

# Use of Recombinant Activated Factor VII for Bleeding Following Operations Requiring Cardiopulmonary Bypass\*

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Postoperative bleeding is a common complication following cardiothoracic surgical procedures requiring cardiopulmonary bypass (CPB). Serious bleeding complications requiring the administration of blood products, hemostatic drugs, and even repeat surgery are associated with considerable morbidity, mortality, and resource consumption. Therapy with recombinant activated factor VII (rFVIIa) may be an effective treatment strategy for patients with refractory bleeding. We report the successful use of rFVIIa for the treatment of intractable postoperative bleeding following aortic aneurysm repair in two patients with Marfan syndrome. In both patients, surgical reexploration was avoided, and the patients' clinical status was stabilized after the administration of rFVIIa. In one patient, hemostasis was rapidly achieved within minutes, whereas hemostasis occurred gradually over several hours in the second patient. Including our personal experience with the two cases, the use of rFVIIa has been reported in 20 patients who required CPB for cardiothoracic surgical procedures. Hemostasis was achieved in all patients. In 14 patients (70%), rapid hemostasis was achieved following a single dose of rFVIIa (mean dose, 57  $\mu\text{g}/\text{kg}$ ). In the remaining six patients, gradual hemostasis was achieved after a mean of 3.4 doses (mean cumulative dose, 225  $\mu\text{g}/\text{kg}$ ). Two patients (10%) were believed to have experienced thromboembolic complications after the administration of rFVIIa (one was fatal), and, in another patient, intracoronary thrombosis was suspected but was not confirmed. In patients experiencing postoperative bleeding complications that are refractory to treatment with blood products, hemostatic agents, and/or repeat surgery, the use of rFVIIa may be considered.

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**Key words:** cardiopulmonary bypass; extracorporeal support; postoperative bleeding; recombinant activated factor VII

**Abbreviations:** CPB = cardiopulmonary bypass; rFVIIa = recombinant activated factor VII

Postoperative bleeding is one of the most common complications following cardiopulmonary bypass (CPB) in patients undergoing cardiothoracic surgical procedures. Treatment strategies for postoperative bleeding include supportive care with volume resuscitation, the administration of blood products, pharmacologic intervention, and surgical reexploration. Massive hemorrhage requiring surgical reexploration occurs in about 6% of the patients and is associated

with considerable morbidity and mortality.<sup>1,2</sup> Surgical reexploration due to excessive bleeding has been associated with a threefold to fourfold increase in mortality and with multiple morbidities, including renal failure, sepsis, atrial arrhythmias, prolonged mechanical ventilatory support, and increased length of hospital stay.<sup>3</sup> Thus, safe and effective strategies to prevent and treat postoperative bleeding are crucial.

## LIMITATIONS OF CURRENTLY AVAILABLE PHARMACOLOGIC AGENTS

Blood products are often used to correct the anemia that ensues and to promote hemostasis. Fresh-frozen plasma, pooled platelets, and cryoprecipitates replenish clotting factors and other important mediators of the clotting cascade, and are helpful in restoring hemostasis. However, the administration of blood products in this setting has several limitations, including a relatively high rate of trans-

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fusion-related reactions and adverse effects as well as the potential for disease transmission. Consequently, various pharmacologic agents are used to achieve hemostasis in this setting, including protamine, aprotinin, aminocaproic acid, tranexamic acid, and desmopressin. Protamine effectively reverses the effects of heparin but is associated with several adverse effects, including hypotension, hypersensitivity reactions, and paradoxical anticoagulation with excessive doses.<sup>4</sup> Aprotinin is a serine protease inhibitor with potent antifibrinolytic effects and is often administered prophylactically to prevent bleeding complications in patients having vascular surgery.<sup>5</sup> However, routine prophylaxis is very costly, and aprotinin has been associated with hypersensitivity reactions, particularly with repeated exposure.<sup>5</sup> Aminocaproic acid and tranexamic acid are lysine analogues that bind to the lysine-binding site on plasminogen, inhibiting the conversion of plasminogen to plasmin and effectively inhibiting fibrinolysis.<sup>5</sup> However, when the administration of these drugs is delayed until after open heart surgery, they are of limited benefit compared to prophylactic administration perioperatively.<sup>5</sup> Last, desmopressin increases the release of von Willebrand factor from endothelial cells and increases the circulating levels of factor VIII, leading to more effective hemostasis.<sup>5-7</sup> However, many patients with severe postoperative bleeding are unresponsive to these drugs.

