

Recombinant Activated Factor VII Significantly Reduces Transfusion Requirements in Cardiothoracic Surgery

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Abstract

Background The off-label use of recombinant activated factor VII (rFVIIa) for intractable bleeding is associated with a risk of thrombotic events. The objective of this study was to evaluate the incidence and predictors of rFVIIa-related thrombotic events and its efficacy in the reduction of transfusion requirements during various surgeries.

Methods Ninety-two cases received rFVIIa for uncontrollable bleeding despite medical and surgical hemostasis. The incidence and risk factors of thrombotic events were analyzed. Blood products transfused in the 24 h before and after rFVIIa injection were calculated. Subgroup analysis was performed to see which types of surgeries benefited most from rFVIIa.

Results The main indication for rFVIIa administration was uncontrollable bleeding during cardiothoracic surgery followed by coagulopathy due to liver failure followed by neurosurgical procedures. Requirements of blood products after rFVIIa decreased significantly by 45 % ($p = 0.012$),

52 % ($p = 0.0001$), and 75 % ($p = 0.0001$) for red blood cells, plasma, and cryoprecipitate, respectively. Subgroup analysis showed that cardiothoracic surgery was the sole group that benefited from rFVIIa with a reduction in transfusion of red blood cells ($p = 0.013$), plasma ($p = 0.0001$), and cryoprecipitate ($p = 0.0001$). Thrombotic events occurred in 9.8 % of the cases mostly on the arterial side (89 %) and have not contributed to mortality. **Conclusion** rFVIIa can significantly reduce transfusion requirements when given for intractable bleeding during cardiothoracic surgery at the expense of thrombotic events in approximately one tenth of the cases. Further prospective studies are necessary to study if this effect of rFVIIa is translated to a favorable outcome.

1 Introduction

Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Copenhagen, Denmark) is a genetically engineered concentrate of the activated form of human coagulation factor VII. The original design and on-label indication of rFVIIa is the treatment of life-threatening hemorrhages in patients with hemophilia A and B and acquired hemophilia [1]. In this group of patients, the prevalence of rFVIIa-related thromboembolic events is less than 1 % and its safety has been well studied in prospective clinical trials. Given the rarity of these diseases, more than 95 % of rFVIIa administration is for off-label indications [2]. Recently, rFVIIa has been increasingly used in a variety of off-label indications including cardiac surgery [3, 4], liver transplantation [5], trauma [6], and extracorporeal membrane oxygenation [7]. Although the use of rFVIIa in uncontrollable bleeding is not associated with mortality benefit [8, 9], several studies have shown an improved

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outcome [10, 11]. Nonetheless, concerns have been raised regarding the increased risk of thrombotic events [12–14], the main argument for limiting rFVIIa off-label use. A Cochrane review of 29 randomized controlled studies including 4290 patients showed weakness of evidence supporting rFVIIa off-label use and suggested that its use should be restricted to clinical trials [9]. Given the lack of sufficient evidence supporting rFVIIa off-label use, a careful risk/benefit assessment is therefore crucial in deciding when to administer rFVIIa to those with uncontrollable bleeding. To examine the safety and efficacy of the off-label use of rFVIIa at our facility we have conducted this observation study. We aim to assess the incidence and independent predictors for the occurrence of thrombotic events and the efficacy of rFVIIa in controlling massive bleeding in various surgical and medical settings.

2 Materials and Methods

2.1 Study Design and Study Population

A retrospective review of medical records was performed for consecutive patients who received rFVIIa for uncontrollable bleeding between October 2011 and December 2013 at a 1018-bed tertiary care facility; Tampa General Hospital. The patients who received rFVIIa were identified from pharmacy records and were included in the study if they were aged 18 years or older and received at least one dose of rFVIIa. Uncontrollable bleeding is defined as persistent bleeding despite the implementation of medical and surgical hemostatic measures. Thrombotic events were determined through review of progress notes and discharge summary of cases receiving rFVIIa. Diagnosis of thrombotic events was made by ultrasonography for peripheral venous or arterial thrombosis and computed tomography scan for ischemic cerebrovascular stroke or pulmonary artery embolism. The Institutional Review Board at the University of South Florida approved the study and waived the need for patient consent.

2.2 Administration of rFVIIa

Commercially available rFVIIa was used in all patients included in the study. The decision to inject the drug was at the onset of uncontrollable bleeding despite transfusion of blood products. The dosage and number of injections of rFVIIa was decided based upon a Tampa General Hospital protocol for non-US Food and Drug Administration-approved uses of rFVIIa (supplementary Appendix).

