

Use of Recombinant Activated Factor VII Concentrate to Control Postoperative Hemorrhage in Complex Cardiovascular Surgery

Lyndsey J. Bowman, Walter E. Uber, Pharm D, Martha R. Stroud, Lydia R. Christiansen, John Lazarchick, Arthur J. Crumbley III, MD, John M. Kratz, MD, John M. Toole, MD, Fred A. Crawford, Jr, MD, and John S. Ikonomidis, MD, PhD

Departments of Pharmacy Services, Cardiothoracic Surgery, and Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina

Background. Complex cardiovascular surgery often results in postoperative hemorrhage. Excessive blood product use may cause systemic thrombosis, end-organ dysfunction, and edema preventing chest closure. Recombinant activated factor VII (rFVIIa) concentrate may decrease hemorrhage where other treatment measures failed. We reviewed our experience with rFVIIa after complex cardiovascular surgery.

Methods. A retrospective review evaluating 846 complex cardiovascular surgery patients of whom 36 received rFVIIa between January 1, 2001, and December 31, 2006, was performed. Efficacy and safety data were collected for the entire cohort in addition to delayed sternal closure requirements, reoperation, and operative mortality in the patient cohort temporally separated into two groups (pre-rFVIIa era, 2001 to 2003, 1 patient received rFVIIa; rFVIIa era, 2004 to 2006, 35 patients received rFVIIa).

Results. A total of 36 patients received 41 rFVIIa doses with an in-hospital survival of 91.7%. Hemorrhage was

controlled in 83.3% of patients, with 1 dose sufficient in 75.0%. There was a significant decrease ($p < 0.005$) in all blood product requirements post-rFVIIa compared with pre-rFVIIa administration. In the intensive care unit ($n = 6$), rFVIIa significantly reduced chest tube output ($p = 0.028$) and prevented reexploration for bleeding in 5 patients. The requirement for delayed sternal closure was significantly higher in the pre-rFVIIa era versus the rFVIIa era ($p = 0.011$). The incidence of thrombosis in all patients receiving rFVIIa was 11.1%. In the rFVIIa era, a higher incidence of postoperative renal failure ($p = 0.005$) and pneumonia ($p < 0.002$) was detected in patients receiving rFVIIa.

Conclusions. Recombinant activated factor VII appears to be effective in patients with refractory coagulopathy undergoing high-risk cardiovascular surgery.

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Coagulopathy resulting in excessive postoperative hemorrhage when encountered in patients after complex cardiovascular surgery is a significant problem [1–4]. Clinically significant coagulopathy is associated with increased morbidity and mortality, prolonged hospital and intensive care unit (ICU) length of stay, and increased healthcare costs [1–4]. Excessive use of blood products may cause considerable edema, preventing sternotomy closure, as well as systemic thrombosis, potentially leading to end-organ dysfunction [5–8]. When standard hemostatic interventions fail, alternative means of reversing coagulopathy are required.

Recombinant activated factor VII (rFVIIa [NovoSeven;

Novo Nordisk, Princeton, New Jersey), is approved by the Food and Drug Administration for use in hemophilia patients with factor inhibitors and patients with congenital factor VII deficiency (see NovoSeven package insert, 2007). Off-label use of rFVIIa continues to expand for the postsurgical population, but concerns have been raised about the potential safety, efficacy, and cost of rFVIIa use in this setting [9–14].

The purpose of this study was to evaluate the use of rFVIIa in high-risk cardiovascular surgery patients at the Medical University of South Carolina (MUSC) to assess its safety and efficacy in the reversal of refractory coagulopathy.

Material and Methods

Patient Population

A retrospective chart review was conducted of all adult cardiovascular surgery patients 18 years of age or older at MUSC between January 2001 and December 2006. The MUSC Institutional Review Board provided approval for

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Address correspondence to Dr Ikonomidis, Division of Cardiothoracic Surgery, Medical University of South Carolina, Suite 409 CSB, 96 Jonathan Lucas St, Charleston, SC 29425; e-mail: ikonomidj@musc.edu.

conduct of this study in addition to a waiver for patient consent. A high-risk subset ($n = 846$) was defined consisting of patients undergoing cardiac transplantation, aortic surgery, redo operations, or multiple cardiac procedures as the primary operation. Patients with isolated valve replacement or coronary artery bypass graft surgery as the primary operation were excluded. All patients who received rFVIIa during the time period examined were enclosed in this cohort. Patient demographics, pre-operative risk factors, rFVIIa dosing characteristics, blood product use, coagulation laboratory values, operative characteristics, the need for reoperation or reexploration for bleeding after the primary procedure, chest tube output for patients receiving rFVIIa in the ICU, and in-hospital outcomes were recorded.

In addition, to evaluate the impact that rFVIIa use may have had in the management of high risk patients with refractory coagulopathy over time, the cohort was divided into two temporally separated groups for comparison: pre-rFVIIa era, 2001 to 2003, $n = 426$; additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) score (mean and range): 8 (2 to 22); rFVIIa era, 2004 to 2006, $n = 420$; additive EuroSCORE (mean and range): 8 (2 to 16); p greater than 0.05 from pre-rFVIIa era.