#### MECHANISM OF ACTION OF RECOMBINANT ACTIVATED FACTOR VII

Recombinant activated factor VII (rFVIIa) is a clotting factor that is commonly used to treat bleeding disorders in patients with acquired hemophilia. Because rFVIIa can initiate coagulation independent of factors VIII and IX, it is useful as treatment in patients with hemophilia A or B complicated by high-responding inhibitors. Coagulation is triggered locally at the site of vascular injury as rFVIIa binds with tissue factor, and activates factors IX and X to their active forms (*ie*, IXa and Xa), ultimately leading to thrombin generation and clot formation.<sup>5,6</sup> Given its local effects at the site of vascular injury, rFVIIa may have a role in achieving hemostasis in patients experiencing refractory postoperative bleeding complications.

#### RATIONALE FOR USE OF rFVIIa

The risk of serious postoperative bleeding complications for patients requiring CPB during cardiothoracic surgical procedures remains high. In these

patients, not only is morbidity and mortality increased, but also health-care utilization and costs are higher.<sup>1,2,8</sup> Postoperative bleeding in this setting is associated with an increased length of stay, increased use of blood products, and increased use of hemostatic agents to control bleeding.<sup>8</sup> Consequently, postoperative bleeding incurs an average incremental cost of \$3,866. In cases of refractory postoperative hemorrhaging requiring surgical reexploration, mortality is more than sevenfold higher (15.4%) and the additional cost is nearly \$10,000.<sup>8</sup>

Although the prophylactic use of hemostatic agents such as aminocaproic acid, tranexamic acid, and aprotinin are effective in reducing bleeding and the need for the transfusion of blood products, treatment options are limited when serious postoperative bleeding occurs. Since rFVIIa triggers hemostasis locally at the site of the vascular injury, it has a role in the management of patients with intractable bleeding. Its use as a hemostatic agent in nonhemophilic patients has been described in several cases of severe hemorrhage from disseminated intravascular coagulation,<sup>9</sup> as well as refractory postoperative bleeding following spinal fusion surgery,<sup>10</sup> total hip arthroplasty,<sup>11</sup> major abdominal surgery,<sup>12</sup> pelvic surgery,<sup>13</sup> neurosurgery,<sup>14</sup> and hysterectomy.<sup>15</sup>

#### PERSONAL EXPERIENCE

Our experience with rFVIIa in this setup consists of two patients (Table 1). Both patients had vasculopathies that were associated with Marfan syndrome. One patient presented with a chronic enlarging thoracoabdominal dissecting aneurysm, and the other with an ascending aortic root aneurysm. The first case was considerably more complex as the extent of aortic dissection extended from the distal aortic root to the infrarenal aorta and was complicated by dense adhesions from two prior surgeries. This patient experienced profound hemorrhaging (estimated blood loss, approximately 50 L) postoperatively that was refractory to a massive administration of blood products (approximately 140 U) and hemostatic drugs perioperatively. The use of rFVIIa (120  $\mu$ g/kg) had a dramatic effect on hemostasis. Within minutes of administration, the chest tube output decreased from nearly 1 L/h to < 100 mL/h (Fig 1, *top*, A). The need for blood products was substantially decreased (*ie*, only 1 U packed RBCs was necessary in the 10 h following administration), hemodynamics were stabilized, and surgical reexploration was avoided. The second patient who had been given rFVIIa following the repair of an aortic root aneurysm using hypothermic circulatory arrest had a more gradual response to the drug, despite repeated doses (Fig 1, *bottom*, B). Eventually, hemostasis was achieved after