2.3 Study Endpoints

The main outcome variable of this study was to determine the incidence and predictors of occurrence of thrombotic events related to rFVIIa administration. We reviewed medical records for baseline risk factors that may increase the risk for thromboembolism. Approximately 20 risk factors were investigated including age, sex, body mass index, diabetes mellitus, prior history of thrombotic events, history of cancer, rFVIIa dose, number of rFVIIa doses given, and concomitant administration of blood products to determine independent predictors of rFVIIa-related thromboembolic events. The secondary outcome variable was to assess the efficacy of rFVIIa in reducing transfusion requirements in various surgical and medical indications. Various blood products administered, including packed red blood cells (RBCs), platelets, plasma, and cryoprecipitate, were collected in the 24 h before and after injecting rFVIIa to observe its effect on reducing transfusion requirements. Subgroup analysis was performed to identify which subgroup benefited most from rFVIIa administration.

2.4 Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of distribution of investigated parameters. Continuous data were expressed as means \pm standard deviations and were compared using two-tailed independent Student *t* tests. Categorical variables were compared using Chi-Square or Fisher's exact tests. Subgroup analysis to see the group who benefited most from rFVIIa administration was performed using the paired *t* test. Multivariate logistic regression analysis was used to identify independent predictors for the occurrence of thrombotic events after rFVIIa administration. $p < 0.05$ was considered significant. Data were analyzed using IBM SPSS 21.0 statistical software (Version 21.0., IBM SPSS Statistics for Windows, Armonk, NY, USA).

3 Results

A total of 92 consecutive patients who received rFVIIa were enrolled in the study. rFVIIa was given to control bleeding during surgery in 70 patients (76.1 %) and for various medical indications causing intractable bleeding in 22 patients (23.9 %). rFVIIa was administered in an average dose of 62 $\mu\text{g}/\text{kg}$. Twelve cases received two doses and three cases received three doses of rFVIIa. Figure 1 illustrates the various indications for rFVIIa administration. The main indications for administration of rFVIIa were uncontrollable bleeding during cardiothoracic surgery (46 % of cases) followed by reversal of bleeding due to

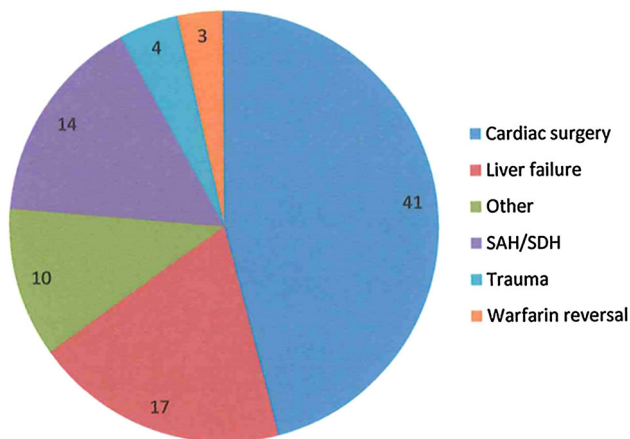


Fig. 1 The various indications for the administration of rFVIIa at Tampa General Hospital between October 2011 and December 2013. *rFVIIa* recombinant activated factor VII, *SAH* subarachnoid hemorrhage, *SDH* subdural hemorrhage

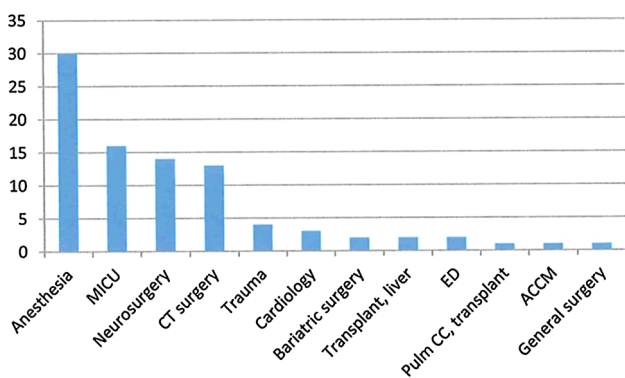


Fig. 2 The various prescribing services of each rFVIIa injection at Tampa General Hospital between October 2011 and December 2013. *ACCM* anesthesia critical care medicine, *CC* critical care, *CT* computed tomography, *ED* emergency department, *MICU* medical intensive care unit, *rFVIIa* recombinant activated factor VII

liver failure (19.1 %), followed by neurosurgical procedures (16 %). Figure 2 lists the various prescribing services of each rFVIIa injection showing that anesthesiologists were the most frequent prescribers of rFVIIa. Demographics and clinical characteristics for patients with and without thrombotic events are summarized in Table 1. There were no significant differences in baseline demographics, clinical characteristics, preoperative coagulation tests, rFVIIa dose and number of injections, and transfusion of various blood products between both groups.

