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The Association Between Antifibrinolytic Agent and Recombinant Factor VIIa (rVIIa) on the Incidence of Perioperative Morbidity and Mortality in Cardiac Surgery Using a Retrospective Study Cohort.

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Master of Science
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B.S., University of Michigan, 1995
M.D., University of California, Davis, 1999

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An abstract of
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Abstract

The Association Between Antifibrinolytic Agent and Recombinant Factor VIIa (rVIIa) on the Incidence of Perioperative Morbidity and Mortality in Cardiac Surgery Using a Retrospective Study Cohort.

By Roman M. Sniecinski, MD

Bleeding is a common problem following complex cardiac surgery utilizing cardiopulmonary bypass (CPB). Recombinant activated Factor VII (rVIIa) is often used as a rescue agent when coagulopathy is resistance to conventional treatment with hemostatic blood products. In this retrospective cohort study, we examined the association of rVIIa administration with perioperative mortality, major adverse cardiac events (MACE), and venous thromboembolic events (VTE). We also examined the association of two different types of antifibrinolytic agents on perioperative mortality in those patients administered rVIIa.

From 1/1/2005 thru 12/31/2012, 4569 patients underwent complex cardiac surgery using CPB at Emory University Hospital and Emory University Hospital Midtown and of these patients, 2,371 experienced severe bleeding. Of the bleeding patients, 610 (25.7%) were administered rVIIa as rescue therapy. Using multivariable logistic regression to control for known confounders, administration of rVIIa was associated with an increased incidence of perioperative mortality compared to bleeding patients not administered rVIIa (OR 1.875, 95% CI 1.390, 2.530). There was no association detected with rVIIa administration and MACE or VTE. When hemophiliac dosing regimens were considered, patients administered doses >90 mcg/kg (i.e. more than a "full dose") had a higher incidence of perioperative mortality compared to patients given a "half dose of ≤45 mcg/kg (OR 3.389 95% CI 1.494, 7.691). Patients who were prophylactically treated with the antifibrinolytic aprotinin had a greater incidence of perioperative death when administered rVIIa than patients given tranexamic acid for an antifibrinolytic (OR 1.880, 95% CI 1.067, 3.313).

Our results confirm that administration of rVIIa to severely bleeding complex cardiac surgical patients is associated with increased perioperative mortality, although the mechanism by which this occurs is not clear. If rVIIa must be used in a rescue situation, then clinicians should start with doses ≤45 mcg/kg and avoid exceeding 90 mcg/kg. Other concomitantly administered medications can have an effect of rVIIa risks and should be considered in future research in this area.

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INTRODUCTION

Cardiopulmonary bypass (CPB) results in a host of insults to the hemostatic system, including platelet dysfunction, consumption of coagulation factors, and fibrinolysis.(1) In an effort to prevent coagulopathy, antifibrinolytic agents are prophylactically administered to cardiac surgical patients during and after CPB. Despite this measure, 5-10% of patients will experience excessive hemorrhage, resulting in increased costs, morbidity, and mortality.(2, 3) When this occurs, transfusion of hemostatic blood products consisting of platelets, fresh frozen plasma (FFP), and cryoprecipitate, is the mainstay treatment. If these conventional measures fail to produce sufficient clot, recombinant Factor VIIa (rVIIa) is often administered as a rescue agent.

Several small randomized controlled trials in adult cardiac surgical patients have shown rVIIa to reduce the need for hemostatic blood product transfusion in the treatment of CPB-associated coagulopathy.(4-7) Its administration as a rescue agent for intractable bleeding is categorized as a Class IIb intervention according to 2011 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists (STS/SCA) guidelines.(8) Recently, however, Alfirevic et al. from the Cleveland Clinic published a large single-center, retrospective, propensity-matched analysis showing rFVIIa administration in cardiac surgery to be associated with increased in-hospital mortality.(9) There seems to be a complex risk-benefit profile of this procoagulant agent that has yet to be fully characterized.

An important variable that has not been considered during studies of rVIIa administration is the concomitant effect of antifibrinolytic agents which may increase the pro-thrombotic potential of rVIIa. Two analyses of large rVIIa registries in Canada and Australia/New Zealand provide no information on concomitant antifibrinolytic administration.(10, 11) Given that rVIIa promotes the initiation of clot, and antifibrinolytics decrease the breakdown of clot, there is a biological reason these agents may have an interaction in their effects.

The current study utilizes a large retrospective cohort of bleeding patients who underwent complex cardiac surgery at Emory University over an 8-year period. This cohort was assembled to determine if the use of rVIIa was associated with increased perioperative mortality, major adverse cardiac events, or venous thromboembolic events. Additionally, since two different types of antifibrinolytic agents were utilized during this timeframe, aprotinin and tranexamic acid, the association of antifibrinolytic agent with perioperative mortality among patients administered rVIIa was also explored.

BACKGROUND

Recombinant activated Factor VII (rVIIa) was originally approved by the FDA in 1999 as an agent to prevent or treat bleeding in hemophilia patients who had inhibitors to standard Factor IX or Factor VIII replacement.(12) Since that time, its use in non-hemophilia patients has increased exponentially. In fact, the off-label use of rVIIa now exceeds its approved indications by more than 20-fold.(13)

Cardiac surgery accounts for approximately 25% of rVIIa's off-label use.(13) Because severe bleeding occurs in 5-10% of cardiac surgical patients, rVIIa is commonly used as a "rescue" therapy when transfusion of conventional hemostatic blood products fails to resolve the coagulopathy. The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists both endorse this use, despite the fact that formal safety and efficacy studies are lacking.(8)

There have been four randomized controlled trials of rVIIa use in the setting of adult cardiac surgery, ranging in size from 20 to 179 patients.(4-7) All have shown rVIIa to reduce bleeding and transfusion requirements without significant increases in complications or mortality. It is important to note that none of these trials considered the effects of concomitant use of other procoagulant medications such as antifibrinolytics. Some trial patients received aprotinin as an antifibrinolytic, some received no antifibrinolytic medication, and one trial failed to report antifibrinolytic use altogether.

Antifibrinolytics are routinely used in complex cardiac surgery to decrease fibrinolytic activity while on extracorporeal circulation (i.e. CPB), thereby reducing bleeding complications.(14) Two classes of antifibrinolytics have been used in this setting: the serine protease inhibitor aprotinin, and the lysine analogs, tranexamic acid (TXA) and aminocaproic acid. Their mechanisms of actions are significantly different on a biological level. Aprotinin is a non-specific inhibitor that neutralizes free plasmin, the effector enzyme of the fibrinolytic system. Similar to the natural inhibitor α_2-antiplasmin, aprotinin has little effect on bound plasmin, and

may have anti-inflammatory properties as well.(15) The mechanism of action of the lysine analogs differs from aprotinin in that these drugs prevent the binding of plasminogen to fibrin, thus inhibiting the formation of plasmin altogether.(16) Aprotinin has been associated with neuroprotection, while TXA has been associated with increased neural stimulation and seizure activity.(17, 18) Whether or not these differences are important in the setting of rVIIa administration has not yet been explored.

Questions regarding the safety of rVIIa in cardiac surgery began to arise in 2011, when several retrospective analyses suggested it was associated with increased thromboembolic events and stroke.(19-22) In 2014, a large propensity analyses from the Cleveland Clinic associated rVIIa use with a perioperative mortality rate of 40% compared to 18% in matched controls.(9) Of note, all patients in the Cleveland Clinic study received the lysine analog aminocaproic acid as an antifibrinolytic agent.

