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Recombinant Factor VII Is Associated with Worse Survival in Complex Cardiac Surgical Patients

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Abstract

Background—Recombinant, activated factor VII(rFVIIa) decreases requirements for allogenic blood transfusion and chest re-exploration in cardiac surgical patients. Whether rFVIIa increases risk for postoperative adverse events is unclear. We tested whether rFVIIa administration was associated with increased mortality, neurologic and renal morbidity in cardiac surgical patients. Risk of thromboembolic complications and the dose-response of rFVIIa on mortality and morbidity was also evaluated.

Methods—Of 27,977 patients who had complex cardiac surgery, 164 patients(0.59%) received rFVIIa perioperatively. Using propensity-matching techniques, patients were matched to a maximum of 3 controls. Patients who received rFVIIa were compared with controls on risk of mortality, neurologic and renal morbidity and thromboembolic complications, including a composite of myocardial infarction, pulmonary embolism, and deep venous thrombosis. A corresponding “dose-response” analysis using multivariable logistic regression was also performed.

Results—Propensity techniques successfully matched 144 patients(88%) with 359 controls. Of patients who received rFVIIa, 40% experienced in-hospital mortality compared to 18% of controls(OR 2.82(1.64, 4.87); $P<0.001$). Furthermore, 31% of patients treated with rFVIIa vs 17% of controls experienced renal morbidity(OR 2.07(1.19, 3.62); $P=0.002$), however neurologic morbidity and thromboembolic complications were not different among groups. High-dose(>60mcg/kg) did not increase risk for mortality compared to treatment with low-dose rFVIIa(<60mcg/kg).

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Conclusion—Administration of rFVIIa is associated with increased mortality and renal morbidity in cardiac surgery patients.

Keywords

bleeding; blood transfusion; stroke

Introduction

Refractory hemorrhage during complex cardiac surgery operations worsens perioperative outcomes and increases risk for mortality(1-3). Recombinant, activated factor VII(rFVIIa), licensed by the US Food and Drug Administration for prevention and treatment of bleeding in patients with hemophilia A or B and factor VII deficiency, has been used for off-label indications in a variety of clinical settings, including cardiac surgery(4-7). Administration of rFVIIa decreases requirements for allogenic blood and blood components transfusion and chest re-exploration for bleeding(8-14). However, despite these favorable effects, the safety of rFVIIa is not well-established.

The inherent pro-coagulant characteristics of rFVIIa may increase risk for serious thrombotic complications(15). Certainly, the risk of thrombotic complications related to rFVIIa administration during cardiac surgery(16, 17) exceeds the risk of rFVIIa use in hemophiliacs(18). Interestingly, despite concerns of increased morbidity with rFVIIa administration, the effect of rFVIIa on postoperative renal function has not been thoroughly explored(9, 17, 19, 20).

Although risk of thromboembolic complications has been investigated(9, 16, 17), studies evaluating risk of mortality after cardiac surgery are limited(6, 14, 19) because they were underpowered(9, 12, 21), lacked a control group(6, 7, 16), examined a diverse patient population(17), or used passive surveillance techniques so the true incidence of adverse outcomes was unknown(22). Further, few investigations were limited to the placement of left ventricular assist device or thoracic aortic surgery, compromising the generalizability of the results(12, 16). Importantly, whether the patient's perioperative risk profile and severity of illness affects risk of mortality and morbidity associated with rFVIIa administration has not been examined. Thus, further analysis is needed to better define the effect of rFVIIa on postoperative mortality and morbidity and improve our understanding of the risk-to-benefit ratio associated with rFVIIa treatment.

The purpose of this investigation was to determine whether administration of rFVIIa increases risk for mortality, neurologic and renal morbidity following cardiac surgery. Further, we assessed the contribution of the patient's perioperative risk profile to risk of adverse outcome and whether rFVIIa dose affects risk of postoperative complications.