3.1 Transfusion Requirements Before and After rFVIIa Administration

For the 92 patients included in the study, bleeding significantly decreased after the administration of rFVIIa as

evidenced by the diminished need for blood products (Table 2). Requirements of blood products after rFVIIa decreased significantly by 45 % ($p = 0.012$), 52 % ($p = 0.0001$), and 75 % ($p = 0.0001$) for RBCs, plasma, and cryoprecipitate, respectively. There was a non-significant reduction in platelet transfusions after rFVIIa by 30 %, $p = 0.142$. Subgroup analysis according to the indication for rFVIIa administration showed that cardiothoracic surgeries had the most benefit after rFVIIa injection in terms of a reduction in transfusion requirements. In patients undergoing cardiothoracic surgery, there was a significant reduction in RBCs ($p = 0.013$), plasma ($p = 0.0001$), and cryoprecipitate ($p = 0.0001$) after rFVIIa administration (Fig. 3). With neurosurgical procedures, there was only a trend towards a decreased need for platelet transfusion after rFVIIa administration ($p = 0.057$) but no significant effect on RBC, plasma, or cryoprecipitate transfusion (Fig. 4). With other procedures, which include trauma, gastrointestinal bleeding, postoperative bleeding, and liver transplant, the use of rFVIIa has not significantly decreased the transfusion of any blood products (Fig. 5).

3.2 rFVIIa-related Thrombotic Events and Predictors of Thrombosis

Thrombotic events were identified in 9/92 patients (9.8 %). Out of the nine thrombotic events, four occurred after cardiac surgery, two after neurosurgery, and three following liver transplant. The majority of thrombotic events occurred in the arterial circulation: two cases in the pulmonary artery, three cases in the cerebral circulation causing cerebrovascular infarcts, and one case in the common femoral vein, radial artery, hepatic artery, and brachiocephalic artery. We found no difference between subjects with and without thrombotic events with regard to various risk factors of thrombosis on univariate analysis (Table 1). At the multivariate logistic regression model (Nagelkerke R^2 : 0.113; p from the Hosmer–Lameshow test = 0.709), we found no independent predictors of occurrence of thrombotic events in patients receiving rFVIIa (Table 1). Mortality data were available for all patients. The mortality rate in the groups that received rFVIIa with and without thrombotic events was 66.7 % and 57.8 %, respectively, $p = 0.609$. Mortality was unrelated to the occurrence of thrombotic events.

4 Discussion

In prior studies, rFVIIa did not show evidence of reducing mortality from uncontrollable bleeding while thrombotic events remained a major concern. This has stimulated recommendations curtailing its off-label use [15]. However, an

Table 1 Characteristics of patients who received rFVIIa with or without the occurrence of thrombotic events at the Tampa General Hospital between October 2011 and December 2013

Characteristic	Thrombotic event (<i>n</i> = 9)	No thrombotic event (<i>n</i> = 83)	<i>p</i> value*	<i>p</i> value**
Age (y)	53.7 ± 18.6	58.6 ± 16.6	0.403	0.246
Weight (kg)	87.4 ± 23.5	86 ± 23.3	0.867	
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.659	
BMI (kg/m ²)	28.2 ± 5.2	28.4 ± 7.4	0.961	0.725
Preop PLT (10 ⁹ /L)	87 ± 33.9	124.5 ± 81	0.526	
Preop PT (s)	20.5 ± 10.4	20.2 ± 15.9	0.945	
Preop PTT (s)	45.7 ± 18	38.9 ± 24.8	0.433	
Preop INR	2 ± 1	1.9 ± 1.5	0.934	
rFVIIa dose (mcg)	5666 ± 3807	5409 ± 3721	0.845	0.824
Sex (% female)	44.4	37.3	0.677	
History of cancer (%)	0	18.1	0.186	0.999
DM (%)	11.1	36.1	0.125	
CAD (%)	44.4	42.2	0.582	
Coagulopathy (%)	44.4	28.9	0.273	
History of thrombosis (%)	22.2	13.3	0.373	
Number of rFVIIa doses	1.1 ± 0.3	1.2 ± 0.5	0.576	0.611
1 dose rFVIIa (%)	88.9	83.1	0.824	
2 doses rFVIIa (%)	11.1	13.3	0.824	
3 doses rFVIIa (%)	0	3.6	0.824	
Concomitant FFP (%)	37.5	50	0.402	
Concomitant amicar (%)	62.5	44.7	0.3	
Concomitant PLT (%)	37.5	36.8	0.634	
Mortality, <i>n</i> (%)	6/9 (66.7)	48 (57.8)	0.446	