Aprotinin was routinely used for all complex cardiac surgery at Emory University Hospital and Emory University Hospital Midtown prior to 2007. It was withdrawn from the market in late 2007, however, following concerns of increased mortality in a multicenter trial known as the BART study, which compared aprotinin's efficacy to that of the lysine analogs.(23) Importantly, the results of the BART study were highly controversial, and it is generally believed aprotinin's benefits outweigh its risks in high risk, but not low risk, cardiac surgery.(24-27) Aprotinin has recently been relicensed for clinical use in Europe since it is viewed as being more effective at preventing life-threatening bleeding than either lysine analog.(28) At Emory University, however, TXA has been used for all complex cardiac surgical procedures from November 15th, 2007 onward. Perhaps predictably, this has resulted in an increased use of rVIIa.(29)

The current study was undertaken to determine if the Emory experience with rVIIa was comparable to that of the Cleveland Clinic. An important limitation of the Cleveland Clinic study was the relatively small number of patients administered rVIIa - 164 over a 6-year period.(9) Comparatively, it was estimated that the incidence of rVIIa administration at Emory would be 3

to 4 times that over the same length of time. More cases would presumably reflect greater experience with the drug and perhaps different patterns of administration or greater awareness of side effects. The antifibrinolytic used at the Cleveland Clinic, aminocaproic acid, was never used at Emory. Additionally, the median doe of rVIIa given at the Cleveland Clinic was 94 mcg/kg, which exceeds the recommended dose for hemophilia patients.(9, 30) It was believed that the doses used at Emory would be less. Given these differences between the two centers, the first aim of this study is to estimate the association between rVIIa administration and perioperative mortality at Emory to compare to the Cleveland Clinic's odds ratio of 2.82 (98.3% CI 1.64, 4.87).(9) The association of rVIIa administration and thromboembolic events (VTE), which was not significant in the Cleveland Clinic study, and the association of major adverse cardiac events (MACE), which was not reported, are also of interest.

The changing of antifibrinolytic agents from aprotinin to TXA at Emory also provides an opportunity to explore the association of antifibrinolytic agent on perioperative mortality in patients administered rVIIa. Given their different mechanisms of action, it is possible that aprotinin and TXA may affect the risk profile of rVIIa differently. The randomized controlled trials of rVIIa in adult cardiac surgery all used either aprotinin or no antifibrinolytic agent.(4-7) As previously pointed out, the large retrospective study from the Cleveland Clinic utilized aminocaproic acid, which is similar to TXA, for antifibrinolysis.(9) It is possible that this could contribute to the reported increased mortality. Therefore, the second specific aim of this study is to determine the association between antifibrinolytic agent and mortality in patients administered rVIIa.

METHODS

Specific Aims

Specific aim #1: Estimate the association between perioperative rVIIa administration in complex cardiac surgery and complications including perioperative mortality (death within 30 days of operation), major adverse cardiac events (MACE), and venous thromboembolic events (VTE) among patients with severe bleeding.

Specific aim #2: Estimate the association of the two types of antifibrinolytic agents, aprotinin and tranexamic acid (TXA), on perioperative mortality among those patients administered rVIIa.

Study Design

This is a retrospective cohort study of adult patients who experienced severe bleeding during complex cardiac surgery at either Emory University Hospital (EUH) or Emory University Hospital Midtown (EUHM) between 1/1/2005 and 12/31/2012. The time of entry into the cohort began on the date of the initial operation. Follow-up time ended at 30 days from this timepoint or date of discharge from the hospital. Patients re-admitted within 30 days were followed thru 30 days of the initial operation.

Inclusion/Exclusion Criteria

Patients were eligible to be entered into the cohort if they were over 18 years old and experienced severe bleeding while undergoing one of the below cardiac surgical procedures requiring cardiopulmonary bypass (CPB):

- Repeat sternotomy
- A combined coronary artery bypass graft (CABG) and valve procedure
- Multiple valve procedures
- Operations of the thoracic aorta

- Other non-transplant cardiac surgery such as intracardiac mass removal or ventricular remodeling procedure

The definition of severe bleeding was based upon slightly modified criteria from the "Universal Definition of Perioperative Bleeding in Cardiac Surgery."(31) Specifically, patients had to have been transfused at least 1 unit of platelets and/or cryoprecipitate and met one of the following criteria:

- ≥ 650 cc of chest tube output within 8 hours of ICU arrival
- ≥ 2000 cc of chest tube output within 24 hours of ICU arrival
- Transfused ≥5 units of packed RBCs either intraoperatively or postoperatively
- Transfused ≥5 units of fresh frozen plasma either intraoperatively or post-operatively
- Returned to the operating room for bleeding

Patients were excluded from the cohort if they were undergoing primary (i.e. 1st time sternotomy) isolated CABG or single valve surgery, heart transplantation, or cardiac surgery not utilizing CPB. The reason for excluding these cases is that antifibrinolytics were not routinely utilized. These procedures are also at very low risk for bleeding complications.(32) Patients were also excluded if they had previously required rVIIa for other operations since this likely represented an on-label use for hemophilia.

Sources of Data

Patient demographics, risk factors, and operative characteristics were obtained from the Emory University internal STS database. This is a professionally abstracted patient registry operated under Emory IRB #00001479, and whose data is uploaded to the national STS database (https://www.sts.org/registries-research-center/sts-national-database).(33) Variables common to versions 2.52, 2.61, and 2.73 (spanning the time period from 1/1/2005 thru 12/31/2012) were used in the analysis. Patient demographics included age, weight, and sex. Morbidity and

mortality risk factors used were history of stroke, myocardial infarction (MI), diabetes, moderate or severe chronic obstructive pulmonary disease, peripheral vascular disease, prior endocarditis, and cardiogenic shock upon presentation for surgery. The preoperative lab values available were creatinine and hemoglobin. Operative characteristics included type of cardiac surgery, minutes on cardiopulmonary bypass (CPB), prior sternotomy, emergency surgery, need for intra-aortic balloon pump (IABP), postoperative chest tube output at 8 and 24 hours, and need to return to the operating room for bleeding.

The administration of rVIIa was obtained from blood bank billing records, which included the date of administration and total milligrams (mg) dispensed. Dose of rVIIa (in mcg/kg) was calculated by dividing dose dispensed by patient weight obtained from STS demographic data. Antifibirinolytic administration was assigned based upon anesthesia protocols for complex cardiac surgery. Patients having a date of operation prior to 11/15/2007 were administered aprotinin, while all subsequent cases were administered tranexamic acid.

Outcomes

All outcome data was obtained from the Emory internal STS database, as described above, and treated as binary yes/no variables. Perioperative mortality was the primary outcome of interest and defined as death from any cause within 30 days of initial operation. Major adverse cardiac event (MACE) was defined as perioperative myocardial infarction, perioperative stroke, or death from a cardiac cause. Venous thrombo-embolism (VTE) was defined as post-operative deep venous thrombosis or pulmonary embolism.

Sample Size and Missing Data Considerations

The surgical case volume of EUH and EUHM was estimated to be 1800 cases/year for a total of 14,400 cases during the study timeframe. It was expected that approximately 10% of these patients would experience severe bleeding based upon previous studies,(31) the majority of which

would be complex cardiac surgical cases. Assuming a 22% perioperative mortality rate for severely bleeding patients,(31) we anticipated approximately 316 perioperative deaths, allowing for up to 31 variables being entered into the multivariable logistic regression model, which is more than the number of available covariates from the STS database.

Data for the STS database is professionally abstracted and has a very low "% missingness" (<2% of all variables). Additionally, since the cost of rVIIa is quite high (~$1000 per mg), it was assumed patients who lacked a billing record for rVIIa did not receive rVIIa, and that all dispensed rVIIa was administered to the patient. Complete case analysis was used for multivariable logistic regression modeling purposes.

Analytic Plan

Summary statistics were generated for the predictor variable of rVIIa use and all available STS covariates for the entire cohort. Normality of continuous variables was assessed by visual inspection of histogram plots. Unadjusted comparison of rVIIa and non-rVIIa patients were performed using unpaired t-tests or Chi square tests for continuous and categorical data respectively. Similarly, among patients who received rVIIa, unadjusted comparisons between those receiving aprotinin and those receiving TXA were performed using 2-sample t-tests or Chi square tests for continuous and categorical data respectively. A level of $\alpha=0.05$ was used for all tests of significance.