Threshold for rFVIIa Use

The decision to administer rFVIIa was made by the surgical team after consideration of four general criteria: (1) exclusion of all surgical causes of bleeding; (2) failure

Table 1. Patient Demographics and Risk Factors for Bleeding in Patients Receiving Recombinant Activated Factor VII ($n = 36$)

Demographic/Risk Factor	Number of Patients
Age (years) \pm SD	58 \pm 15
Male	27 (75%)
Race	
Caucasian	25 (69%)
African American	9 (25%)
Hispanic	1 (3%)
Asian	1 (3%)
Renal insufficiency	9 (25%)
Hemodialysis	2 (6%)
History of thrombosis	
Myocardial infarction	6 (17%)
Intracardiac thrombus	3 (8%)
Cerebrovascular accident	3 (8%)
Deep vein thrombosis	1 (3%)
Redo operation	16 (44%)
Mechanical assistance	1 (3%)
History of coagulopathy	1 (3%)
Anticoagulation use	21 (58%)
Multiple anticoagulants	3 (8%)
Coumadin	3 (8%)
Aspirin	6 (17%)
Coumadin plus aspirin	9 (25%)

Table 2. Operative Characteristics for Patients Receiving Recombinant Activated Factor VII ($n = 36$)

Characteristic	Number of Patients (%)
Type of surgery, n (%)	
Aortic surgery	13 (36)
Multiple procedures	13 (36)
Cardiac transplantation	10 (28)
CPB (minutes, mean + SD)	202 \pm 74
Cross-clamp time (minutes, mean + SD)	110 \pm 46
Circulatory arrest (minutes, mean + SD)	15.6 \pm 7
Antifibrinolytic used, n (%)	
Aprotinin	36 (100)
Anticoagulant used, n (%)	
Heparin	36 (100)
Intraoperative complications, n (%)	
Placement of IABP	5 (14)
Other	3 (8)
Additional agents given to control bleeding, n (%)	
Protamine	6 (17)
Vitamin K	2 (6)
DDAVP	1 (3)
Multiple agents	1 (3)

CPB = cardiopulmonary bypass; DDAVP = desmopressin; IABP = intra-aortic balloon pump; rFVIIa = recombinant activated factor VII.

to reverse coagulopathy with adequate pharmacologic and blood product replacement defined as evidence of normalization of coagulation laboratory values (international normalized ratio ≤ 1.5 , platelets $\geq 100\text{K}/\text{mm}^3$, fibrinogen $> 200\text{ mg/dL}$); (3) correction of the patient's core body temperature to normal ($\geq 36.5^\circ\text{C}$); and (4) adequate heparin reversal with protamine defined as an activated clotting time (ACT) of 120 s or less, or an aPTT of 1.5 times or less than our laboratory control (45 s). In patients requiring rFVIIa in the ICU, chest tube output of $3\text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ or greater for 2 hours or more was required in addition to the above criteria in patients without evidence of cardiac tamponade, mediastinal hematoma, or large hemothorax by chest radiograph or echocardiography that would require reexploration for evacuation.

Endpoints

The primary endpoints were rFVIIa efficacy and safety. Efficacy was determined by (1) observation of the success of the agent in controlling (ceasing) hemorrhage intraoperatively, allowing for primary chest closure without the need for reexploration or reoperation for bleeding; and (2) comparison of blood product use before and after rFVIIa administration. For patients who received rFVIIa in the ICU, chest tube outputs both before and after rFVIIa administration were evaluated. In the temporally separated groups, delayed sternal closure requirements, the need for reexploration or reoperation for bleeding, length of stay, pneumonia, adult respiratory distress syndrome, sepsis, and operative death were compared.

In addition, high-risk patients who received rFVIIa during the rFVIIa era were compared with patients in the same era who did not receive rFVIIa with regard to the incidence of a combined thrombosis endpoint (cerebrovascular accident, myocardial infarction, or pulmonary embolism, as well as the incidence of acute renal failure, defined as an increase of serum creatinine to greater than 2 mg/dL and 2 times the most recent preoperative creatinine level or a new requirement for dialysis postoperatively.

Statistical Analysis

Continuous variables are reported as mean ± SD. Medians and ranges are included owing to nonparametricity of the data where appropriate. Categorical variables are reported as percentages. The pre-rFVIIa and post-rFVIIa

Table 3. Threshold for rFVIIa Use, rFVIIa Dosing Characteristics, and Efficacy of rFVIIa