**Table 1—Review of Cases Using rFVIIa for Refractory Bleeding in Patients Requiring CPB\***

Study/Year	Age/Gender	Surgery	Interventions to Achieve Hemostasis Prior to rFVIIa	Blood Products Used Prior to rFVIIa	rFVIIa Dose, $\mu\text{g}/\text{kg}$	Outcome
Aldouri et al <sup>16</sup> /2000	2.5 yr/M	Arterial switch operation, atrial septal defect closure, pulmonary artery construction	None within 48 h	PRBCs, Plts, 1 U; FFP, 1 U; EBL, 4.5 L	30	Rapid hemostasis and correction of coagulopathy within 1 h; blood loss at 4 h, 85 mL total
	73 yr/F	MVR, tricuspid valve repair	Surgical reexploration, none within 48 h	Conventional blood products	30	Rapid hemostasis and correction of coagulopathy within 1 h; blood loss decreased from 900 to < 50 mL/h
	48 yr/F	MVR, AVR, RVAD, intraaortic balloon pump	Surgical reexploration; none within 48 h	Conventional blood products	30	Rapid hemostasis and correction of coagulopathy within 1 h; blood loss decreased from 300 to < 100 mL/h; patient died on POD 3 due to heart failure
	66 yr/M	AVR, aortic root replacement	None within 48 h	Conventional blood products; EBL, 5 L	30	Rapid hemostasis and correction of coagulopathy within 1 h; blood loss decreased to < 70 mL/h allowing patient to come off CPB and chest closure to proceed
	48 yr/M	MVR, right aorta-ventricular fistula repair	None within 48 h	Conventional blood products; EBL, 8 L	30	Blood loss decreased to 300 mL in first postoperative hour and was negligible at 4 h; rapid correction of coagulopathy within 30 min
Hendriks et al <sup>17</sup> /2001	65 yr/M	Mitral and tricuspid valve repair	Protamine, aprotinin, tranexamic acid, surgical reexploration $\times$ 2	PRBCs, 30 U; 90 Plts, 30 U; FFP, 20 U	90	Rapid hemostasis and correction of coagulopathy; good recovery
Potapov et al <sup>18</sup> /2002	57 yr/F	BiVAD placement	Protamine, aprotinin, desmopressin, antithrombin III	PRBCs, 30 U; Plts, 4 U; FFP, 56 U	120 $\times$ 1 60 $\times$ 1	Bleeding decreased from > 1 L/h to 500 mL/h after first dose of rFVIIa; bleeding decreased to < 100 mL/h within 2 h of second rFVIIa dose, allowing closure of chest
von Heymann et al <sup>19</sup> /2002	65 yr/M	Redo CABG	Aprotinin, desmopressin, surgical reexploration	PRBCs, 9 U; Plts, 1 U; FFP, 6 U	50 $\times$ 2	Hourly chest tube output decreased by 50% after first rFVIIa dose and was reduced to 40 mL/h immediately after second dose 2 h later; patient extubated on POD 8 and discharged from ICU on POD 10
Kastrup et al <sup>20</sup> /2002	26 yr/M	AVR	Aprotinin	PRBCs, 3 U; Plts, 2 U; FFP, 4 U	40	Rapid hemostasis, cardiac enzyme levels were elevated on POD 1, necessitating emergent cardiac catheterization but no coronary pathology was identified; patient discharged from ICU on POD 2

**Table 1—Continued**

Study/Year	Age/Gender	Surgery	Interventions to Achieve Hemostasis Prior to rFVIIa	Blood Products Used Prior to rFVIIa	rFVIIa Dose, $\mu\text{g}/\text{kg}$	Outcome
Bui et al <sup>21</sup> /2002	56 yr/M	Repeat lung transplant requiring CPB and ECMO	Protamine, surgical reexploration, APCCs	Continued transfusion of blood components	$90 \times 1$ $55 \times 1$	Gradual hemostasis after each dose of rFVIIa, but bleeding persisted at a rate of approximately 300 mL/h necessitating administration of APCCs; several minutes into the APCC infusion patient developed cardiogenic shock and expired 20 min later from suspected massive intracardiac and ECMO thromboses
Naik et al <sup>22</sup> /2003	75 yr/F	Bioprosthetic AVR and supracoronary ascending aorta replacement	Protamine, desmopressin, aprotinin, surgical reexploration $\times 2$	PRBCs, 14 U; Plts, 15 U; FFP, 21 U	107	Bleeding decreased from 400–500 mL/h in preceding 11 h to only approximately 40 mL/h over next 12 h; patient was discharged home on POD 17
Tanaka et al <sup>23</sup> /2003	74 yr/F	MVR; Jehovah's witness	Protamine, aprotinin, surgical repair of left atriotomy tear	Cell saver	45	Rapid hemostasis and correction of coagulopathy allowing chest closure; postoperative bleeding: 200 mL at 4 h, 740 mL at 24 h; patient required prolonged ventilatory support but was discharged from the ICU on POD 20
	49 yr/M	MVR; Jehovah's witness	Protamine, aprotinin	None	60	Rapid hemostasis within 3 min, allowing chest closure; coagulopathy also improved; postoperative bleeding: 270 mL upon ICU arrival, decreased to approximately 55 mL/h, total of 1,090 mL at 24 h; patient discharged from ICU on POD 4
Tobias et al <sup>24</sup> /2003	4 mo/F	ASD repair	Protamine	Cryo, 2 U	70	Rapid hemostasis and correction of coagulopathy; rFVIIa repeated on POD 7 to rapidly correct recurrent coagulopathy prior to removal of transthoracic pulmonary artery catheter; patient discharged home on POD 21
Leibovitch et al <sup>25</sup> /2003	10 wk/F	AV canal repair	Tranexamic acid, protamine	PRBCs, Plts, FFP	$100 \times 4$ doses	Gradual hemostasis achieved, no additional blood products required; patient discharged from ICU on POD 4, discharged home on POD 7
Wahlgren and Swedenborg <sup>26</sup> /2003	62 yr/M	AAA repair	Protamine, tranexamic acid	PRBCs, 16 U, Plts, FFP, 22 U	80	Rapid hemostasis; discharged to rehabilitation facility after lengthy hospital course
Lucey and Myburgh <sup>27</sup> /2003	15 yr/M	Bilateral lung transplant	NA	NA	NA	Rapid hemostasis; cardiac tamponade developed due to large mediastinal thrombosis requiring surgical evacuation