For modeling purposes, the continuous covariates of age, baseline creatinine, and CPB time were dichotomized into the highest risk group for mortality based upon previously published literature: age≥70, creatinine ≥2.0 mg/dL, and CPB time >180 minutes.(34-36) These cut-off points also represented the top third to top quartile of values within the dataset. In order to account for low blood volume, and thus a higher risk of transfusion and bleeding, a simplified red cell mass was calculated using the formula 'weight (kg) x baseline Hgb.' Patients with a value

<800 were classified as high transfusion risk ("Hi_tx_risk"). Since no standard dose exists for using rVIIa as a rescue agent in cardiac surgery, rVIIa administration ("Dose") was modeled three ways: 1) as a binary yes/no variable, 2) as a categorical variable based upon quintiles, and 3) as a categorical variable based upon hemophiliac dosing (≤45 mcg/kg – i.e. up to half dose, more than half dose up to the full dose of 90 mcg/kg, or greater than full dose).(30)

Multivariable logistic regression was used to control for covariates and assess associations. For the primary outcome of perioperative mortality, the full model consisted of:

$$\begin{aligned}\text{Logit (periop\_death)} = {} & \beta_0 + \beta_1\,\text{Dose} + \beta_2\,\text{Sex} + \beta_3\,\text{Age} + \beta_4\,\text{Hi\_tx\_risk} + \\ & \beta_5\,\text{Preop\_Cr} + \beta_6\,\text{MI\_History} + \beta_7\,\text{Stroke\_History} + \beta_8\,\text{PVD\_History} + \\ & \beta_9\,\text{Diabetes\_History} + \beta_{10}\,\text{COPD\_History} + \beta_{11}\,\text{Endocarditis\_History} + \\ & \beta_{12}\,\text{Cardiogenic\_shock} + \beta_{13}\,\text{Redo\_Sternotomy} + \beta_{14}\,\text{emergency} + \\ & \beta_{15}\,\text{CPB\_time} + \beta_{16}\,\text{Procedure\_type} + \beta_{17}\,\text{IABP\_use} + \\ & \beta_{18}\,\text{Return\_to\_OR} + \beta_{19}\,\text{Antifibrinolytic\_agent}\end{aligned}$$

The same full model was used for the outcome MACE. Given that the expected frequency of thromboembolic events in cardiac surgery is one-half to one-tenth of non-cardiac surgery,(37) a more parsimonious model was created. The model for venous thromboembolism was based upon previously published risk factors with rVIIa use also incorporated:(37-39)

$$\begin{aligned}\text{Logit (VTE)} = {} & \beta_0 + \beta_1\,\text{Dose} + \beta_2\,\text{Sex} + \beta_3\,\text{Age} + \beta_4\,\text{PVD\_History} + \beta_5\,\text{MI\_History} + \\ & \beta_6\,\text{Diabetes\_History} + \beta_7\,\text{IABP\_use} + \beta_8\,\text{CPB\_time}\end{aligned}$$

Backwards, forwards, and stepwise selection at the $\alpha<0.05$ level were also performed to determine the best fit for reduced models. Significance of reduced models were evaluated using a Wald chunk test. All calculations were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

There were 4,569 patients undergoing complex cardiac surgery during the specified timeframe, of which 2,371 met the stated severe bleeding criteria and were entered into the cohort. Of the bleeding patients, 610 (25.7%) received rVIIa (Figure 1). Demographic, mortality risk factors, and operative characteristics of the bleeding cohort, and unadjusted comparison between rVIIa and non-rVIIa groups are provided in Table 1. Important differences included longer CPB times, more aortic surgery, more emergency surgery, higher initial chest tube output, more frequent return to the operating room, and more tranexamic acid use in the rVIIa group. The non-rVIIa group included more women, as well as more patients with a prior history of myocardial infarction.

The outcomes for the cohort as well as unadjusted comparisons between rVIIa and non-rVIIa groups are provided in Table 2. Among all bleeding patients, 312 (13.2%) experienced the primary outcome of perioperative mortality. The outcomes of MACE and VTE for the cohort were experienced by 306 (12.9%) and 74 (3.1%) respectively. Figure 2 displays the crude mortality percentage by year for patients undergoing complex cardiac surgery, those who experienced severe bleeding, and those who were administered rVIIa. There was a general trend toward decreased mortality for all groups over the eight-year study period. Figure 3 displays the primary cause (i.e. first inciting event) of death for patients who did and did not receive rVIIa. Patients administered rVIIa had a statistically significant higher percentage of perioperative mortality (20.5% vs, 10.6%, $p<0.0001$) and MACE (17.4% vs. 11.4%, $p<0.001$) compared to patients not given rVIIa. A greater percentage of patients given rVIIa also experienced VTE (3.9% vs. 2.8%, $p=0.1801$), although this was not statistically significant.

The odds ratios for rVIIa administration and all covariates in each full multivariable logistic regression model using rVIIa administration as a binary variable are provided for each outcome in Table 3. Administration of rVIIa was associated with increased perioperative mortality (OR 1.875, 95% CI 1.390, 2.530) when controlling for other known covariates. However, rVIIa

administration was not statistically significant at the $\alpha=0.05$ level for the outcomes of MACE or VTE. The model fit statistics of full and reduced models for all outcomes are provided in Table 4. The odds ratio for rVIIa administration on outcomes did not significantly change between the full and more parsimonious models.

The logistic plot of perioperative death suggested there might be a dose effect of rVIIa administration (Figure 4), with a significant increase in mortality occurring around the 40 mcg/kg dose. Dose information for the entire cohort of patients administered rVIIa, as well as comparison between the two types of antifibrinolytics is provided in Table 5. A boxplot of the doses in each antifibrinolytic group is provided in Figure 5, as well as the median doses. Patients who were given aprotinin as an antifibrinolytic received significantly higher doses of rVIIa compared to patients who were given TXA (67.0 ± 42.8 mcg/kg vs. 42.1 ± 25.9 mcg/kg, $p<0.0001$).

The odds ratios for perioperative death among rVIIa treated patients in models incorporating the dose of rVIIa using either quintile based, or standard hemophilia range doses are presented in Table 6. Dosing based upon hemophilia ranges provided a better model fit, with doses >90 mcg/kg having significantly higher odds of perioperative death (OR 3.389, 95% CI 1.494, 7.691) compared to patients given half ($\leq$45 mcg/kg) of a standard hemophiliac dose. The intermediate range dose (>45 mcg/kg up to 90 mcg/kg) was not statistically significant for increased perioperative death compared to the half dose (OR 1.345, 95% CI 0.839, 2.158). No matter how the dose of rVIIa was modeled, the odds ratio for perioperative mortality among aprotinin treated patients compared to TXA treated patients was significantly higher.

DISCUSSION

Complex cardiac surgery utilizing cardiopulmonary bypass (CPB) presents a tremendous hemostatic challenge to the clinician. Profound anticoagulation must be achieved while the patient is supported via extracorporeal circulation, but then must be rapidly reversed following its termination. Coagulopathy frequently develops as a result of CPB in addition to the actual surgical insult. Preventative measures, such as administering antifibrinolytic agents, and transfusion of hemostatic blood products, such as fresh frozen plasma and platelets, represent standard practices, but are not always effective.(40) In these situations, recombinant activated Factor VII (rVIIa) is often used as a recue agent to treat refractory bleeding. Little safety data exists for the off-label use of rVIIa, however, and the current study was undertaken to determine the association of rVIIa administration with perioperative mortality, major adverse cardiac events (MACE), and venous thromboembolic events (VTE).