Patients and Methods

We utilized data from the Cardiothoracic Anesthesia Patient Registry of the Department of Cardiothoracic Anesthesia and Cardiovascular Information Registry of the Heart and Vascular Institute at the Cleveland Clinic. Data were prospectively collected in a

standardized fashion according to strict definitions of preoperative characteristics, intraoperative variables, and postoperative outcomes. The study protocol was approved by the Institutional Review Board.

Anesthetic and surgical management

Complex cardiac surgical procedures including multiple valve replacements, thoracic aortic procedures, heart and lung transplants, and mechanical circulatory support were included. Routine strategies for implementation of cardiopulmonary bypass, antegrade/retrograde cold blood cardioplegia, heparinization and antifibrinolytic therapy using aminocaproic acid infusion were followed. Indications for rFVIIa included protracted bleeding and severe coagulopathy refractory to blood and blood component transfusion during the intraoperative or postoperative period. rFVIIa was administered intravenously in a dose of 20-90 mcg/kg, and repeated for refractory coagulopathy.

Statistical analysis

To control for confounding variables each patient who received rFVIIa was matched to maximum of three patients who did not receive rFVIIa (control) using exactly matching and propensity score matching. Specifically, we first estimated the probability of receiving rFVIIa (i.e., the propensity score) for each patient using logistic regression with rFVIIa as the outcome and using all pre-specified potential confounding variables listed in Table 1. rFVIIa and control patients were matched (up to 1:3) using a greedy distance matching algorithm(SAS macro:gmatch), restricting successful matches to those with the same units of red blood cell transfusion and those whose logit of the estimated propensity scores(i.e., $\log(p/\hat{p}(1-\hat{p}))$ estimated propensity score) were within 0.2 standard deviation on the logit of propensity score(i.e. $0.2 \times 1.22 = 0.244$) of one another. All analyses used this subset of matched patients.

Assessment of covariable balance was performed using standardized differences(i.e., difference in means or proportions divided by pooled standard deviation). Imbalance was defined as an absolute standardized difference (STD) greater than 0.19 in absolute value(i.e.,

$1.96 \times \sqrt{\frac{1}{144} + \frac{1}{359}}$); any such covariables would have been entered into the models comparing rFVIIa and control patients on outcomes to reduce potential confounding.

Primary outcomes

Our primary outcomes as previously described(23) were: 1) all-cause in-hospital mortality; 2) neurologic morbidity, defined as new postoperative focal (aphasia, decrease in limb function, or hemiparesis confirmed by clinical findings and/or neurologic imaging) or global neurologic deficit (diffuse encephalopathy with >24 hours of severely altered mental status, and/or failure to awaken); and 3) renal morbidity, defined as postoperative anuria or oliguria (urine output <400 mL/24 hrs) and/or institution of renal dialysis or ultrafiltration. Rather than analyzing the vector of outcomes as a collapsed composite of “any-versus-none”, a multivariate(i.e., multiple outcomes per patient) analysis simultaneously captured complete information on each component for a patient and correlations among components. The association between rFVIIa and each of the three primary outcomes was assessed

individually using a “distinct effects” generalized estimating equation model with unstructured covariance matrix.(24) Imbalanced covariables after matching(STD>0.19 in absolute value) were adjusted for, in the analysis. Three sensitivity analyses were conducted using additional ways of adjusting for observed confounding variables: 1) adjustment for covariables with STD>0.10 in absolute value after propensity score matching; 2) adjustment for all covariables used to estimate propensity score; and 3) adjustment for propensity score. Secondarily, we assessed treatment effect within quintiles of the propensity score. Bonferroni correction for multiple comparisons was employed to control Type I error at 0.05, thus $P < 0.017$ was considered significant for each primary outcome (i.e., $0.05/3 = 0.017$).

In addition, we conducted a sensitivity analysis comparing rFVIIa and control patients based on the AKIN criteria for the acute kidney injury previously defined in the literature.(25) We used a multivariable logistic regression model with a backward selection procedure(alpha-to-enter=0.20 and alpha-to-stay=0.30), where preoperative creatinine and all potential confounders used for the matching were considered for inclusion.