BMI body mass index, CAD coronary artery disease, DM diabetes mellitus, FFP fresh frozen plasma, INR International Normalized Ratio, Preop preoperative, PLT platelet, PT prothrombin time, PTT partial thromboplastin time, rFVIIa recombinant activated factor VII

* *p* value for univariate analysis

** *p* value for multivariate analysis

Table 2 Transfusion of blood products before and after the administration of rFVIIa at the Tampa General Hospital between October 2011 and December 2013

Blood product	24 h before rFVIIa (mean ± SD)	24 h after rFVIIa (mean ± SD)	Absolute difference (before-after) ^a	95 % CI	<i>p</i> value
RBC	11.8 ± 17.3	6.5 ± 14.8	5.3	1.2 to 9.4	0.012*
Platelet	18 ± 26.4	12.6 ± 26.1	5.5	-1.9 to 12.8	0.142
Plasma	9.7 ± 9.9	4.7 ± 7	5	2.6 to 7.5	0.0001*
Cryoprecipitate	22.6 ± 33	5.7 ± 17.1	16.9	9.4 to 24.4	0.0001*

^a The absolute difference in blood products in the 24 h before and 24 h after rFVIIa administration

CI confidence interval, RBC red blood cells, rFVIIa recombinant activated factor VII, SD standard deviation

improved outcome was found with the off-label use of rFVIIa in cases with uncontrollable coagulopathic bleeding unresponsive to conventional therapy [16–21] and this has been supported by two major studies. In a recent multicenter study at 16 Canadian hospitals for which 1378 cases received rFVIIa, transfusion requirements were substantially decreased after the administration of rFVIIa and the rate of adverse events was strongly related to the severity of

bleeding [10]. The severity of bleeding undermined any potential risks related to thrombotic events and authors felt that major bleeding was the main determinant of outcome. Additionally, the Australian and New Zealand Registry found a strong relationship between lack of response to rFVIIa and mortality [22]. This promoted many to favor the use of rFVIIa when the risk/benefit ratio is favorable, as in life-threatening coagulopathy after surgery or trauma.

Fig. 3 Effect of rFVIIa on the transfusion of blood products during cardiothoracic surgery. *Cryo* cryoprecipitate, *RBC* red blood count, *rFVIIa* recombinant activated factor VII

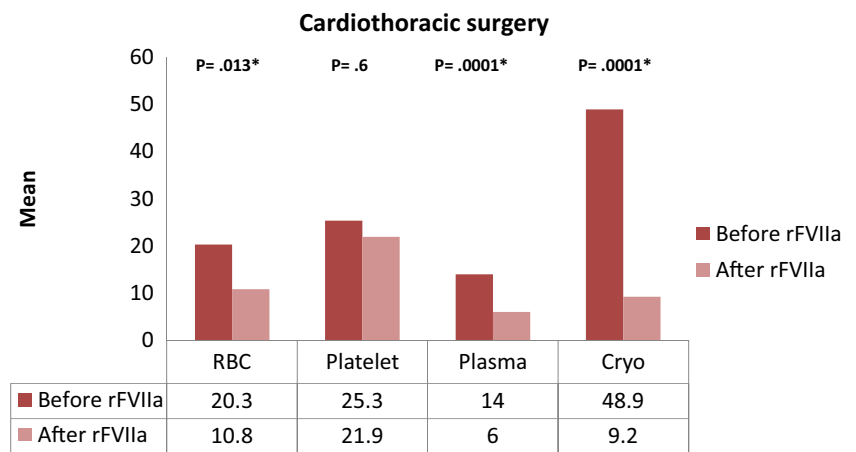


Fig. 4 Effect of rFVIIa on the transfusion of blood products during neurosurgery. *Cryo* cryoprecipitate, *RBC* red blood count, *rFVIIa* recombinant activated factor VII