In our large retrospective cohort of bleeding patients who underwent complex cardiac surgery, the administration of rVIIa was associated with an increased risk of perioperative mortality compared to patients not given rVIIa (OR 1.875, 95% CI 1.390, 2.530) after controlling for available covariates. This is consistent with results from a propensity study from the Cleveland Clinic which reported an odds ratio of 2.82 (98.3% CI 1.64, 4.87) for perioperative mortality compared to matched controls in a similar patient population.(9) The observed mortality rate of patients administered rVIIa in our cohort was approximately half that reported by the Cleveland Clinic (20.5% vs 40%).(9) This is consistent with 28-day mortality rates reported by national rVIIa registries from Australia/New Zealand (28%) and Canada (32%).(10, 41)

One reason for the comparatively lower observed mortality rate in our patients administered rVIIa could be due to using lower doses. Our median dose of 37.0 mcg/kg (IQR 29.4) is on the low end of that reported in observational studies. The Cleveland Clinic study had a median dose of 94 mcg/kg (IQR 95), the Canadian registry had a median dose of 62 mcg/kg (IQR 49), and the Australian/New Zealand registry had a median dose of 91 mcg/kg (IQR 31). When put in the

context of hemophilia dosing, we observed a significant increased odds of mortality with doses exceeding the recommended 90 mcg/kg range compared to “half doses” of 45 mcg/kg (OR 3.389, 95% CI 1.494, 7.691).

Few prior studies have looked at rVIIa dosing in the context of a rescue medication in cardiac surgery. In a retrospective analysis of 804 bleeding cardiac surgical patients, Willis et al. found no difference in mortality between dose ranges of ≤40 mcg/kg, 41-60 mcg/kg, 61-80 mcg/kg, 81-100 mcg/kg, and >100 mcg/kg.(42) A limitation to that study, however, was that <20% of the patients were in the 2 lowest dosing regimens, while more than 2/3 were in the highest 2 dosing regimens. More recently, a small retrospective study matching 51 rVIIa patients to controls found no difference in mortality using a median dose of only 12 mcg/kg.(43) Our data would seem to support the use of lower doses of rVIIa, and avoiding doses exceeding those used to treat hemophilia patients. This represents total administered dose, however, and it is not possible to know from our dataset if higher doses represented multiple smaller administrations. Patients requiring multiple doses could have suffered from separate bleeding events or have been non-responders to rVIIa, which is known to have a worse prognosis in bleeding patients.(11)

Although we found a trend toward increased MACE (OR 1.235, 95% CI 0.905, 1.684), this was not statistically significant. Not surprisingly, cardiac cause of death was the most common primary cause of death for all patients undergoing cardiac surgery (Figure 3). MACE would include stroke, and so a neurological cause of death might also be expected to increase if rVIIa increased mortality via this mechanism, which we did not observe. In a small meta-analysis using 254 cardiac surgical patients who received rVIIa, Ponschab et al. found an increased rate of stroke in rVIIa patients (4.7% vs 0.9% in the control arm, p= 0.03), but not increased mortality.(20) In the Cleveland Clinic study, no significant difference in neurological events was found between rVIIa patients and propensity matched controls despite experiencing increased mortality.(9) While our data supports the association of rVIIa administration with increased mortality, increased MACE is not likely the only mechanism leading to this increased mortality.

A trend toward increased VTE in patients administered rVIIa (OR 1.620, 95% CI 0.948, 2.767) was also noted, although this was not statistically significant. This is likely due to the low incidence of VTE in this population, which our study was not powered to detect. In a Cochrane meta-analysis of 13 randomized controlled trials looking at rVIIa as a rescue treatment and involving 2929 non-hemophilia patients from a wide variety of bleeding situations, the trend toward increased thromboembolic events was also non-significant (RR 1.14, 95% CI 0.89 to 1.47).(22) Inappropriate clot formation on the arterial side (as reflected by MACE) seems to be more common than inappropriate venous clotting (i.e. VTE) in this patient population.

In our full model of perioperative mortality using the entire bleeding cohort with rVIIa administration as a binary variable, aprotinin had an increased odds ratio of death compared to TXA (OR 1.751, 95% CI 1.320, 2.324). During the course of the analysis for specific aim #1, however, it became apparent that a dose effect might be important, and patients given aprotinin as an antifibrinolytic received higher doses of rVIIa than patients given TXA (see Table 5, Figure 5). In the reduced model with only patients given rVIIa, the odds ratio of perioperative mortality was increased with aprotinin use compared to TXA whether controlling for dose by quintile or hemophilia dose ranges (1.821, 95% CI 1.023, 3.242 and 1.880, 95% CI 1.067, 3.313 respectively). Our data does not support the use of aprotinin as antifibrinolytic prophylaxis if rVIIa might be used as a hemostatic agent post-operatively. This is in contrast to the findings of Meybohm et al., who performed a meta-analysis on controlled and observational studies involving more than 4700 high risk cardiac surgical patients and found no significant risk of mortality for aprotinin compared to the lysine analogs (RR 1.03, 95% CI 0.67–1.58) in this patient population.(27)

Of course, given the longitudinal nature of our study, decreases in perioperatively mortality would be expected to occur over the 8 years due to unmeasured improvements in perioperative care, surgical experience, and perfusion technology. For example, the risk adjusted perioperative mortality rate, using similar STS variables contained in our dataset, for coronary re-operations,

one of the operations included within our dataset, decreased from 6.0% to 4.6% from 2000 to 2009.(44) Given that aprotinin and TXA administration are completely separated by time, it is not possible to separate the effects of antifibrinolytic agent from those of continued surgical improvement in this dataset.

The study, of course, has other weaknesses. As a retrospective observational study, we could only control for known and available covariates. In an effort to capture some aprotinin use, one of the earliest available versions of the STS database, version 2.52, which had a limited number of variables collected, had to be used. Since 2005, the number of collected variables has significantly increased. For example, the data collection form for 2.52 was about 7 pages, while the current version, 2.9 – available February 2017, has 33 pages. The limitation of available covariates for the outcomes of interest is particularly important given rVIIa is used as a rescue drug and confounding by indication must be considered. It is possible that unfavorable surgical events leading to excessive hemorrhage could have influenced clinicians' decision to administer rVIIa. Such events would certainly be harmful, thus contributing to increased perioperative mortality, but difficult to capture and quantify in a retrospective dataset. Use of later versions of the STS database containing more operative covariates may help account for such rVIIa administration selection bias.

Another limitation of the study is failing to control for blood product use. Transfusion itself is known to influence mortality.(45-47) No protocols for transfusion of hemostatic blood products existed during the study period. Quantities dispensed from the blood bank varied over the study period as well. For example, in 2005 "1 unit of cryoprecipitate" was a single non-pooled aliquot, while "1 unit of cryoprecipitate" in 2008 represented a pooled aliquot of 10 individual units, which was then changed to mean 5 individual units sometime in 2010. Such changes across years make extracting exact transfusion data from the STS database alone very difficult. Some clinicians could have elected to administer more blood products than others, thus creating a differential exposure to the risk of transfusion on mortality. This bias is somewhat minimized

since rVIIa is considered a rescue therapy after conventional treatment and all patients included in the cohort had to be transfused at least some hemostatic blood products.

Despite the above limitations, a strength of the study is the number of patients administered rVIIa in a single institution. Our sample size of 610 patients compares favorably to multi-center national registries. The Canadian registry, involving 18 centers, collected 503 patients over 4 years, and the Australia/New Zealand registry, involving 96 centers, collected 1513 cardiac patients over 10 years.(10, 41) Having a large collection at a single institution helps reduce practice variability.

Future research on the use of rVIIa in cardiac surgery should include concomitant medication use. Of particular interest would be antithrombin concentrates, which have been shown to affect rVIIa's generation of thrombin in ex-vivo models, and might mitigate some of the risks associated with its administration.(48, 49) It is unclear why rVIIa administration is associated with higher mortality, but increased death from vascular events, which would include thrombotic phenomena, may be a potential explanation. Limiting rVIIa's pro-coagulant effects to sites of vascular injury would be beneficial in this regard and may be a way to decrease this cause of mortality. Natural anticoagulant proteins, such as antithrombin, may be a way to protect uninjured endothelium from thrombosis and represent a target for future research.