For the primary outcomes in which we observed significant difference between matched rFVIIa and control patients, a corresponding “dose-response” analysis using multivariable logistic regression was conducted. All potential confounders used for the propensity score matching were considered for and included in the model through use of a backward selection procedure. Since low- vs. high-dose of rFVIIa is not clearly defined, 60mcg/kg dose was used as a cut-off.

Secondary outcomes

Propensity-score matched rFVIIa and control patients were compared on total intubation time(days), total intensive care unit(ICU) length of stay(days), duration of hospitalization(days), and a composite outcome of deep venous thrombosis, pulmonary embolism, and myocardial infarction, using multivariable logistic regression or Cox proportional hazard regression, as appropriate. Patients who died before the event (extubation/discharge) were considered failures in the corresponding analysis, with time censored at the worst observation. $P\text{-value} < 0.0125$ was considered significant (i.e., $0.05/4 = 0.0125$, Bonferroni correction). SAS software version 9.3 (SAS Institute, Cary, NC, USA) was used for all statistical analysis.

Results

Of 27,977 adult patients who underwent major cardiovascular surgery between January 2006 and December 2011, 164(0.59%) patients received rFVIIa treatment perioperatively. One-hundred forty-four(88%) of these patients were successfully matched with 359 control patients. Among those, 41(28%) received rFVIIa intraoperatively, 92(64%) postoperatively and 11(8%) both intraoperatively and postoperatively. Seventy-five(52%) patients received more than one dose of rFVIIa.

Patients who received rFVIIa were in worse medical condition and with more comorbidities including heart failure, end-stage kidney disease, requiring emergency surgery and receiving

more blood transfusions (Table 1, left panel). Propensity score techniques successfully balanced most variables in the matched subset, which were used to assess the association with the outcomes (Table 1, right panel). Amounts of fresh frozen plasma, platelets, and cryoprecipitate transfusions remained slightly imbalanced ($STD > 0.19$) between groups. To be conservative, we adjusted for these factors when comparing groups on the outcomes.

Of the propensity-matched patients, 40% of patients who received rFVIIa experienced in-hospital mortality vs 18% of control patients after adjusting for imbalanced covariables and within-patient correlation (OR (98.3% CI) 2.82(1.64, 4.87); $P < 0.001$) (Figure 1). Similarly, 31% of patients treated with rFVIIa experienced renal morbidity vs 17% of controls (2.07(1.19, 3.62); $P = 0.002$). However, neurologic morbidity was not increased in patients who received rFVIIa (17% vs 11%; OR 1.60(0.81, 3.15); $P = 0.10$). Additional ways of risk-adjustment yielded similar results (Table 2). Furthermore, associations depended upon quintiles of the propensity score. For each primary outcome, the association was stronger for patients at lower risk (lower quintiles) (Figure 2).

The sensitivity analysis of acute kidney injury using AKIN criteria provided consistent results. Both pre- and post- creatinine levels were available for 455 patients, including 128 rFVIIa patients and 327 controls. Forty-one (32%) rFVIIa patients and 77 (24%) controls experienced stage 1 injury; no patients experienced stage 2 or 3 injury. We found that patients who were treated with rFVIIa were 1.80 times (95% CI: 1.04, 3.12) more likely to experience acute kidney injury within 48 hours after surgery compared to controls.

The secondary outcome analysis found no difference in risk of deep venous thrombosis, pulmonary embolism, or myocardial infarction between groups. rFVIIa patients were more likely to require mechanical ventilation and to remain in the ICU and hospital postoperatively (Table 3).

Dose-Response Analysis

The median dose [interquartile range] for overall patient population group was 94 [78, 173] mcg/kg. The median dose was 117 [86, 176] mcg/kg for the high-dose and 42 [25, 55] mcg/kg for the low-dose group. Twenty (14%) patients received low dose rFVIIa (i.e., < 60 mcg/kg). No “dose effect” was found on in-hospital mortality [OR (97.5% CI) 1.36 (0.30, 6.10); $P = 0.65$] or renal morbidity [0.76(0.21, 2.76); $P = 0.64$] for low-dose versus high-dose, after adjusting for confounding variables.

