating clinicians in our study.18,19 This may also explain why the median time between repeated rFVIIa doses was shorter in infants <12 months compared with the older age groups. Because there is little evidence to guide clinicians on the most effective or safe dose of rFVIIa for off-label indications of rFVIIa, with most data derived from studies for the treatment of hemophilia, variation in practice is to be expected. There is also the possibility of dosing errors contributing to the higher doses of rFVIIa administered. Quantitative errors represent the most common medication error in pediatric patients, especially infants.20,21 Misplaced decimal points or zeros can result in large (10-fold or greater) dosing errors as well as the use of adult-sized vials, particularly for neonates.31,32 In our cohort, the dose administered was not associated with response to rFVIIa, and there were no more TEAs reported in patients who received higher doses (>200 μg/kg) of rFVIIa compared with those who received lower doses.

There are some important limitations to our study that should be considered. First, complete data were not available for all patients. However all patients were included in the analysis to avoid introducing bias. Second, the patients represent a heterogeneous group with regard to age as well as the clinical context in which they received rFVIIa. Third, there was no control group to compare outcome and rate of adverse events, which limits conclusions that can be made regarding both efficacy and safety of rFVIIa in this context.

Notwithstanding any limitations, this study reports the largest case series of rFVIIa use in pediatric patients and also the single largest series of rFVIIa use in pediatric cardiac surgery patients. The design of the registry, which ensures that all cases of off-label rFVIIa are included regardless of outcome, limits bias and prevents reporting of only positive experiences. This may explain the higher mortality and adverse event rate observed compared with other case series. Although randomized controlled studies are needed to evaluate the efficacy and safety of rFVIIa use in off-label indications, there are both practical and ethical challenges in conducting such studies in pediatric patients with uncontrolled hemorrhage. In the absence of such studies, registry data reporting current practice across a large number of hospitals is valuable for identifying trends in outcomes and adverse events.

CONCLUSIONS
In this case series of 388 pediatric patients who received off-label use of rFVIIa, we found a reduction in blood product requirements after rFVIIa administration and a reported response rate of 82%. Both pH and the clinical context were associated with response to rFVIIa and mortality. Overall, 5.4% of patients had a TEA. There was no association between dose administered and response rate or risk of TEAs.

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Haemostasis Registry Steering Committee: Professor Peter Cameron, Dr Scott Dunkley, Dr Roger Houben, Professor James Isbister (chair), Professor John McNeil, Dr Louise Phillips, Ms Wendy Thomas, and Dr Amanda Zatta. Participating Hospitals: Australian Capital Territory: The Canberra Hospital; New South Wales: The Children’s Hospital at Westmead, Concord Hospital, John Hunter Hospital, Liverpool Hospital, Prince of Wales Hospital, St Vincent’s Hospital, Sydney Children’s Hospital; Northern Territory: Alice Springs Hospital, Royal Darwin Hospital; Queensland: Mater Children’s Hospital, Prince Charles Hospital, Princess Alexandra Hospital, Royal Brisbane & Women’s Hospital, Royal Children’s Hospital; South Australia: Royal Adelaide Hospital, Women’s & Children’s Hospital; Victoria: Monash Medical Centre, Royal Children’s Hospital, Royal Women’s Hospital; Tasmania: North West Regional Hospital; Western Australia: Princess Margaret Hospital for Children, Royal Perth Hospital; New Zealand: Auckland City Hospital, Middlemore Hospital, Waikato Hospital, Wellington Hospital.

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## APPENDIX Variables Included in Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entered in model</th>
<th>Details</th>
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</tr>
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<td>Age</td>
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<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male = 1</td>
<td></td>
</tr>
<tr>
<td>Clinical context</td>
<td>Surgical = 1</td>
<td>Nonsurgical = 2</td>
</tr>
<tr>
<td></td>
<td>Trauma = 3</td>
<td></td>
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<tr>
<td><strong>Dose</strong></td>
<td>Dose</td>
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<tr>
<td><strong>Laboratory values</strong></td>
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<tr>
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<td>Celsius</td>
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</tr>
<tr>
<td>pH at time rFVIIa given</td>
<td>Continuous (in 0.1 U)</td>
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<tr>
<td>Hemoglobin before dose</td>
<td>g/L</td>
<td></td>
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<tr>
<td>Platelet count before dose</td>
<td>10^9/L</td>
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<tr>
<td>APTT before dose</td>
<td>Seconds</td>
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<tr>
<td>INR before dose</td>
<td>Continuous</td>
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<td>Transfused red blood cells before dose</td>
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<td>Transfused FFP before dose</td>
<td>Units</td>
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<td>Transfused platelets before dose</td>
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<td></td>
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<tr>
<td>Transfused cryoprecipitate before dose</td>
<td>Units</td>
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