In conclusion, we have shown that administration of rVIIa in a large retrospective cohort of complex cardiac surgical patients experiencing severe bleeding is associated with an increased risk of perioperative mortality. This risk likely increases with dose, and amounts ≤45 mcg/kg (i.e. half-dose for hemophilia patients) should be given first, and doses >90 mcg/kg (i.e. more than full dose for hemophilia patients) should be avoided. Antifibrinolytic effects, which are almost always administered in patients with a high bleeding risk – and thus potential candidates for needing rVIIa therapy – should be taken into account in future research in this area.

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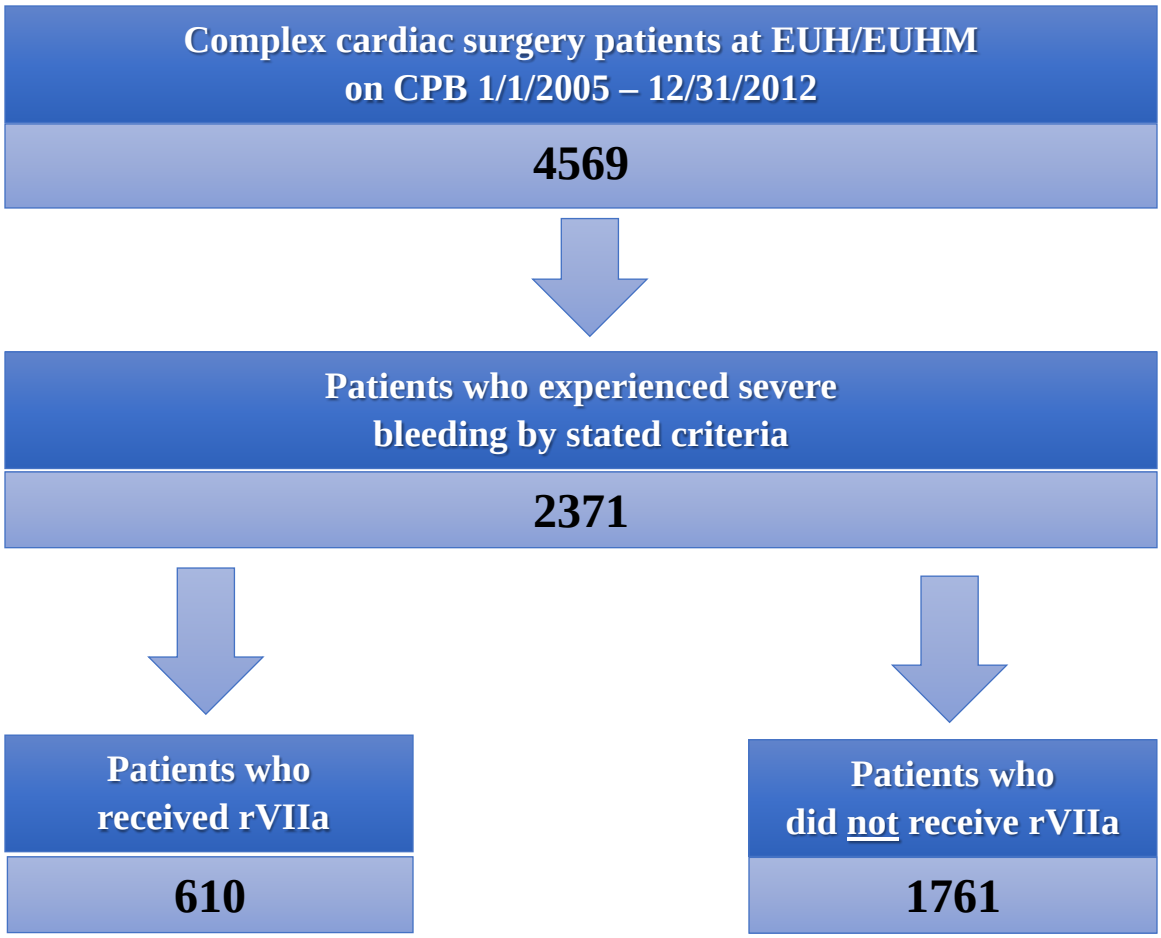
FIGURE 1



This is a diagram showing the number of patients who were identified as undergoing a complex cardiac surgical procedure at either Emory University Hospital or Emory University Hospital Midtown during the study period of 1/1/2005 thru 12/31/2012. The stated criteria for severe bleeding required the administration of platelets and/or cryoprecipitate and at least one of the following: ≥ 650 cc of chest tube output within 8 hours of ICU arrival, ≥ 2000 cc of chest tube output within 24 hours of ICU arrival, transfusion of ≥5 units of packed red blood cells (intra- or post-op), transfusion of ≥5 units of fresh frozen plasma (intra- or post-op), or return to the operating room for bleeding.

TABLE 1

	All Subjects	rVIIa	Non-rVIIa	p
n (% of cohort)	2371	610 (25.7%)	1761 (74.3%)	
Age (years)	60.9 ±15.0	60.0 ±14.8	61.3 ±15.1	0.0567
Number of females	831 (35.1%)	193 (31.6%)	638 (36.2%)	0.0406
Weight (kg)	82.7 ±20.5	83.4 ±20.0	82.4 ±20.4	0.3316
Pre-op Hgb (g/dL)	12.3 ±2.1	12.1 ±2.1	12.4 ±2.1	0.0060
High transfusion risk	680 (28.7%)	191 (39.3%)	489 (27.8%)	0.0954
Pre-op Cr (mg/dL)	1.53 ±1.60	1.59 ±1.61	1.51 ±1.44	0.3104
Baseline Cr ≥2.0 mg/dL	290 (12.2%)	84 (13.8%)	206 (11.7%)	0.1782
Prior MI	679 (28.8%)	144 (23.9%)	535 (30.5%)	0.0020
History of carotid disease	466 (19.7%)	110 (18.0%)	356 (20.2%)	0.2423
History of diabetes	328 (14.0%)	82 (13.7%)	246 (14.1%)	0.8042
History of COPD	612 (26.0%)	140 (23.1%)	472 (26.9%)	0.0632
History of endocarditis	108 (4.6%)	21 (3.5%)	87 (5.0%)	0.1369
In cardiogenic shock	181 (7.7%)	54 (9.1%)	127 (7.3%)	0.1585
Re-do sternotomy	947 (39.9%)	289 (47.4%)	656 (37.4%)	<0.0001
Emergency procedure	271 (11.4%)	110 (18.0%)	161 (9.1%)	<0.0001
Procedure type • Isolated CABG/valve • CABG+valve/≥2valves • Aortic surgery • Other	 410 (17.3%) 623 (26.3%) 1026 (43.3%) 312 (13.2%)	 72 (11.8%) 92 (15.1%) 350 (57.4%) 96 (15.7%)	 338 (19.2%) 531 (30.2%) 676 (38.4%) 216 (12.3%)	<0.0001
CPB time (minutes)	171.4 ±68.4	206.0 ±84.3	159.3 ±57.3	<0.0001
CPB time ≥180 minutes	886 (37.4%)	355 (58.2%)	531 (30.2%)	<0.0001
Aprotinin for antifibrinolytic	673 (28.4%)	82 (13.4%)	591 (33.6%)	<0.0001
Re-explored for bleeding	287 (12.1%)	132 (21.6%)	155 (8.8%)	<0.0001
Pre-/Intra-op IABP use	82 (3.5%)	17 (2.8%)	65 (3.7%)	0.2922