Characteristics Before rFVIIa Dose	Number of Patients (%)
No evidence of surgical bleeding	36 (100)
Temperature ≥ 36.5°C	24 (67)
ACT ≤ 120 seconds	26 (72)
PTT ≤ 1.5 times control	23 (64)
INR ≤ 1.5	22 (61)
Platelet count ≥ 100K/mm ³	19 (53)
Fibrinogen ≥ 200 mg/dL	29 (81)
Patients meeting criteria for use	
All criteria	21 (58)
3 of the 4 criteria	11 (31)
2 of the 4 criteria	3 (8)
1 of the 4 criteria	1 (3)
Dose of rFVIIa	
90 µg/kg	34 (94)
40 to 50 µg/kg	2 (6)
Number of doses administered	
1 dose	31 (86)
2 doses	5 (14)
Location of dose 1	
OR during primary operation	27 (75)
ICU after primary operation	5 (14)
OR during reexploration	3 (8)
ICU after reexploration	1 (3)
Location of dose 2 (n = 5)	
OR during primary operation	4 (80)
OR during reexploration	1 (20)
Success of first rFVIIa dose	
Yes	27 (75)
Time to leaving OR after dose (23 patients, min ± SD)	87 ± 51
Overall success of rFVIIa	
Yes	30 (83)

ACT = activated clotting time; ICU = intensive care unit; INR = international normalized ratio; OR = operating room; PTT = partial thromboplastin time; rFVIIa = recombinant activated factor VII.

Table 4. Coagulation Laboratory Measures Before and After rFVIIa Administration

	Pre-rFVIIa Dose	Post-rFVIIa Dose	p Value
PTT, median (range)	42.2 (31.4-150)	41.6 (29-85)	0.026
PT, median (range)	17.8 (11.5-100)	12.1 (10.3-17.2)	<0.0005
INR, median (range)	1.37 (0.81-12.0)	.86 (0.71-1.3)	<0.0005
Fibrinogen, median (range)	256 (139-392)	276 (159-398)	0.348
Platelets, median (range)	105 (39-262)	109 (30-191)	0.317

INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; rFVIIa = recombinant activated factor VII.

variables were examined with the Wilcoxon matched-pairs signed-ranks test. High-risk patient risk factors for the two eras were compared with Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Fisher's exact test was also used to examine the incidence of postoperative thrombotic events and acute renal failure.

Results

Demographic and Procedural Data

In the overall cohort, 37 patients received rFVIIa. One patient who required bivalirudin anticoagulation management was removed, leaving 36 patients for analysis. Patient demographics and preoperative risk factors for bleeding are summarized in Table 1. The mean age in this series was 58 years, and approximately 25% of patients had renal insufficiency before operation. In the 36.1% of patients who had a history of a thrombotic event, myocardial infarction was the most common.

Operative characteristics are summarized in Table 2. The type of surgery performed distributed into three high-risk categories, with approximately one third of the

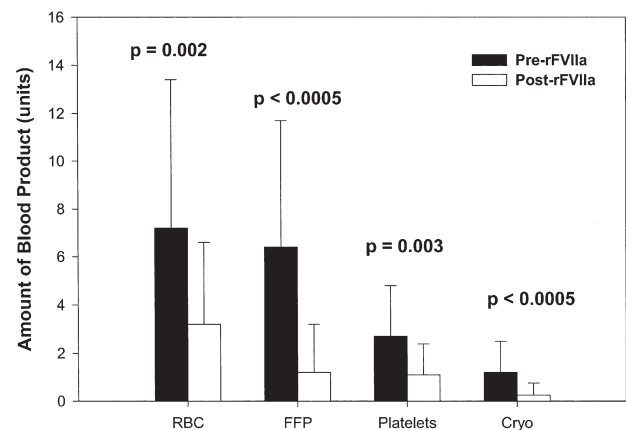


Fig 1. Transfusion requirements before (solid bars) recombinant activated factor VII administration and after (open bars) administration (n = 36). (Cryo = cryoprecipitate; FFP = fresh frozen plasma; RBC = red blood cells.)

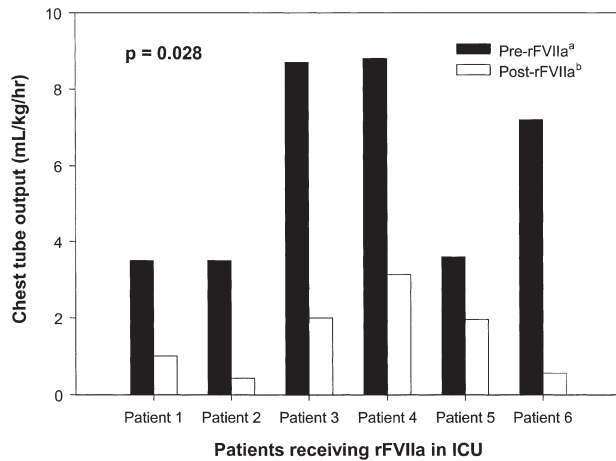


Fig 2. Chest tube output before (solid bars) recombinant activated factor VII (rFVIIa) administration (output averaged over 4 hours before receiving rFVIIa in the intensive care unit [ICU]) and after (open bars) administration (output averaged over 4 hours after receiving rFVIIa in the ICU).

patient population undergoing an aortic surgical procedure (36.1%), multiple cardiac procedures (36.1%), or cardiac transplantation (27.8%). Approximately 44% of the operative procedures were redo operations, the majority of which were cardiac transplants (50%). Aprotinin was the antifibrinolytic used in all of the procedures with heparin used as the anticoagulant. One patient required placement of a left ventricular assist device (ABIOMED AB5000; Abiomed, Danvers, Massachusetts) preoperatively before cardiac transplantation, and 1 patient had a documented history of factor V deficiency. The majority (58.3%) of patients received anticoagulation therapy before operation, most commonly with the combination of aspirin and warfarin.