**Table 1—Continued**

Study/Year	Age/Gender	Surgery	Interventions to Achieve Hemostasis Prior to rFVIIa	Blood Products Used Prior to rFVIIa	rFVIIa Dose, $\mu\text{g}/\text{kg}$	Outcome
Verrijckt et al <sup>25</sup> /2004	12 d/M	Arterial switch operation, arterial duct ligation, atrial septostomy closure; ECMO required postoperatively	Aprotinin, protamine, aminocaproic acid, surgical reexploration $\times 2$	PRBCs, 7.7 mL/kg/h; Plts, 4.1 mL/kg/h; FFP, 2.6 mL/kg/h	30	Rapid hemostasis and correction of coagulopathy; died on POD 11 due to persistent heart failure
DiDomenico et al/2004	51 yr/M	Thoracoabdominal aneurysm repair	Aprotinin, protamine, aminocaproic acid	PRBCs, 47 U, FFP, 47 U, Cryo, 36 U, Plts, 9 U	120	Rapid hemostasis and correction of coagulopathy; discharged to rehabilitation facility after lengthy hospital course; alive and well 1 year postoperatively
	28 yr/M	MVR, AVR, aortic root repair, reimplantation of coronary arteries	Aprotinin, protamine, desmopressin	PRBCs, 6 U; FFP, 4 U; Cryo, 10 U; Plts, 2 U; Cell saver, 4 L	100 $\times$ 3 doses	Gradual hemostasis; bleeding decreased significantly after aminocaproic acid initiation and third dose of rFVIIa; patient discharged home on POD 18 without complications

\*M = male; PRBC = packed RBC; Plt = platelet; FFP = fresh-frozen plasma; EBL = estimated blood loss; F = female; MVR = mitral valve replacement; AVR = aortic valve replacement; RVAD = right ventricular assist device; POD = postoperative day; BiVAD = biventricular assist device; CABG = coronary artery bypass graft; ECMO = extracorporeal membrane oxygenation; APCC = activated prothrombin complex concentrates; ASD = atrial septal defect; AV = atrioventricular; cryo = cryoprecipitate; AAA = abdominal aortic aneurysm; NA = not available.

three doses of rFVIIa were given and therapy with aminocaproic acid was initiated. Surgical reexploration was also avoided in this patient.

#### PUBLISHED WORLD EXPERIENCE

Including the two cases described herein, the use of rFVIIa has been reported in 20 patients with refractory bleeding following procedures requiring CPB or postoperative extracorporeal circulatory support (Table 1).<sup>16–28</sup> The patients who received rFVIIa ranged in age from 12 days to 75 years and included 13 male patients and 7 female patients. Six patients had undergone valve replacement and/or repair,<sup>16,17,20,23</sup> four patients had undergone valve replacement with aortic root repair/replacement,<sup>16,22</sup> two patients had undergone arterial switch operations,<sup>16,28</sup> two patients had undergone lung transplant operations,<sup>21,27</sup> and two patients had undergone repair of an aortic aneurysm.<sup>26</sup> Additionally, repair of the atrioventricular canal,<sup>25</sup> placement of a biventricular assist device,<sup>18</sup> coronary artery bypass surgery,<sup>19</sup> and repair of an atrial septal defect were each performed in one patient.<sup>24</sup>