Comment

Our analysis found that cardiac surgical patients who require rFVIIa perioperatively are severely ill and require high-risk surgery complicated by coagulopathy, refractory to massive blood and blood component transfusion. Perioperative administration of rFVIIa was associated with increased risk of mortality, renal morbidity, and prolonged hospital stay. In contrast, thromboembolic complications were not increased. Additionally, rFVIIa did not have a dose-dependent effect on postoperative outcomes.

The cause of increased mortality with rFVIIa administration is unclear; however, increased renal morbidity with rFVIIa use may contribute, at least in part, to higher mortality.(26, 27) Surprisingly, thromboembolic events were not increased with rFVIIa. Stratification of patients by perioperative risk profile and severity of illness using quintile propensity analysis demonstrated a consistent trend of increased mortality in all quintiles, with the exception of patients with the highest perioperative risk.

The results of our investigation conflict with another retrospective study, which reported no mortality difference, although a trend toward increased mortality was suggested(14). However, that report(14), was limited by poorly described matching techniques, which resulted in an imbalance in preoperative EuroScores. This suggested that controls may have been at higher risk than patients receiving rFVIIa. Our analysis, in contrast, matched patients on multiple variables representing patient co-morbidities and perioperative variables ensuring well-balanced propensity-matched groups. Moreover, several sensitivity analyses produced consistent results.

Patients treated with rFVIIa experienced more kidney injury for unclear reasons. rFVIIa, with a dual, tissue factor dependent and independent mechanism of action, restores thrombin production and augments hemostasis at the site of vessel injury(28). Thus increased tissue factor expression after cardiopulmonary bypass(29) with inflammatory modulating properties of rFVIIa(30) may promote a pro-coagulant state. These prothrombotic effects in the renal vascular bed and increased tissue factor expression in renal glomeruli may increase renal morbidity(31). Interestingly, risk of renal morbidity was increased in all quintile subsets of patients, except for patients with the highest risk profile.

Investigations of the risk of stroke, myocardial infarction, and pulmonary embolism associated with rFVIIa administration have reported mixed results(9, 17, 20, 22). Our investigation found no difference in the risk of neurologic injury or thromboembolic complications, perhaps because the severity of patients' comorbidities overshadowed the risk of rFVIIa(11). Nevertheless, the high incidence of serious complications demonstrates that the study cohort represents the highest-risk population and may not be applicable to all cardiac surgery patients.

The optimal dose of rFVIIa for treatment of coagulopathy without increasing risk of adverse events is unknown. Initial dosing recommendations for rFVIIa of 90-120mcg/kg in cardiac surgery were extrapolated from the treatment of hemophiliacs.(32) Low-dose rFVIIa (10 - 60 mcg/kg)(9, 12, 16), is effective(7, 12, 33, 34), and may decrease risk of thromboembolic events(16). Our dose-response analysis, however, found no difference in risk of renal morbidity and mortality in patients receiving high-dose (>60mcg/kg) compared to low-dose (<60mcg/kg) rFVIIa. However, only 14% of patients received low-dose rFVIIa, which may have limited our analysis. Similar to another investigation(34), adverse outcomes were associated with rFVIIa, regardless of dose. Benefits of low-dose rFVIIa includes cost-savings, which may, however, be offset by the cost of postoperative complications(12).

The primary limitation of present analysis is that despite using nonparsimonious propensity-score matching, we cannot exclude possible influence of unmeasured confounders. Second,

as with any retrospective analysis, we can only identify association rather than a cause-and-effect relationship. Third, we studied gross neurologic outcomes. Use of more sensitive outcomes, such as neurocognitive studies, may have influenced our findings. Also, use of rFVIIa is dependent upon the physicians' discretion, thus selection bias may have occurred. Our study did not differentiate between intraoperative or postoperative times of administration, thus it is possible that timing of rFVIIa administration affected the results. A major strength of this analysis, however, is that multiple sensitivity analyses produced consistent results. Further, quintile analysis that stratified patients based on severity of illness adds to the strength of this study by evaluating the impact of rFVIIa on the "sickness" of the patients providing important insight into the patient's risk of complications related to rFVIIa administration.