Intraoperative complications included the inability to separate from cardiopulmonary bypass secondary to either right or left ventricular failure requiring placement of an intra-aortic balloon pump, a protamine reaction, heart block during separation from bypass, and vein graft obstruction requiring redo anastomosis. If an additional agent was administered to control bleeding, protamine was most commonly used.

Threshold and Dosing Characteristics for rFVIIa Use

Threshold and dosing characteristics for rFVIIa use are summarized in Table 3. Absence of surgically correctable bleeding was noted in all 36 patients before rFVIIa administration. Approximately 89% of patients met at least 3 of the 4 defined criteria for rFVIIa administration.

The majority of patients (94.4%) received a 90 µg/kg dose of rFVIIa (Table 3). Thirty-one patients (86.1%) received only 1 dose of rFVIIa, with the majority (75%) of first-time doses given in the operating room during the operative procedure. Two patients who received rFVIIa had clopidogrel bisulfate preoperatively; rFVIIa was effective in controlling bleeding with one dose in both patients. Five patients (13.9%) required a second dose of

rFVIIa to control bleeding. Of these patients, 4 patients (80%) received the second dose also while in the operating room during the primary operation. The 2 patients (5.6%) who received a 40 to 50 µg/kg dose of rFVIIa, did not require more than 1 dose and did not undergo reexploration for bleeding after the dose. Six patients received rFVIIa for bleeding in the ICU.

Efficacy of rFVIIa and Coagulation Laboratory Values

Based on previously stated criteria, rFVIIa was found to be effective in 30 patients (83.3%; Table 3), with one dose being sufficient to control bleeding in 27 patients (75%).

Table 5. High-Risk Group Patient Demographics and Medical History

Demographics	Pre-rFVIIa Era (n = 426)	rFVIIa Era (n = 420)	p Value
Age (years)			
Mean ± SD	62 ± 14	61 ± 16	0.445
Median	63	63	
Range	18-88	18-90	
Height (cm)			
Mean ± SD	171 ± 11	172 ± 11	0.106
Median	173	175	
Range	125-198	130-198	
Weight (kg)			
Mean ± SD	81 ± 19	82 ± 20	0.694
Median	80	80	
Range	40-173	36-195	
Ejection fraction (%)			
Mean ± SD	47 ± 17	47 ± 16	0.629
Median	50	50	
Range	5-83	9-80	
Race (%)			
African American	27	25	0.726
Caucasian	71	73	
Other	2	2	
Sex (%)			
Male	62	64	0.569
Medical history (%)			
Diabetes mellitus	24	26	0.477
Renal failure	16	12	0.198
Dialysis	5	3	0.104
COPD	13	13	0.760
Hypertension	70	66	0.237
Peripheral vascular disease	15	13	0.621
Cerebrovascular disease	12	15	0.158
Cerebrovascular accident	9	9	1.000
Immunosuppressive medications	6	6	1.000
Myocardial infarction	26	21	0.145
Redo operations	36	32	0.276
Heart failure (NYHA class III-IV)	78	76	0.568

COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; rFVIIa = recombinant activated factor VII.

Table 6. Outcomes Between Eras

Outcome	Pre-rFVIIa Era (n = 426)	rFVIIa Era (n = 420)	p Value
Delayed sternal closure, n (%)	16 (4)	4 (1)	0.011
Reoperation for bleeding, n (%)	30 (7)	24 (6)	0.483
LOS, days, median (range)	11 (0–132)	10 (0–182)	0.543
Pneumonia, n (%)	13 (3)	34 (8)	0.002
ARDS, n (%)	9 (2)	4 (1)	0.143
Sepsis, n (%)	16 (4)	16 (4)	1.000
Mortality, n (%)	29 (7)	20 (5)	0.239

ARDS = adult respiratory distress syndrome; LOS = length of stay; rFVIIa = recombinant activated factor VII.

The 6 patients in whom rFVIIa was not efficacious included 4 who received one dose and 2 of 5 patients who received 2 doses. Of the reexploration patients, 5 had no surgically correctable bleeding site at the time of reexploration. Despite near normalization of coagulation factors before rFVIIa administration, rFVIIa use was associated with a significant decrease in prothrombin time and international normalized ratio values ($p < 0.0005$) as well as paratimal thromboplastin time ($p = 0.026$; Table 4).