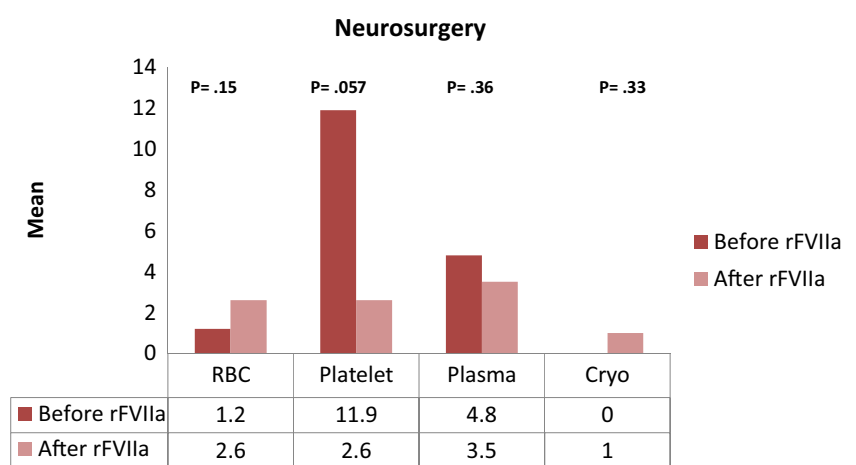
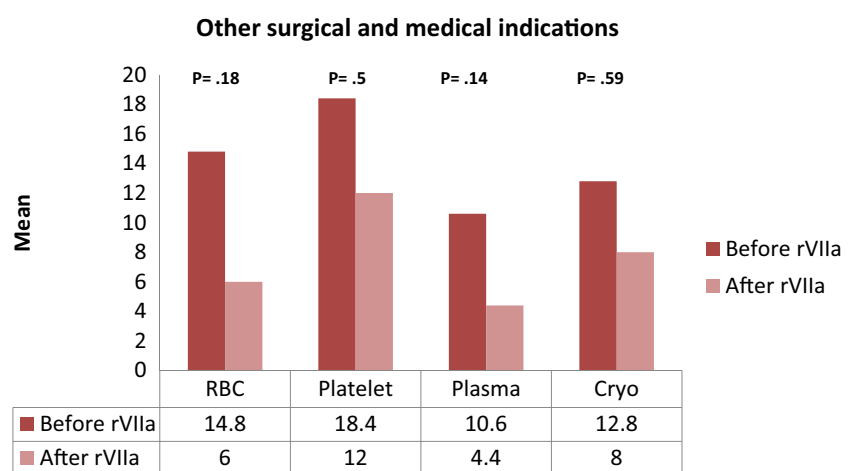


Fig. 5 Effect of rFVIIa on the transfusion of blood products for other surgical and medical indications. *Cryo* cryoprecipitate, *RBC* red blood count, *rFVIIa* recombinant activated factor VII



In our study, the administration of rFVIIa reduced bleeding as evidenced by the significant reduction in transfusion requirements of RBCs, plasma, and cryoprecipitate in the 24 h after its injection compared with the blood products required in the prior 24 h. For accuracy, the amount of transfusion products rather than estimated blood

loss was used as a marker of severity of bleeding. rFVIIa was used mainly in uncontrollable bleeding after cardiothoracic surgery followed by reversal of coagulopathy due to liver cell failure followed by neurosurgical procedures. Analysis of transfusion requirements in various subgroups show that those undergoing cardiothoracic surgery

benefited the most from rFVIIa administration in terms of a reduction in transfusion requirements, as they demonstrated a significant reduction in RBCs, plasma, and cryoprecipitate transfusion after rFVIIa injection. The reduction in transfusion requirements has not been significant in the neurosurgical group and other procedures, suggesting a favorable benefit of rFVIIa in cardiothoracic surgery. Possible explanation for this difference in efficacy is the vascular nature of cardiac surgery in addition to the likely significantly higher use of antiplatelet medications and possible continued effect of anticoagulant medications in this group compared with liver cell failure and neurosurgical groups.