In conclusion, administration of rFVIIa is associated with increased mortality and renal morbidity in cardiac surgery patients. We did not find an association between administered dose of rFVIIa and risk of adverse outcome. Caution is advised in the off-label administration of rFVIIa to cardiac surgical patients.

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References

1. Karkouti K, Wijeyesundera DN, Yau TM, et al. The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion*. 2004; 44(10):1453–1462. [PubMed: 15383018]
2. Vivacqua A, Koch CG, Yousuf AM, et al. Morbidity of bleeding after cardiac surgery: Is it blood transfusion, reoperation for bleeding, or both? *Ann Thorac Surg*. 2011; 91(6):1780–1790. [PubMed: 21619974]
3. Whitson BA, Huddleston SJ, Savik K, Shumway SJ. Bloodless cardiac surgery is associated with decreased morbidity and mortality. *Journal of cardiac surgery*. 2007; 22(5):373–378. [PubMed: 17803571]
4. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor vii for acute intracerebral hemorrhage. *The New England journal of medicine*. 2008; 358(20):2127–2137. [PubMed: 18480205]
5. Hauser CJ, Boffard K, Dutton R, et al. Results of the control trial: Efficacy and safety of recombinant activated factor vii in the management of refractory traumatic hemorrhage. *The Journal of trauma*. 69(3):489–500. [PubMed: 20838118]
6. Hacquard M, Durand M, Lecompte T, Boini S, Briancon S, Carteaux JP. Off-label use of recombinant activated factor vii in intractable haemorrhage after cardiovascular surgery: An observational study of practices in 23 french cardiac centres (2005-7). *Eur J Cardiothorac Surg*. 2011; 40(6):1320–1327. [PubMed: 21550261]
7. Willis C, Bird R, Mullany D, Cameron P, Phillips L. Use of rfvii for critical bleeding in cardiac surgery: Dose variation and patient outcomes. *Vox sanguinis*. 2010; 98(4):531–537. [PubMed: 19878495]
8. Diprose P, Herbertson MJ, O'Shaughnessy D, Deakin CD, Gill RS. Reducing allogeneic transfusion in cardiac surgery: A randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. *British journal of anaesthesia*. 2005; 94(3):271–278. [PubMed: 15591329]

9. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor vii: A randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation*. 2009; 120(1):21–27. [PubMed: 19546387]
10. Karkouti K, Beattie WS, Wijeyesundera DN, et al. Recombinant factor viia for intractable blood loss after cardiac surgery: A propensity score-matched case-control analysis. *Transfusion*. 2005; 45(1):26–34. [PubMed: 15647015]
11. Karkouti K, Beattie WS, Arellano R, et al. Comprehensive canadian review of the off-label use of recombinant activated factor vii in cardiac surgery. *Circulation*. 2008; 118(4):331–338. [PubMed: 18606914]
12. Andersen ND, Bhattacharya SD, Williams JB, et al. Intraoperative use of low-dose recombinant activated factor vii during thoracic aortic operations. *Ann Thorac Surg*. 2012; 93(6):1921–1929. [PubMed: 22551846]
13. Ranucci M, Isgro G, Soro G, Conti D, De Toffol B. Efficacy and safety of recombinant activated factor vii in major surgical procedures: Systematic review and meta-analysis of randomized clinical trials. *Arch Surg*. 2008; 143(3):296–304. discussion 304. [PubMed: 18347278]
14. Chapman AJ, Blount AL, Davis AT, Hooker RL. Recombinant factor viia (novoseven rt) use in high risk cardiac surgery. *Eur J Cardiothorac Surg*. 2011; 40(6):1314–1318. discussion 1318-1319. [PubMed: 21601468]
15. Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor vii (novoseven) in children vs. Adults with haemophilia a. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2004; 10(4):352–359. [PubMed: 15230949]
16. Bruckner BA, DiBardino DJ, Ning Q, et al. High incidence of thromboembolic events in left ventricular assist device patients treated with recombinant activated factor vii. *J Heart Lung Transplant*. 2009; 28(8):785–790. [PubMed: 19632574]
17. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor vii in randomized clinical trials. *The New England journal of medicine*. 363(19):1791–1800. [PubMed: 21047223]
18. Abshire T, Kenet G. Safety update on the use of recombinant factor viia and the treatment of congenital and acquired deficiency of factor viii or ix with inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2008; 14(5):898–902. [PubMed: 18684126]
19. Mitra B, Phillips L, Cameron PA, Billah B, Reid C. The safety of recombinant factor viia in cardiac surgery. *Anaesthesia and intensive care*. 2010; 38(4):671–677. [PubMed: 20715730]
20. Ponschab M, Landoni G, Biondi-Zoccai G, et al. Recombinant activated factor vii increases stroke in cardiac surgery: A meta-analysis. *Journal of cardiothoracic and vascular anesthesia*. 2011; 25(5):804–810. [PubMed: 21596585]
21. Gelsomino S, Lorusso R, Romagnoli S, et al. Treatment of refractory bleeding after cardiac operations with low-dose recombinant activated factor vii (novoseven): A propensity score analysis. *Eur J Cardiothorac Surg*. 2008; 33(1):64–71. [PubMed: 17996457]
22. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor viia. *Jama*. 2006; 295(3):293–298. [PubMed: 16418464]
23. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Parandhi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. *Jama*. 1992; 267(17):2344–2348.
24. Bull SB. Regression models for multiple outcomes in large epidemiologic studies. *Statistics in medicine*. 1998; 17(19):2179–2197. [PubMed: 9802177]
25. Endre ZH. Acute kidney injury: Definitions and new paradigms. *Advances in chronic kidney disease*. 2008; 15(3):213–221. [PubMed: 18565473]
26. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettila V. Acute renal failure after cardiac surgery: Evaluation of the rifle classification. *Ann Thorac Surg*. 2006; 81(2):542–546. [PubMed: 16427848]
27. Loeff BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *Journal of the American Society of Nephrology : JASN*. 2005; 16(1):195–200. [PubMed: 15563558]

28. Pusateri AE, Park MS. Mechanistic implications for the use and monitoring of recombinant activated factor vii in trauma. *Critical care (London, England)*. 2005; 9(Suppl 5):S15–24.
29. Dietrich W, Spannagl M. Caveat against the use of activated recombinant factor vii for intractable bleeding in cardiac surgery. *Anesthesia and analgesia*. 2002; 94(5):1369–1370. author reply 1370-1361. [PubMed: 11973226]
30. Ernofsson M, Thelin S, Siegbahn A. Monocyte tissue factor expression, cell activation, and thrombin formation during cardiopulmonary bypass: A clinical study. *J Thorac Cardiovasc Surg*. 1997; 113(3):576–584. [PubMed: 9081105]
31. Drake TA, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues. Implications for disorders of hemostasis and thrombosis. *The American journal of pathology*. 1989; 134(5):1087–1097. [PubMed: 2719077]
32. Kenet G. High-dose recombinant factor viia therapy in hemophilia patients with inhibitors. *Seminars in hematology*. 2006; 43(1 Suppl 1):S108–110. [PubMed: 16427376]
33. van de Garde EM, Bras LJ, Heijmen RH, et al. Low-dose recombinant factor viia in the management of uncontrolled postoperative hemorrhage in cardiac surgery patients. *Journal of cardiothoracic and vascular anesthesia*. 2006; 20(4):573–575. [PubMed: 16884993]
34. Willis CD, Cameron PA, Phillips L. Variation in the use of recombinant activated factor vii in critical bleeding. *Internal medicine journal*. 2010; 40(7):486–493. [PubMed: 19712199]

Figure 1.