As demonstrated in Figure 1, there was a statistically significant decrease for all blood products after rFVIIa administration compared with pre-rFVIIa administration ($p < 0.005$). For the 6 ICU patients, rFVIIa administration resulted in a significant reduction in chest tube output ($p = 0.028$; Fig 2).

rFVIIa Era Outcomes

In the temporally separated patient cohorts, 1 patient of 426 received rFVIIa in the pre-rFVIIa era. In the rFVIIa era, 35 patients (additive EuroSCORE: mean 8 [range, 3 to 16]) received rFVIIa and 385 patients did not (additive EuroSCORE: mean 8 [range, 2 to 16]; $p > 0.05$ from rFVIIa era patients receiving rFVIIa). Table 5 summarizes the comparison of patient demographic data and risk factors between these groups when divided by era. Patient demographics and medical history were overall well matched. Outcomes between the eras are shown in Table 6. The requirement for delayed sternal closure was significantly higher in the pre-rFVIIa era versus the rFVIIa era ($p = 0.011$). Reoperation for bleeding, length of stay, adult respiratory distress syndrome, sepsis, and hospital mortality were not significantly different between the two eras. However, the incidence of pneumonia was significantly higher in the rFVIIa era (Table 6). Within the rFVIIa era, pneumonia developed in 29% of patients who received rFVIIa in contrast to 6% in the patients not receiving rFVIIa ($p < 0.002$).

Safety and Survival

The overall in-hospital survival for those patients who received rFVIIa was 91.7%, with an overall incidence of thrombosis of 11.1%. The 2 patients that experienced

cerebrovascular accident underwent aortic surgery as their operative procedure. One patient who underwent multiple cardiac procedures had a deep vein thrombosis after rFVIIa administration. The 1 patient who had a pulmonary embolism after rFVIIa administration had aortic surgery. The incidence of the combined endpoint of thrombosis between patients in the rFVIIa era who received rFVIIa (11.4%) versus those who did not receive rFVIIa (5.5%) was not statistically significantly different ($p = 0.145$).

Significantly more patients experienced postoperative renal failure (23.1% versus 5.6%), and required dialysis (11.5% versus 1.2%) in the rFVIIa group compared with patients who did not receive rFVIIa in the rFVIIa era ($p = 0.005$ and 0.009 , respectively). Serum creatinine returned to baseline in 3 of the 6 patients with evidence of acute renal failure after rFVIIa use before hospital discharge.

Comment

Abnormal or excessive blood loss after cardiovascular surgery has been reported to occur in 3% to 14% of cases [1, 13, 15]. Reexploration for bleeding after cardiac surgical procedures may be required in as many as 5% of patients [1–4]. Patients undergoing complex cardiac procedures, defined as any cardiac surgery other than an isolated coronary artery bypass graft surgery, may be at risk of a threefold increase in the rates of reoperation for bleeding [3]. Conventional measures for control of postoperative hemorrhage in cardiovascular surgery patients include transfusion of blood products and administration of various pharmacologic agents (for example, desmopressin, protamine, vitamin K) [16]. Both surgical reexploration and excessive blood product replacement have been associated with an increase in infection risk, multiorgan dysfunction and failure, increased hospital and ICU length of stay, and increased short- and long-term mortality [6, 17–21]. In addition, blood transfusions increase circulating inflammatory mediators, causing capillary leak and tissue edema that may hinder or prevent immediate sternotomy closure [5, 7]. Data supporting the use of various pharmacologic agents used to control postoperative bleeding are limited to a few clinical trials, which at times have provided conflicting results with clinical evidence for these agents limited to a small subset of patients [16]. When use of traditional pharmacologic and blood product replacement fails, other options to control refractory hemorrhage are required.

Recombinant factor VIIa, a hemostatic agent first introduced in the United States in 1999, is FDA-approved for the prevention and management of bleeding episodes after invasive procedures in hemophilia patients with factor inhibitors and patients with congenital factor VII deficiency. The postulated mechanism by which rFVIIa exerts its hemostatic effects involves the binding of this agent to exposed tissue factor at the site of tissue injury, leading to thrombin formation and platelet activation [15]. Recombinant factor VIIa further accelerates platelet activation either directly or through enhancement of thrombin generation independent of tissue factor, lead-

ing to formation of an insoluble cross-linked fibrin clot [22]. Clot stabilization is maintained by down-regulation of fibrinolysis by activation of thrombin activatable fibrinolysis inhibitor [23].

Beneficial results in achieving hemostasis with rFVIIa administration in an array of surgical and nonsurgical situations, in combination with its proposed mechanism of action, has led to its expanding use for refractory bleeding after cardiac surgery [24]. Published experiences using rFVIIa after cardiac surgery have varied with regard to patient selection, dosing strategy (dose, timing), and outcome [9-14, 24, 25]. The present study identified 36 high-risk patients who received rFVIIa after cardiac surgery at our institution. Nearly half of these patients were redo operations, with approximately 58% also receiving some form of anticoagulation therapy before surgery.