Successful hemostasis was achieved in all 20 patients who had received rFVIIa in this setting. Overall, in the 19 patients for whom dosing data were available, the patients received an average of 1.4 doses of rFVIIa, and the mean cumulative dose of rFVIIa was 101  $\mu\text{g}/\text{kg}$ . In 14 patients (70%), hemostasis was rapid (within the first hour of administration) after a single dose of rFVIIa (mean rFVIIa dose, 57  $\mu\text{g}/\text{kg}$ ). In the remaining patients, hemostasis was more gradual, over several hours, necessitating multiple doses of rFVIIa (mean number of rFVIIa doses, 3.4; mean cumulative dose of rFVIIa, 225  $\mu\text{g}/\text{kg}$ ).

#### PITFALLS AND RISKS OF rFVIIa USE

The use of rFVIIa is not without its pitfalls. The primary concern when administering rFVIIa for intractable hemorrhage after extracorporeal circulation is promoting a hypercoagulable state. Thrombotic adverse events have been reported<sup>29</sup> in 17 hemophilia patients who received rFVIIa between 1996 and 2001. It has been postulated<sup>30,31</sup> that bleeding after cardiac surgery is akin to disseminated intravascular coagulation and that activating the hemostatic system with rFVIIa in this setting may increase the risk of thromboembolic events. Indeed, 2 of the 20 patients (10%) who received rFVIIa following extracorporeal circulation experienced thromboembolic events, and such an event was suspected in a third patient.<sup>20,21,27</sup> Both