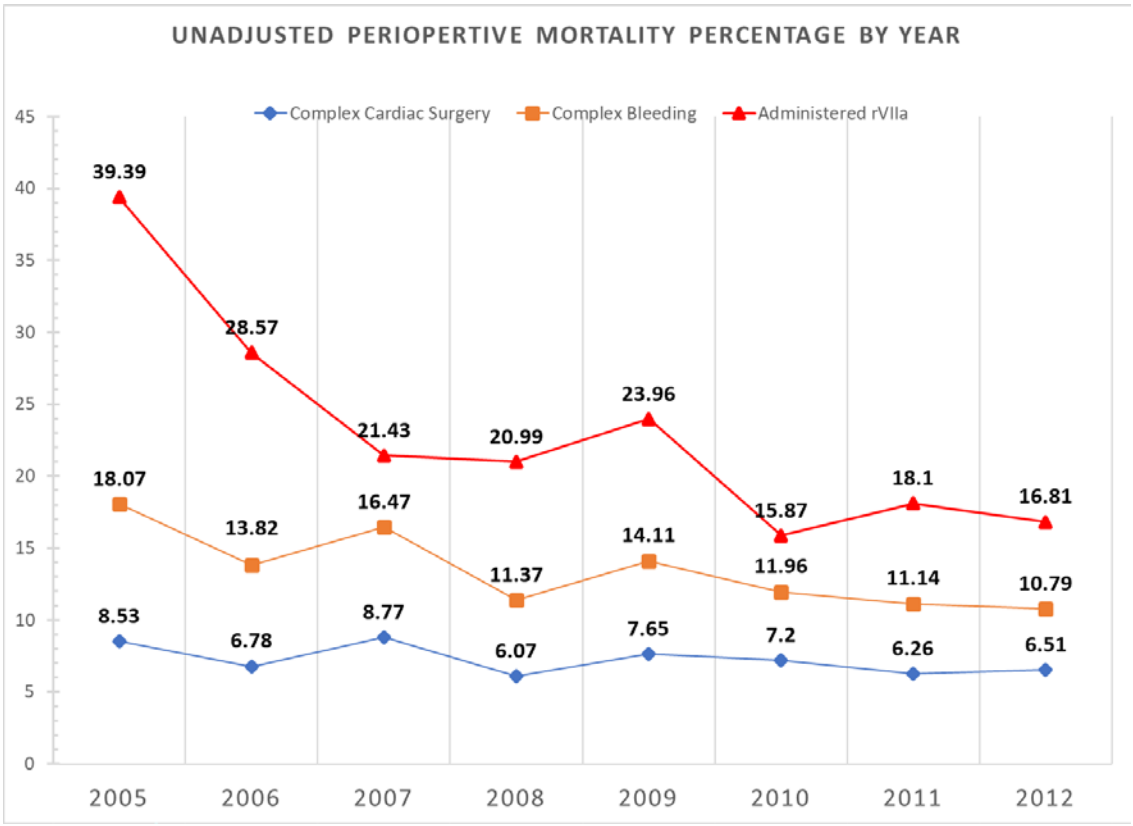
Baseline characteristics are presented for the entire cohort of severely bleeding patients as well as an unadjusted comparison between the groups of patients who were and were not administered recombinant activated Factor VII (rVIIa). Results are presented as mean ±standard deviation for continuous variables, and number (%) as categorical variables. Comparisons between rVIIa and non-rVIIa groups were performed using 2-sample t-tests for continuous variables are Chi-square tests for categorical variables. Hbg=hemoglobin, Cr=creatinine, MI=myocardial infarction, COPD=moderate or severe chronic obstructive airway disease, CABG=coronary artery bypass graft, CPB=cardiopulmonary bypass, IABP = intra-aortic balloon pump.

TABLE 2

	All Subjects	rVIIa	No rVIIa	p*
n	2371	610	1761	
Perioperative Mortality	312 (13.2%)	125 (20.5%)	187 (10.6%)	<0.0001
Major Adverse Cardiac Events	306 (12.9%)	106 (17.4%)	200 (11.4%)	<0.0001
Venous Thrombotic Events	74 (3.1%)	24 (3.9%)	50 (2.8%)	0.1801

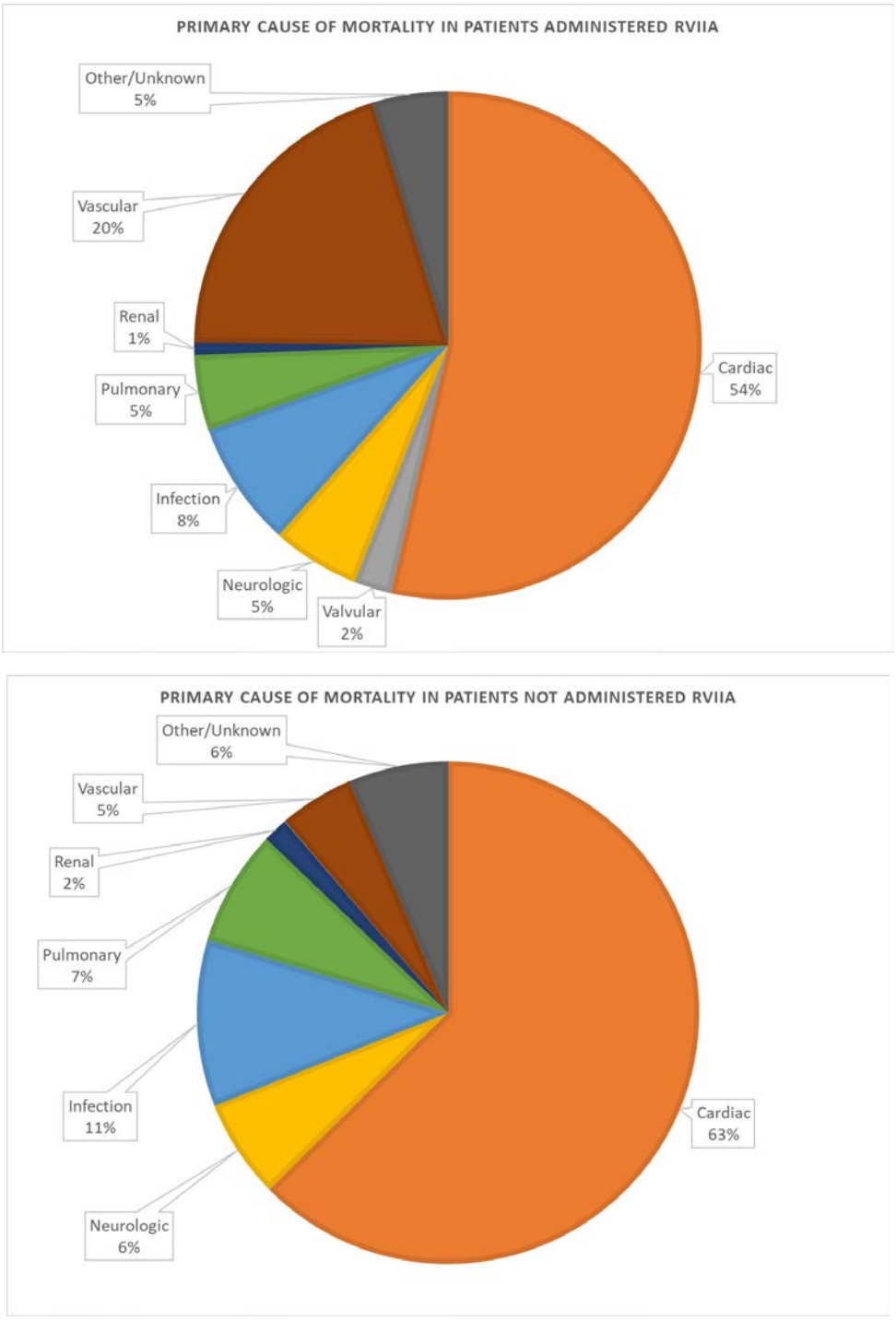
Outcomes for the entire cohort of severely bleeding patients as well as an unadjusted comparison of patients who were and were not administered rVIIa are presented. Results are given as number and percentage and comparisons evaluated using Chi-square test. Perioperative mortality is defined as death from any cause within 30 days of initial operation. Major adverse cardiac events are defined as postoperative heart attack, stroke, or death from a cardiac cause. Venous thrombotic events are defined as postoperative deep venous thrombosis or pulmonary embolism.