In our series, rFVIIa given at a dose of 40 $\mu\text{g}/\text{kg}$ to 90 $\mu\text{g}/\text{kg}$ for one to two doses was efficacious in allowing for primary chest closure without the need for reexploration or reoperation for bleeding or death due to refractory coagulopathy in approximately 83% of patients. This efficacy rate is consistent with previous reports in high-risk cardiac surgery patients demonstrating reversal of refractory coagulopathy in 82% to 100% of patients [10-12, 14]. Although in our study, a single 90 $\mu\text{g}/\text{kg}$ dose of rFVIIa was sufficient to achieve hemostasis in the majority of patients, rFVIIa doses used to control postoperative hemorrhage in cardiac surgery patients have varied widely, ranging between 11 $\mu\text{g}/\text{kg}$ and 190 $\mu\text{g}/\text{kg}$ per dose, in published reports [10-14, 24]. Romagnoli and colleagues [9] conducted a matched case-control analysis evaluating the use of 1.2 mg of rFVIIa (11 to 21.5 $\mu\text{g}/\text{kg}$ per dose), demonstrating a significant decrease in the need for reexploration for bleeding, and a trend toward a decrease in mortality in the rFVIIa group. Two patients in our series achieved hemostasis after receiving a lower, single dose (40 to 50 $\mu\text{g}/\text{kg}$) of rFVIIa. With regard to dosage timing, Karkouti and colleagues [13] evaluated early (≤ 8 units red blood cells) versus late (> 8 units red blood cells) administration of rFVIIa at an average dose of 56 ± 25 $\mu\text{g}/\text{kg}$. Patients in the early rFVIIa treatment group showed a similar mortality rate of 7.6% to the present study [13]. However, patients in the late rFVIIa treatment group demonstrated a mortality rate of 27.1% [13]. Late administration of rFVIIa has also been associated with an increase in mortality in other series [25]. The potential for the use of lower doses and proper timing of rFVIIa in cardiac surgery may warrant further exploration.

In this series, approximately 89% of patients met at least three of the four defined criteria before rFVIIa utilization. Bishop and colleagues [10] obtained similar outcomes in a high-risk cohort of patients treated with a dose of 100 $\mu\text{g}/\text{kg}$ of rFVIIa following a similar coagulopathy management protocol. However, McCall and colleagues [14] demonstrated higher morbidity and mortality rates despite using a similar dosing and threshold management strategy. Two other studies [11, 12] also had higher morbidity and mortality rates associated

with rFVIIa use in high-risk cardiac surgery patients that may be explained by variability in dosing [12] or inadequate blood product replacement at the time of rFVIIa administration [11].

Despite the development of the above criteria, the "trigger" for factor VII administration is complicated and, practically speaking, depends on factors that include but are not limited to the above four criteria. For example, during treatment of the patient after weaning from bypass, the body temperature may begin to fall owing to lack of or ineffective rewarming combined with nonnormothermic blood product administration, and thus negatively impacts on the coagulation system. Also, administration of large volumes of blood products can cause cardiac and systemic edema and begin to interfere with the ability to ventilate and oxygenate the patient. These occurrences may mandate administration of rFVIIa before all four criteria are satisfied, as illustrated in this report. As such, it is difficult to develop a concrete algorithm for rFVIIa administration, but rather to use the above four criteria in conjunction with other less definable clinical conditions in the decision-making process in this difficult patient population. Recent studies have shown that rFVIIa reverses thromboelastographic abnormalities, reflecting effects of rFVIIa on the physical properties of the clot not detectable by standard coagulation tests [9]. Also, thromboelastography has been used to show that rFVIIa exerts similar effects on anticoagulation brought about by different agents, including heparin, enoxaparin, fondaparinux, argatroban and bivalirudin [26]. Hence, platelet function testing may prove useful in both directing the decision to use rFVIIa and in monitoring treatment success after administration of the agent.

Delayed chest closure may be required in cases where cardiac dysfunction or severe cardiac edema from long bypass runs may prevent apposition of the sternum. However, refractory coagulopathy intraoperatively may also result in the inability for primary chest closure. That may occur secondary to continued coagulopathy requiring frequent chest reexploration or incapability for chest closure due to extreme tissue swelling and edema from excessive blood product replacement [5, 7]. That may result in the need for the chest to remain open with temporary sterile coverage for several days before primary closure of the sternum. With the introduction of rFVIIa to our practice, analysis revealed that delayed sternal closure requirements were significantly higher in the pre-rFVIIa era versus the rFVIIa era. Use of rFVIIa in these patients, while expensive (as much as \$10,000 per dose in larger patients) may reduce overall hospital costs through avoidance of delayed sternal closure; this possibility requires further study. However, reoperation for bleeding and operative death were not significantly different between the two eras. That rFVIIa administration did not modify reexploration rates over time could be explained by reexploration for complications such as tamponade or hemothorax or requirement for surgical repair of specific bleeding sites, all of which would not be manageable with pharmacologic therapy alone.