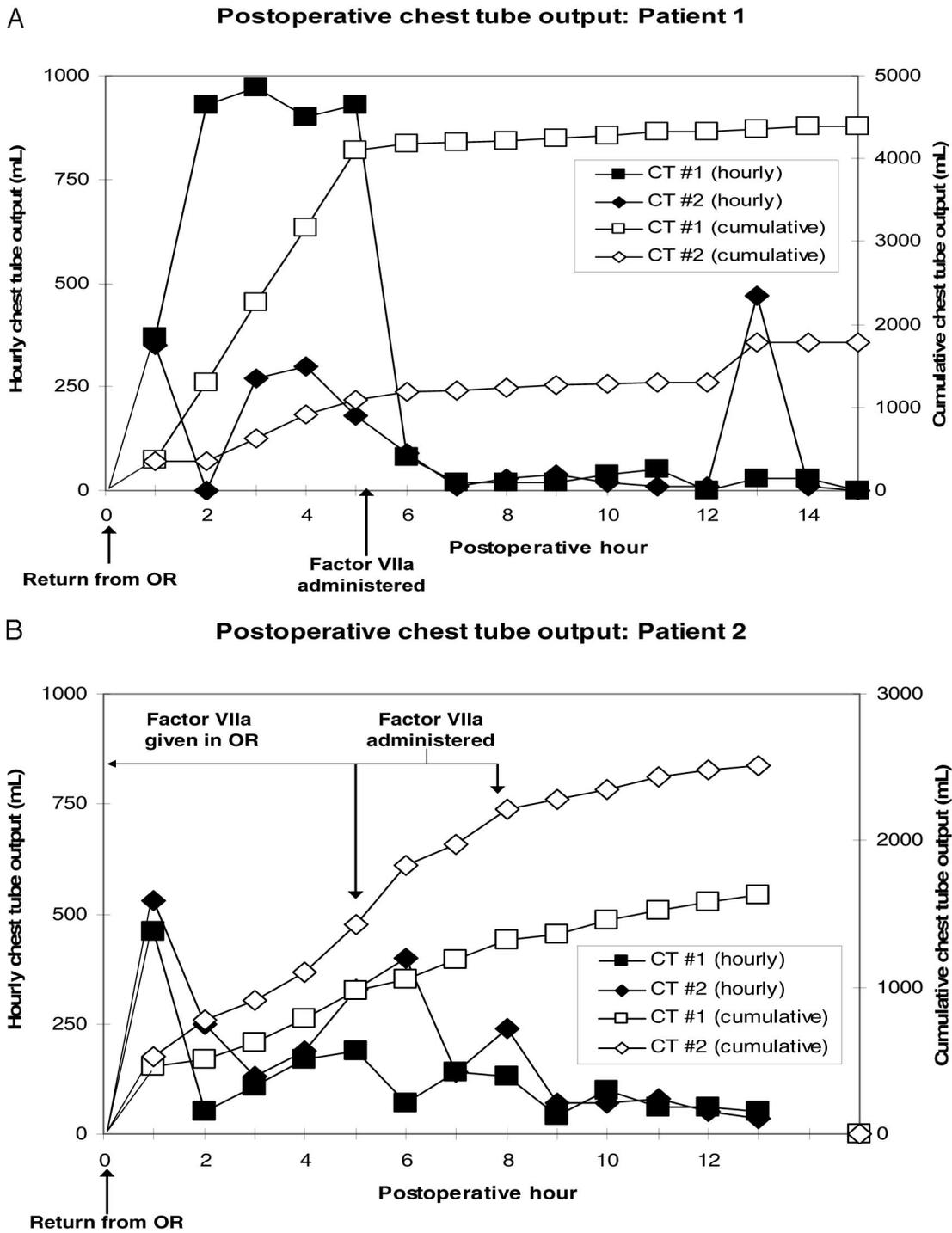


FIGURE 1. Preoperative chest tube (CT) drainage before and after administration of factor VIIa in two patients (top, A, and bottom, B) who underwent aortic operations. OR = operating room.

patients who developed thromboembolic events hemorrhaged following lung transplantation.<sup>21,27</sup> One patient was believed to have experienced massive intracardiac and extracorporeal membrane oxygenation circuit thromboses following the administration of both rFVIIa and activated prothrombin complex concen-

trates; this patient developed cardiac arrest and died.<sup>21</sup> The other patient developed cardiac tamponade requiring surgical intervention to evacuate a large mediastinal thrombosis following rFVIIa administration.<sup>27</sup> In the third patient, cardiac enzyme levels were elevated on postoperative day 1, and coronary thrombosis

was suspected, but coronary angiography failed to reveal any coronary pathology.<sup>20</sup>

The other concern regarding the use of rFVIIa in nonhemophiliac patients experiencing severe postoperative bleeding complications is cost. The acquisition cost for a 1.2-mg vial of rFVIIa is \$1,480.<sup>32</sup> When considering the use of rFVIIa in this setting, the cost of the drug must be weighed against the costs of nondrug therapy, including the administration of blood products and surgery. Given the high costs and adverse outcomes associated with the administration of blood products and surgical reexploration for bleeding complications, the administration of rFVIIa may be a cost-effective treatment strategy in certain instances.

### CONCLUSIONS

Serious bleeding complications following cardiothoracic surgical procedures requiring extracorporeal circulation remain troublesome. Effective treatment strategies are lacking. Although the successful use of rFVIIa in such instances has been reported in 20 patients to date, its use in this setting has not been studied in a controlled clinical trial. Therefore, the safety and efficacy of rFVIIa for the treatment of bleeding complications following cardiothoracic surgical procedures requiring CPB cannot be fully elucidated until it has been evaluated formally in a clinical trial. Nevertheless, anecdotal reports have suggested that it is effective in achieving rapid hemostasis. For patients with postoperative bleeding that is refractory to blood product administration and hemostatic drugs, therapy with rFVIIa may be considered as a treatment option. Although the dose of rFVIIa is truly unknown, an initial dose of approximately 60 µg/kg may be appropriate. If hemostasis is not achieved within 30 to 60 min, consideration may be given to a second dose; however, the cost-effectiveness of repeated dosing is questionable given the limited number of experiences reported to date.