FIGURE 2



This is an unadjusted graph of the percentage of patients experiencing perioperative death by year for all patients who had complex cardiac surgery (blue line), the subset of those patients who experienced severe bleeding (yellow line), and the subset of severely bleeding patients who were administered rVIIa (red line).

FIGURE 3



There were 125 deaths (20.5% mortality) in the bleeding group administered recombinant activated Factor VII (rVIIa) and 187 deaths (10.6% mortality) in the bleeding group not administered rVIIa. The two pie graphs display the primary cause of mortality of each group for

comparison. According to STS database data harvesting guidelines, “primary cause” is defined as “the first significant abnormal event which ultimately led to death.”

(available at: https://www.sts.org/sites/default/files/documents/ACSDTrainingManual_V2-9_February2018.pdf)

TABLE 3

	Perioperative Mortality	Major Adverse Cardiac Event	Venous Thrombo-Embolic Event
Administration of rVIIa	**1.875** (1.390, 2.530)	1.235 (0.905, 1.684)	1.620 (0.948, 2.767)
Age ≥ 70 years	**1.583** (1.189, 2.107)	**1.601** (1.203, 2.132)	0.909 (0.543, 1.523)
Sex (female vs. male)	0.784 (0.590, 1.041)	0.878 (0.658, 1.171)	0.749 (0.456, 1.229)
High transfusion risk	1.116 (0.831, 1.500)	0.973 (0.719, 1.318)	----
Baseline Cr ≥2.0 mg/dL	**2.038** (1.443, 2.879)	**1.979** (1.397, 2.804)	----
Prior myocardial infarction	**1.358** (1.012, 1.824)	1.177 (0.874, 1.584)	**2.486** (1.499, 4.123)
History of carotid disease	**1.391** (1.027, 1.882)	**1.640** (1.218, 2.209)	----
Peripheral vascular disease	**1.501** (1.065 2.116)	**1.794** (1.286, 2.503)	**2.714** (1.595, 4.617)
History of diabetes	1.165 (0.869, 1.563)	1.166 (0.870, 1.562)	0.791 (0.456, 1.371)
History of COPD	1.644 (0.984, 2.748)	1.372 (0.805, 2.340)	----
History of endocarditis	0.988 (0.605, 1.612)	0.831 (0.497, 1.389)	----
In cardiogenic shock	**1.922** (1.133, 3.258)	1.687 (0.986, 2.888)	----
Redo sternotomy	**1.360** (1.019, 1.816)	1.158 (0.863, 1.555)	----
Emergency surgery	**2.088** (1.413, 3.085)	**2.409** (1.636, 3.546)	----
Procedure (versus isolated CABG/valve)			----
• Combined	1.054 (0.670, 1.657)	0.856 (0.549, 1.335)	
• Aortic	1.317 (0.859, 2.020)	0.967 (0.633, 1.476)	
• Other	**1.931** (1.186, 3.144)	1.497 (0.924, 2.427)	
CPB time ≥180 minutes	**1.682** (1.264, 2.239)	**1.845** (1.385, 2.458)	0.846 (0.494, 1.448)
Antifibrinolytic (aprotinin vs. TXA)	**1.751** (1.320, 2.324)	**1.503** (1.133, 1.994)	----
Returned to OR	**2.114** (1.504, 2.971)	**2.216** (1.571, 3.125)	----

Intra-aortic balloon pump use	1.501 (0.787, 2.864)	1.358 (0.701, 2.632)	**3.545** (1.631, 7.705)

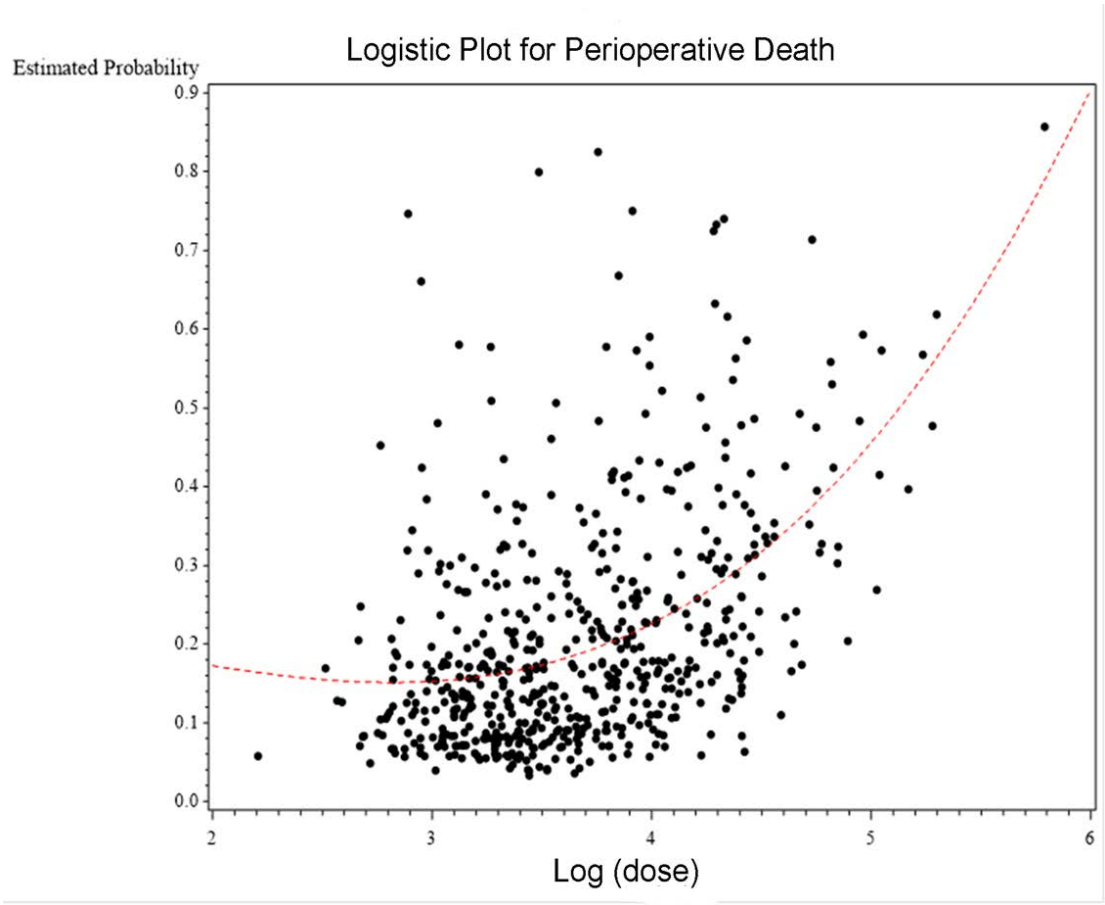
The odds ratio point estimates (95% confidence intervals) are provided for rVIIa and all covariates in the full model for the outcomes of perioperative mortality, major adverse cardiac events (MACE), and venous thromboembolic events (VTE). The full models for perioperative mortality and MACE were the same, each of which excluded 33 observations (1.4% of bleeding cohort) due to incomplete data. The model for VTE, which excluded 29 observations (1.2% of bleeding cohort) due to incomplete data, contained rVIIa with established covariates published in the literature and contained within the STS database. These models included only rVIIa as a binary variable and did not account for dose effects. Bolded values indicate significance at the $\alpha<0.05$ level using a Wald Chi-square test. Hbg=hemoglobin, Cr=creatinine, MI=myocardial infarction, COPD=moderate or severe chronic obstructive airway disease, CABG=coronary artery bypass graft, CPB=cardiopulmonary bypass, IABP = intra-aortic balloon pump, 'Combined' procedures included either a CABG with valve(s) replacement or multiple valve replacements.