After rFVII administration, a statistically significant

decrease in the need for all blood products was demonstrated in our series. This finding has also been observed in previous studies assessing blood product requirements before and after rFVIIa administration after high-risk cardiac surgery [10, 11, 13, 14]. Recombinant factor VIIa administration to 6 patients in the ICU after surgery in our study resulted in a significant reduction in chest tube output in all and avoidance in the need for reexploration in 5 of the 6 patients. Previous studies evaluating chest tube output also demonstrated a significant reduction after rFVIIa administration [11, 12]. As noted in three other trials assessing rFVIIa use in high-risk cardiac surgery patients, our study also demonstrated a significant decrease in prothrombin time and international normalized ratio values when given rFVIIa [10, 11, 14].

In-hospital mortality observed in our cohort of patients who received rFVIIa after cardiovascular surgery was approximately 8.3%, which is consistent with results observed in two previous studies evaluating rFVIIa use in high-risk cardiac surgery patients [10, 13]. However, other studies in this population have reported mortality rates ranging between 19% and 29% [11, 12, 14].

The incidence of thrombosis in our cohort of patients was approximately 11.1% after rFVIIa use. The incidence of thrombotic complications after rFVIIa administration ranged between 0% to 25% in previous high-risk cardiac surgery studies [9–12, 14]. The potential role rFVIIa may have played in the incidence of thrombosis is difficult to determine because of other confounding variables that coexist in our high-risk series, such as the use of aprotinin, the existence of other comorbid conditions, and the development of refractory coagulopathy requiring excessive blood product replacement. In our analysis comparing patients in the rFVIIa era who received rFVIIa versus those who did not receive rFVIIa, there was no significant difference in the incidence of the combined endpoint of thrombosis. This is consistent with results found by Karkouti and colleagues [13], demonstrating no associated risk of adverse events after adjustment for confounders. However, the lack of significance in our series may reflect inadequate statistical power. Larger, prospective trials evaluating this agent are warranted.

Renal failure postoperatively was observed in 6 patients receiving rFVIIa in our series, of whom 3 recovered before hospital discharge. Within the rFVIIa era, there was a higher incidence of renal failure and dialysis requirements in patients who received rFVIIa versus those who did not. It is important to note, however, that within this era, 9 of the 35 patients (26%) receiving rFVIIa had a history of renal failure, while 43 of 385 (11%) not receiving rFVIIa had this risk factor ($p = 0.019$). While this may provide some explanation for the increased observation of renal failure with rFVIIa use, it does not completely discount the possibility of adverse renal effects with this agent. A previous study done by Karkouti and colleagues [24] demonstrated an increased incidence of renal dysfunction after rFVIIa administration. The authors attributed this finding to their inability to fully match patients for confounders such as the amount of perioperative blood transfusion. In this series, excluding

those patients with a history of renal failure, the 6 rFVIIa patients who went into renal failure received 25 ± 25 units of blood in comparison with 9 ± 5 units in the 20 rFVIIa patients who did not go into renal failure ($p = 0.003$). Another important potential determinant of renal failure in this series is use of aprotinin; it is possible that decreased use of aprotinin may modify the frequency of renal failure observed with rFVIIa use.

Finally, an increased incidence of pneumonia was demonstrated in the rFVII era. This finding has not been shown in other reports and its cause is unclear. An effect of rFVIIa cannot be discounted; however, it is possible the rFVIIa patients had more respiratory compromise from excessive blood and product transfusions predisposing them to impaired respiratory clearance. Whether rFVIIa administration is directly related to the development of pneumonia, acute renal failure, or other thrombotic events in patients with refractory coagulopathy after high-risk cardiac surgery requires further study.

Several important limitations to this study exist. First, owing to the retrospective nature and the small sample size of this case series, most findings should be viewed as associative rather than causative, and provide the template for larger prospective evaluations of this agent. Second, historical control groups were used for comparison based on the complexity of the primary operation, and as such, the inability to fully match patients may have led to potential confounders such as differences in transfusion of blood products. Although a prospective, randomized trial comparing treatment with rFVIIa versus no treatment would be difficult to conduct, it would nevertheless be helpful to fully assess the safety and efficacy of rFVIIa in high-risk cardiac surgery patients. Diprose and colleagues [27] randomly assigned high-risk cardiac surgery patients to receive either rFVIIa or placebo immediately after cardiopulmonary bypass and reversal of heparin. Recombinant factor VIIa significantly reduced the need for allogeneic transfusion without causing adverse events [27]. Despite the limitations of a small sample size and lack of a transfusion protocol, this study suggests that early use of rFVIIa in patients at high-risk for refractory coagulopathy may be beneficial. Further studies of this are warranted.

In conclusion, rFVIIa appears to be effective, and may modify treatment strategies in patients with refractory coagulopathy undergoing high-risk cardiovascular surgery. At this time, we consider rFVIIa to be an important tool in our armamentarium for the treatment of refractory coagulopathy in this population. Future studies are required to refine patient selection, dosing and timing of administration, and adverse event profiles.

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DISCUSSION

DR MARC MOON (St. Louis, MO): Thanks, John, that was a great talk as always, and I have got to commend you on your efforts to turn an anecdotal experience into scientific data and analysis. Anyway, we have the same anecdotal experience at Wash University, and we have been generally pleased so far with our use of NovoSeven; however, we tried it once on a patient with extracorporeal membrane oxygenation (ECMO) and the results were dismal. So my first question is, do you have any patient subgroups in which you recommend that we don't use NovoSeven?