Forest plot showing associations between rFVIIa and primary outcomes among propensity-score matched patients.

Figure 2. Forest plot showing associations between rFVIIa and primary outcomes by quintiles of propensity-score, adjusting for propensity score as covariate.

Table 1

Baseline characteristics and intraoperative factors before and after propensity score matching (Data reported as mean $\pm$ SD or as median [25, 75 percentile])

Factor	All patients			Matched patients		
	rFVIIa (N=164)	Control (N=27,813)	STD ^a	rFVIIa (N=144)	Control (N=359)	STD ^a
Demographic variables						
Age(yrs)	60 $\pm$ 14	63 $\pm$ 14	0.18	61 $\pm$ 14	63 $\pm$ 16	0.15
Female gender	30 %	37 %	0.14	28 %	32 %	0.07
Race			0.20			0.05
White	83 %	87 %		85 %	84 %	
African American	13 %	7 %		10 %	12 %	
Others	4 %	6 %		5 %	4 %	
Body mass index(kg/m ²)	27 [23, 31]	28 [24, 31]	0.11	27 [23, 31]	27 [24, 31]	0.03
Medical history						
Heart failure	53 %	20 %	0.74	56 %	55 %	0.01
Myocardial infarction	15 %	6 %	0.28	15 %	15 %	0.00
Hypertension	66 %	51 %	0.30	68 %	74 %	0.14
Pulmonary hypertension	30 %	15 %	0.37	33 %	34 %	0.03
Chronic obstructive pulmonary disease	17 %	9 %	0.25	18 %	16 %	0.04
Diabetes mellitus	27 %	18 %	0.22	26 %	26 %	0.01
Stroke	12 %	6 %	0.21	13 %	14 %	0.03
Atrial arrhythmias	32 %	18 %	0.33	34 %	34 %	0.00
Carotid disease	12 %	11 %	0.04	14 %	16 %	0.06
Vascular disease	21 %	9 %	0.33	23 %	23 %	0.00
Anticoagulation/antiplatelet medication	3 %	1 %	0.15	3 %	3 %	0.02
Dialysis	10 %	0 %	0.45	6 %	7 %	0.02
Mitral valve insufficiency	17 %	16 %	0.04	19 %	18 %	0.02
Left ventricular function			0.82			0.21
Normal(EF: 60%)	21 %	39 %		22 %	26 %	
Mild dysfunction(EF: 50-59%)	25 %	39 %		27 %	31 %	
Mild – Moderate dysfunction(EF: 46-49%)	1 %	1 %		1 %	0 %	
Moderate dysfunction(EF: 41-45%)	3 %	5 %		3 %	3 %	
Moderately severe dysfunction (EF: 35-40%)	4 %	4 %		5 %	5 %	
Severe dysfunction (EF: <35%)	46 %	12 %		43 %	35 %	
Preoperative mechanical circulatory support	4 %	0 %	0.24	13 %	10 %	0.11
ASA physical status			0.86			0.13
I	0 %	0 %		0 %	0 %	
II	0 %	2 %		0 %	0 %	
III	3 %	27 %		3 %	6 %	
IV	85 %	69 %		85 %	83 %	