Our study confirms the results of prior studies including a randomized placebo-controlled trial that showed a significant reduction in the number of patients requiring reoperation after cardiac surgery as a result of bleeding ($p = 0.03$), as well as a reduction in allogenic transfusions ($p = 0.01$) [23]. Another randomized controlled study comparing the efficacy of the prophylactic use of rFVIIa given after weaning from cardiopulmonary bypass (CPB) showed a significant reduction in postoperative bleeding and transfusion requirements [24]. Anderson and colleagues reported the value of low-dose rFVIIa given after CPB in improving postoperative hemostasis in a propensity-matched cohort of 88 patients undergoing thoracic aortic operations [25]. In a multicenter observational study, Hacquard and colleagues demonstrated the value of rFVIIa in reducing hourly blood loss ($p < 0.001$) and transfusion requirements ($p < 0.001$) in patients with intractable hemorrhage after cardiothoracic surgery [26]. This reduction in blood loss and transfusion requirements with rFVIIa was also demonstrated in children undergoing cardiac surgery with CPB [27].

However, these results should be taken with caution after a study by Alfirevic and colleagues of 144 propensity-matched patients who received rFVIIa before complex cardiac surgery showed a higher in-hospital mortality (40 vs 18 % of control patients, odds ratio 2.82; 98.3 % confidence interval 1.64–4.87; $p < 0.001$) and renal morbidity (31 vs 17 % of control patients (odds ratio 2.07; 98.3 % confidence interval 1.19–3.62; $p = 0.002$) after adjustment for major confounding variables [28]. Additionally, in an earlier study by Chapman and colleagues who matched 236 patient receiving rFVIIa for bleeding after cardiac surgery, although there was no significant difference in mortality between both groups, there was a higher trend in 30-day mortality (7.7 vs 4.3 % in the rFVIIa group and control group, respectively, $p = 0.14$) [29]. However, in these studies the possibility of influence of unmeasured confounders cannot be totally excluded.

We found a 9.8 % incidence of thrombotic events conforming to prior studies showing similar incidence [30].

None of these events have contributed directly to mortality. We examined all possible predictors for occurrence of thrombotic events but none showed significance. This can also be a function of small sample size. Eighty-nine percent (eight of nine cases) of thrombotic events occurred on the arterial side with only one case of venous thrombosis in the common femoral vein. This confirms the results of a prior meta-analysis that included 35 randomized clinical trials and showed a significantly higher rate of arterial thromboembolic events among those who received rFVIIa than among subjects who received placebo, but a comparable rate of venous thromboembolic events among both groups [12].

The main study limitation is the small cohort and the retrospective design. We have not used blood loss data because of concerns of accuracy of provided values and instead used transfusion requirements as a marker of severity of bleeding. The benefit of rFVIIa in reducing transfusion requirements should not be generalized to the whole study population, as it is mainly driven by a highly significant reduction in the transfusion of blood products in the cardiothoracic surgery group and this benefit was responsible for continued statistical significance when the whole group was analyzed. Another limitation is the unclear description of intractable bleeding in our study. rFVIIa was given at the discretion of the various prescribers as outlined in Fig. 2 without clear-cut definitions and therefore some of these injections might be unnecessary and cause more harm than benefit. The dosage and number of rFVIIa injections were also not standardized across the study subjects, which is an inherent limitation in most retrospective studies. Subgroup analysis is inherently challenging as one must account for the heterogeneity in baseline characteristics in different subgroups, loss of power with repeated analysis, and the risk of type 1 error. However, the fact that the p value for the reduction in plasma and cryoprecipitate transfusion after rFVIIa administration in cardiothoracic surgery is 0.0001 suggests that these results will likely be reproducible. Because our main study objective was to find predictors for the occurrence of thrombotic events after rFVIIa injection, a control group of patients (who had not received rFVIIa) was not included in the study, and therefore mortality and morbidity after rFVIIa injection was not analyzed and can be related to other non-thrombotic side effects.

5 Conclusion

This observational study demonstrates a significant reduction in transfusion requirements in the patients undergoing cardiothoracic surgery with thrombotic events occurring in approximately one tenth of the cases with no clear

predictors for the occurrence of these events. In this study, thrombotic events had not contributed directly to mortality. rFVIIa may therefore be of benefit in reducing transfusion requirements from intractable bleeding during cardiothoracic surgery. Further randomized prospective studies are necessary to study the morbidity and mortality outcomes of rFVIIa compared with placebo.

Conflicts of interest The authors have no conflicts of interest to disclose.

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