TABLE 4

	AIC	C-statistic	-2LogL	Wald Chunk	OR rVIIa (95% CI)
Perioperative Mortality (Full)	1645.144	0.741	1600.141	----	1.875 (1.390, 2.530)
Perioperative Mortality (Reduced)	1641.631	0.736	1607.631	(6 df) 0.2780	1.854 (1.376, 2.497)
MACE (Full)	1643.564	0.721	1599.564	----	1.235 (0.905, 1.684)
MACE (Reduced)	1634.672	0.715	1606.672	(9 df) 0.6259	1.233 (0.909, 1.672)
VTE (Full)	618.289	0.709	600.289	----	1.620 (0.948, 2.767)
VTE (Reduced)	613.014	0.701	603.014	(4 df) 0.6049	1.519 (0.909, 2.538)

The model fit statistics of full and reduced models are provided for each outcome of interest. Reduced models were derived using forward, backward and stepwise selection for covariates at the $\alpha<0.05$ significance level for entry or staying as indicated and administration of recombinant activated Factor VII (rVIIa) being forced into the model. The reduced model with the lowest Akaike information criterion (AIC) is shown. Wald 'chunk' tests were performed between full and reduced models using a Chi-square distribution with degrees of freedom (df) corresponding to difference in model variables. The odds ratio with 95% confidence intervals for recombinant activated Factor VII (rVIIa) is also shown for each model. MACE=major adverse cardiac event including stroke, post-operative myocardial infarction, or death by cardiac cause. VTE=postoperative deep venous thrombosis or pulmonary embolism.

FIGURE 4



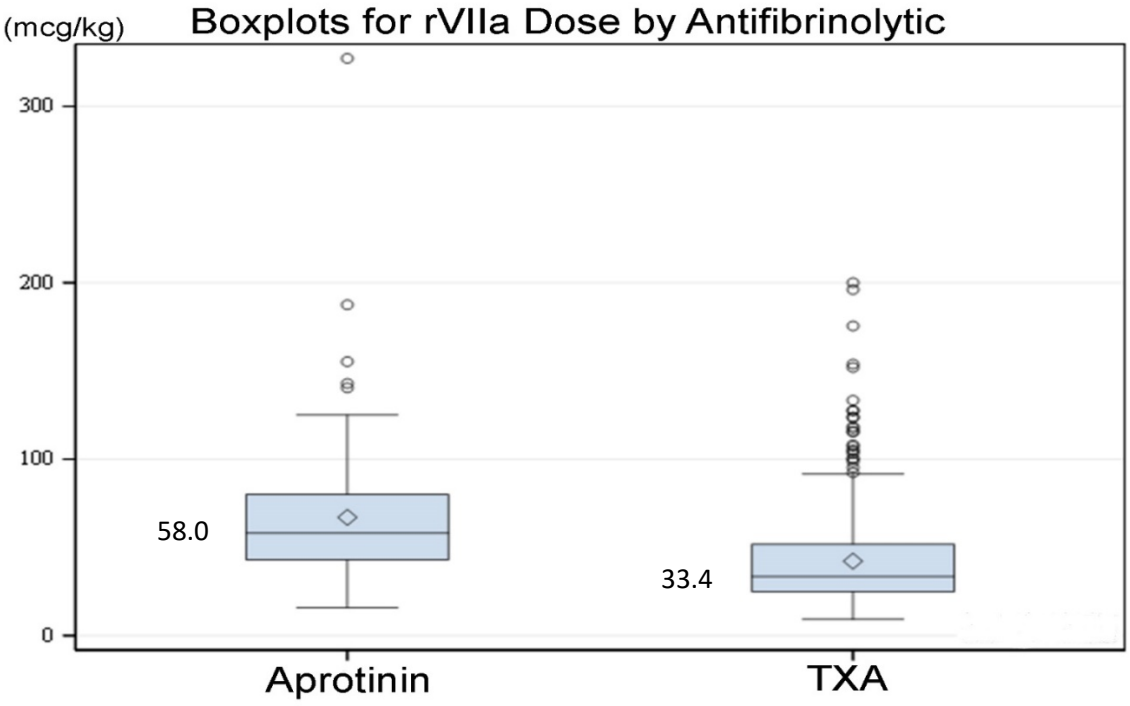
This is a scatterplot of the estimated probability of perioperative death against the log of the dose of recombinant activated Factor VII (rVIIa) administered for all bleeding patients who received it. The red dashes represent the regression line.

TABLE 5

	All Patients Administered rVIIa	**Aprotinin + rVIIa**	**TXA + rVIIa**	**p***
n	610	82 (13.4%)	528 (86.6%)	<0.0001
Mean Dose (mcg/kg)	45.5 ± 29.9	67.0 ± 42.8	42.1 ± 25.9	<0.0001
Perioperative Mortality	125 (20.5%)	27 (32.9%)	98 (18.6%)	0.0027

The average dose of recombinant activated Factor VII (rVIIa) administered to all patients who received it (mean ±standard deviation), as well as the outcome of perioperative mortality for patients receiving rVIIa is presented. Comparisons between patients given aprotinin and tranexamic acid (TXA) were made using Chi-square for proportions and Wilcoxon rank sum test for continuous variables.

FIGURE 5



These boxplots show the difference in recombinant activated Factor VII (rVIIa) doses that were administered to the patients given the two types of antifibrinolytic treatment. The numbers on the graph represent the respective median dose. TXA = tranexamic acid.

TABLE 6

rVIIa Dose Variable	OR Perioperative Mortality (95% CI)	Model Fit Statistics
Dose of rVIIa by Quintile in Dataset Versus lowest quintile of <24.8 mcg/kg)		
• 24.80 – 31.25 mcg/kg	0.937 (0.456, 1.922)	
• 31.26 – 43.69 mcg/kg	0.890 (0.429, 1.847)	AIC = 589.393 c-statistic = 0.710
• 43.70 – 61.59 mcg/kg	1.093 (0.547, 2.187)	-2LogL = 551.393
• ≥ 61.60 mcg/kg	1.703 (0.840, 3.453)	
Aprotinin vs. TXA	1.821 (1.023, 3.242)	
Hemophiliac Dosing of rVIIa Versus ≤45cmg/kg		
• >45 mcg/kg up to 90 mcg/kg	1.345 (0.839, 2.158)	AIC = 581.511 c-statistic = 0.716
• > 90 mcg/kg	3.389 (1.494, 7.691)	-2LogL = 547.511
Aprotinin vs. TXA	1.880 (1.067, 3.313)	

The odds ratios (95% confidence intervals) for perioperative mortality among patients given recombinant activated Factor VII (rVIIa) are presented based upon the following reduced model (as noted in Table 4):

$$\text{Logit (periop\_death)} = \beta_0 + \beta_1\ \text{Dose} + \beta_2\ \text{Age} + \beta_3\ \text{Preop\_Cr} + \beta_4\ \text{CPB\_time} + \beta_5\ \text{Antifibrinolytic\_agent} + \beta_6\ \text{PVD\_History} + \beta_7\ \text{MI\_History} + \beta_8\ \text{Stroke\_History} + \beta_9\ \text{Cardiogenic\_Shock} + \beta_{10}\ \text{Redo\_Sternotomy} \beta_{11}\ \text{Emergency} + \beta_{12}\ \text{Procedure\_type} + \beta_{13}\ \text{Return\_to\_OR}$$

‘Dose’ was divided into quintiles in one model and was divided based upon hemophiliac dosing (≤ half dose, between half and up to full dose, and greater than full dose) in the other. The odds ratio for perioperative mortality is also provided for aprotinin versus tranexamic acid (TXA) in each model, as well as the model fit statistics. 11 cases (1.8%) were excluded due to incomplete data.