Secondly, I think almost all of your patients, or nearly all of them, were on aprotinin, and now with the recent fall from glory of aprotinin, do you see an increased use for NovoSeven or are you going to try some other avenue to replace that drug?

And finally, NovoSeven, as you said, is an expensive agent, but while you and I will realize that decreasing operating room time by 2 or 3 hours or preventing a redo is great, it is hard to convince an administrator that those virtual costs are equivalent to the hard costs they have to pay for the drug. Are you planning on doing anymore hard cost analysis or do you have any

potential avenues we may be able to go down in order to increase third-payer payments for this agent? Thanks again.

DR IKONOMIDIS: Thanks, Mark. I appreciate your questions. There are some subgroups in which there could be concern. Certainly ECMO is one of the subgroups. Patients on ventricular assist devices who have bleeding postoperatively also are potentially a subgroup in which one might be cautious about administering factor VII. We have utilized the agent in this situation but usually used quarter doses and half doses and gone very carefully, monitoring for new fibrin deposits. Another potentially tenuous situation is after composite root replacement with a mechanical valve, the concern being that administration of factor VII, might cause thrombosis of the valve. At the present time, however, we really haven't seen any unusual thrombotic events that are directly attributable to the use of this agent.

You mentioned the potential expanded use of NovoSeven, especially with the removal of aprotinin from clinical use, and I think your statement is valid. I think that it may prove now to be a more commonly used agent in the setting of intractable

hemorrhage. For those of you in the audience who have used it, I think you will agree, sometimes the results are just remarkable.

And finally, you talked about third-payer reimbursement, and it is possible to get some reimbursement in certain cases. For example, in Medicare patients, the use of factor VII may be reimbursed as an add-on payment to the diagnosis-related group if you link it to certain *International Classification of Diseases-9* codes, for example, 286.5, which is hemorrhagic disorder due to circulating anticoagulants, or the more commonly used 286.7, which is acquired coagulation factor deficiency, which is probably appropriate here. In these situations, Medicare will reimburse at approximately \$1.16 per microgram. Hence, if you do the math, you can get several thousands of dollars reimbursement in those patients. For private carriers, the reimbursement really depends on the carrier, and for Medicaid and self-pay, there is no reimbursement.

DR JOHN W. HAMMON (Winston-Salem, NC): Thank you very much. I rise to give more anecdotal data. The experience of VIIa in our institution resulted in two cases of massive thrombosis, and under the advice of our pharmacy and hematology service, we switched to another product called Bebulin. This is a mixture of lower concentrations of factor VIIa, factor IX, and factor XI, and have achieved what we feel is good results without major complications, although, as I say, this is anecdotal information. Another piece of good news, it is about half as expensive.

DR IKONOMIDIS: Thank you. Certainly the literature, which has quite a few reports now of factor VII in cardiac surgery, has thankfully not reported a high incidence of massively devastating thrombotic events, but, as you stated, there is still a concern.

DR L. HENRY EDMUNDS (Philadelphia, PA): Bleeding in cardiac surgery has been as old as the specialty, but we have to think of mechanisms. What factor VIIa does is increase the circulating amount of factor VIIa recombinant to about 15 in micrograms percent rather than 1, which is normal. Now, the key thing is tissue factor. With a surgical wound, you have a lot

of cellular tissue factor, but you also have an awful lot of plasma tissue factor, much higher than the normal 1 to 3 picomolar. So that when you give the factor VII, the plasma tissue factor with monocytes are probably activating the clotting mechanism.

Now, you all are flying blind most of the time in these cases. What you need to know is F1.2 and D-dimer so that you can then treat the fibrinolysis and also the thrombin formation as you are dealing with these cases. The laboratory can do these things but they are expensive, and you have got to lean on your laboratories to get the data, because these patients are really expensive and they are very sick, but if you know what you are doing, then you have a better chance of saving them.

DR IKONOMIDIS: Thank you, Dr Edmunds. Many of these patients were transplants and dissections that were done in the middle of the night. Sometimes it is not possible to get D-dimer and other sorts of complex hematologic analyses that would help to direct your therapy as stated. And the other point I would like to make is that we are talking about a situation now in which you have reversed the heparin, you have corrected all the coagulation abnormalities with blood products, the patient is normothermic, and you can't stop the bleeding. A lot of times, this agent is administered as a last-ditch effort before you pack off the mediastinum and invoke damage control. I think there is a lot more science that is required in terms of the mechanism of action of this agent and the directions for its use, and I admit that these are very early data regarding its use.

DR KIT V. AROM (Bangkok, Thailand): I enjoyed your talk very much, John. A simple question. Can you use more than two doses and how often?

DR IKONOMIDIS: Yes.

Dr Hammon discloses that he has a financial relationship with Bayer Pharmaceuticals.