Factor	All patients			Matched patients		
	rFVIIa (N=164)	Control (N=27,813)	STD ^a	rFVIIa (N=144)	Control (N=359)	STD ^a
V	12 %	2 %		11 %	11 %	
Surgical history						
Previous carotid surgery	3 %	3 %	0.01	3 %	4 %	0.02
Previous vascular surgery	10 %	4 %	0.25	12 %	13 %	0.04
Previous cardiac surgery	49 %	17 %	0.71	53 %	60 %	0.14
Perioperative variables						
Emergency procedure	30 %	6 %	0.67	28 %	25 %	0.07
Type of procedure						
Left ventricular assist device	2 %	0 %	0.22	8 %	5 %	0.11
Right ventricular assist device	13 %	0 %	0.53	1 %	0 %	0.12
ECMO	1 %	2 %	0.04	14 %	11 %	0.09
Aortic valve repair/replacement	33 %	29 %	0.09	36 %	40 %	0.07
Mitral valve repair	15 %	8 %	0.22	9 %	9 %	0.01
Mitral valve replacement	20 %	7 %	0.38	15 %	22 %	0.17
Tricuspid valve repair /replacement	27 %	31 %	0.10	19 %	19 %	0.00
Coronary artery bypass grafting	30 %	37 %	0.14	30 %	31 %	0.02
Thoracic aortic surgery*	27 %	11 %	0.43	30 %	32 %	0.05
Heart/lung Transplantation ^b	3 %	1 %	0.18	3 %	4 %	0.02
Surgery duration(hrs)	8.5 ± 3.2	5.4 ± 2.2	1.13	8.5 ± 3.0	9.0 ± 2.8	0.16
Aortic clamp time(min)	73 [0, 134]	58 [0, 87]	0.22	84 [0, 137]	89 [50, 137]	0.16
Circulatory arrest time (min)	0 [0, 0]	0 [0, 0]	0.39	0 [0, 0]	0 [0, 0]	0.16
Red blood cell transfusion (units)	7.0 [2.5, 12.0]	0 [0, 0]	1.73	7.0 [2.0, 12.0]	6.0 [2.0, 10.0]	0.16
Fresh frozen plasma transfusion (units)	7.0 [3, 11]	0 [0, 0]	1.98	7.0 [3, 10.5]	5.0 [3, 8]	0.30
Transfusion of platelets (units)	8.4 [3.6, 13.2]	0 [0, 0]	1.72	8.4 [3.6, 12.6]	6.0 [2.4, 9.6]	0.24
Transfusion of cryoprecipitate (units)	1.0 [0, 2.5]	0 [0, 0]	1.51	1.0 [0, 2]	0 [0, 2]	0.26

ASA = American Society of Anesthesiologist; ECMO = Extracorporeal membrane oxygenation; EF = Ejection fraction; STD = Standardized difference

^a Standardized differences: the difference (rFVIIa minus control) in means or proportions divided by the pooled standard deviation.

^b Variables were balanced between groups and not included in propensity score matching

Table 2

Sensitivity analyses demonstrating additional methods for confounding adjustments using the matched subset (N = 503)

Primary outcome	Odds ratio (98.3% CI) (rFVIIa/control)	P-value
Adjust for covariables with STD^a > 0.10		
In-hospital mortality	3.50 (1.93, 6.34)	<0.001
Neurologic morbidity	1.62 (0.79, 3.30)	0.11
Renal morbidity	2.10 (1.16, 3.81)	0.003
Adjust for all covariables		
In-hospital mortality	3.86 (1.65, 9.05)	<0.001
Neurologic morbidity	3.09 (1.06, 9.03)	0.012
Renal morbidity	2.61 (1.14, 5.98)	0.006
Adjust for propensity score		
In-hospital mortality	2.72 (1.60, 4.63)	<0.001
Neurologic morbidity	1.45 (0.73, 2.87)	0.19
Renal morbidity	1.98 (1.14, 3.45)	0.003

CI = confidence interval; STD = Standardized difference

Table 3

Associations between rFVIIa and secondary outcomes among propensity score matched patients (N = 503)

Secondary outcome	rFVII N = 144	Control N = 359	Odds ratio (98.75 % CI) (rFVII/ control)	P
Deep venous thrombosis / pulmonary embolism / Myocardial infarction	17 (12%)	31 (9%)	1.33 (0.59, 2.98)	0.38
Hazard Ratio (98.75% CI)				
Total intubation time(days)	8 [4, 20]	3[1, 7]	1.89 (1.42, 2.51)	<0.001
Length of ICU stay(days)	13 [6, 22]	6 [3, 12]	1.92 (1.43, 2.58)	<0.001
Length of hospital stay(days)	36 [21, 68]	21 [14, 33]	2.15 (1.58, 2.93)	<0.001

CI = Confidence interval; ICU = Intensive care unit