### REFERENCES

- 1 Dacey LJ, Munoz JJ, Baribeau YR, et al. Re-exploration for hemorrhage following coronary artery bypass grafting: incidence and risk factors. *Arch Surg* 1998; 133:442–447
- 2 Unsworth-White MJ, Herriot A, Valencia O, et al. Re-sternotomy for bleeding after cardiac operation: a marker for increased morbidity and mortality. *Ann Thorac Surg* 1995; 59:664–667
- 3 Moulton MJ, Creswell LL, Mackey ME, et al. Re-exploration for bleeding is a risk factor for adverse outcomes after cardiac operations. *J Thorac Cardiovasc Surg* 1996; 111:1037–1046
- 4 Park KW. Protamine and protamine reactions. *Int Anesthesiol Clin* 2004; 42:135–145
- 5 Porte RJ, Leebeek FWG. Pharmacologic strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002; 62:2193–2211
- 6 Dahlbäck B. Blood coagulation. *Lancet* 2000; 355:1627–1632
- 7 Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost* 2003; 1:682–689
- 8 Herwaldt LA, Swartzendruber SK, Zimmerman MB, et al. Hemorrhage after coronary artery bypass graft procedures. *Infect Control Hosp Epidemiol* 2003; 24:44–50
- 9 Moscardo F, Perez F, de la Rubia J, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001; 113:174–176
- 10 Tobias JD. Synthetic factor VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. *Anesthesiology* 2002; 96:1522–1525
- 11 Slappendel R, Huvers FC, Benraad B, et al. Use of recombinant factor VIIa (NovoSeven) to reduce postoperative bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenia. *Anesthesiology* 2002; 96:1525–1527
- 12 Svartholm E, Annerhagen V, Toste L. Treatment of bleeding in severe necrotizing pancreatitis with recombinant factor VIIa [letter]. *Anesthesiology* 2002; 96:1528
- 13 Danilos J, Goral A, Paluszkiwicz P, et al. Successful treatment with recombinant factor VIIa for intractable bleeding at pelvic surgery. *Obstet Gynecol* 2003; 101:1172–1173
- 14 Park P, Fewel ME, Garton HJ, et al. Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients. *Neurosurgery* 2003; 53:34–39
- 15 Boehlen F, Morales MA, Fontana P, et al. Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: case report and review of the literature. *BJOG* 2004; 111:284–287
- 16 Aldouri M, Shafi T, Alkhudairi E, et al. Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinolysis* 2000; 11(suppl):S121–S127
- 17 Hendriks HGD, van der Maaten J, de Wolf J, et al. An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. *Anesth Analg* 2001; 93:287–289
- 18 Potapov EV, Pasic M, Bauer M, et al. Activated recombinant factor VII for control of diffuse bleeding after implantation of ventricular assist device. *Ann Thorac Surg* 2002; 74:2182–2183
- 19 von Heymann C, Hotz H, Konertz W, et al. Successful treatment of refractory bleeding with recombinant factor VIIa after redo coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2002; 16:615–616
- 20 Kastrup M, von Heymann C, Hotz H, et al. Recombinant factor VIIa after aortic valve replacement in a patient with osteogenesis imperfecta. *Ann Thorac Surg* 2002; 74:910–912
- 21 Bui JD, Bespotis GD, Trulock EP, et al. Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. *J Thorac Cardiovasc Surg* 2002; 124:852–854
- 22 Naik VN, Mazer CD, Latter DA, et al. Successful treatment using recombinant factor VIIa for severe bleeding post cardiopulmonary bypass. *Can J Anaesth* 2003; 50:599–602
- 23 Tanaka KA, Waly AA, Cooper WA, et al. Treatment of excessive bleeding in Jehovah's witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology* 2003; 98:1513–1515

- 24 Tobias JD, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. *Pediatr Crit Care Med* 2003; 4:49–51
- 25 Leibovitch L, Kenet G, Mazor K, et al. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. *Pediatr Crit Care Med* 2003; 4:444–446
- 26 Wahlgren CM, Swedenborg J. The use of recombinant activated factor VII to control bleeding during repair of suprarenal abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2003; 26:221–222
- 27 Lucey MA, Myburgh JA. Recombinant activated factor VII for exsanguinating hemorrhage post bilateral lung transplantation for extra-corporeal lung support-dependent respiratory failure. *Anaesth Intensive Care* 2003; 31:465–469
- 28 Verrijckt A, Proulx F, Morneau S, et al. Activated recombinant factor VII for refractory bleeding during extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg* 2004; 127:1812–1813
- 29 Erhardtson E. Ongoing NovoSeven trials. *Intensive Care Med* 2002; 28(suppl):S248–S255
- 30 Dietrich W, Spannagl M. Caveat against the use of activated recombinant factor VII for intractable bleeding in cardiac surgery. *Anesth Analg* 2002; 94:1369–1370
- 31 von Heymann C, Ziemer S, Kox WJ, et al. Caveat against the use of FEIBA in combination with recombinant factor VIIa. *J Thorac Cardiovasc Surg* 2003; 126:1667–1668
- 32 Medical Economics Co. 2003 drug topics red book. Montvale, NJ: Medical Economics Co., 2003