Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery

[Évaluation du facteur VIIa pour contrer les saignements rebelles au traitement traditionnel qui suit une intervention chirurgicale cardiaque complexe]

Peter McCall MBBS FANZCA, David A. Story MD FANZCA, Darshi Karapillai MBBS

Purpose: There are an increasing number of anecdotal reports and trials of recombinant activated factor VII (rFVIIa) for bleeding during surgery. The reports of rFVIIa during cardiac surgery are limited. We report our experience using rFVIIa, in the operating room; to treat bleeding that prevented chest closure, despite appropriate conventional treatment, following complex cardiac surgery.

Methods: Retrospective chart review, at an Australian University hospital and associated private hospital, of cardiac surgery patients given rFVIIa (usual dose 90 $\mu\text{g}\cdot\text{kg}^{-1}$). We used rFVIIa for bleeding that prevented closure of the chest despite administration of blood products, protamine, and surgical attempts to secure hemostasis.

Results: Recombinant activated factor VII was administered on 55 occasions to 53 patients. Most patients had complex aortic or valve surgery. Median bypass time was 266 min. Before administering rFVIIa, patients received (median): packed red cells four units; platelets 15 units; fresh frozen plasma eight units; and cryoprecipitate ten units. After administering rFVIIa the median doses of donor blood products up to 12 hr after intensive care unit admission were: packed red cells one unit; platelets zero units; fresh frozen plasma zero units; and cryoprecipitate zero units. The decrease in doses of all blood products was significant ($P < 0.001$). We could not determine if rFVIIa played a role in significant mortality (19%) and morbidity (17%).

Conclusion: Use of rFVIIa in cardiac surgery may be effective, but definitive clinical trials are needed to clarify its role in clinical practice and safety. We present an rFVIIa guideline developed during the audit period.

Objectif : Un nombre croissant d'articles et d'essais isolés traitent du facteur VII recombinant activé (rFVIIa) utilisé contre les saignements chirurgicaux. Peu d'articles mentionnent le rFVIIa pendant la chirurgie cardiaque. Nous présentons son utilisation en salle d'opération pour contrer les saignements qui entravent la fermeture du thorax malgré le traitement approprié habituel suivant une opération cardiaque complexe.

Méthode : Une revue rétrospective a été faite des dossiers des patients de chirurgie cardiaque, d'un hôpital universitaire australien et d'un hôpital privé associé, qui ont reçu une dose habituelle de 90 $\mu\text{g}\cdot\text{kg}^{-1}$ de rFVIIa. L'usage du rFVIIa visait à contrer les saignements qui surviennent malgré les produits sanguins et la protamine administrés et des tentatives chirurgicales pour assurer l'hémostase.

Résultats : Le rFVIIa a été administré à 55 reprises chez 53 patients qui ont subi, en majorité, une opération aortique ou valvulaire complexe avec une CEC d'une durée moyenne de 266 min. Les patients ont d'abord reçu en moyenne : quatre unités de culots globulaires, 15 unités de plaquettes, huit unités de plasma frais congelé et dix unités de cryoprécipité. Après le rFVIIa, la moyennes des produits sanguins administrés jusqu'à 12 h après l'arrivée à l'unité des soins intensifs a été de : une unité de culot globulaire, aucune unité de plaquettes, de plasma frais congelé et de cryoprécipité, donc une diminution significative ($P < 0,001$). Un rôle possible du rFVIIa dans les taux significatifs de mortalité (19 %) et de morbidité (17 %) n'a pu être déterminé.

Conclusion : Le rFVIIa en chirurgie cardiaque peut être efficace, mais des études cliniques approfondies devront clarifier son rôle dans une pratique clinique sûre. Nous présentons une ligne de conduite concernant le rFVIIa, élaborée pendant la période d'évaluation.

From the Department of Anaesthesia, Austin Health, Heidelberg, Victoria, Australia.

Address correspondence to: Dr. Peter McCall, Dept of Anaesthesia, Austin Hospital, Studley Rd, Heidelberg, Victoria, 3084, Australia. Phone: 61 3 9496 5704; Fax: 61 3 9459 6421; E-mail: peter.mccall@austin.org.au

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RECOMBINANT activated factor VII (rFVIIa) was introduced to manage bleeding and surgery in patients with congenital hemophilia with antibodies to transfused factor VIII or IX and acquired hemophilia with auto-antibodies.^{1,2} Because of its mechanism of action there has been a rapidly expanding interest in using rFVIIa to manage other types of acquired bleeding in major surgery including cardiac surgery.² Fewer than 200 cases of rFVIIa utilization in cardiac surgery have been reported in the peer-reviewed literature²⁻⁸ up to January 2006. The policy at our hospital has been to use rFVIIa in the operating room only when bleeding has prevented closure of the chest despite adequate conventional treatment, both at primary surgery and re-exploration. This policy aims to avoid the use of rFVIIa when bleeding is associated with inadequate surgical hemostasis. In other reported series, rFVIIa was administered as rescue therapy in the intensive care unit (ICU) after surgery,⁷ or in the ICU and (less frequently) in the operating room.³⁻⁶ In the only randomized trial in cardiac surgery, a small pilot study, rFVIIa was administered in the operating room as prophylaxis.⁸

We present an audit from a major Australian hospital of 53 patients who received rFVIIa³ for bleeding in complex cardiac surgery that continued despite administration of blood products, heparin reversal and surgical attempts to secure hemostasis.

Methods

This audit was conducted at the Austin Hospital and Warringal Private Hospital. The Austin Hospital is a tertiary referral public hospital affiliated with The University of Melbourne. Warringal Private Hospital is located nearby and has shared anesthesia, surgical and intensive care teams. The Human Research Ethics Committee from Austin Health (which also covers Warringal Private Hospital) approved this study. Because this study was an effectiveness audit of clinical use of rFVIIa the Human Research Ethics Committee waived the need for informed consent from individual patients.

We conducted a retrospective audit of the charts of patients who had undergone cardiac surgery and who received rFVIIa (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark). Patient care during surgery was at the discretion of the individual anesthesia, perfusion, and surgical teams. All but one of the 53 patients was assessed, preoperatively, as at high risk of perioperative bleeding and received antifibrinolytics: 45 received aprotinin (2 million units load, 2 million units in bypass circuit, 500,000 units-hr⁻¹

infusion), four received tranexamic acid (10 mg·kg⁻¹ load, 2 mg·kg⁻¹ in bypass circuit, 5 mg·kg⁻¹·hr⁻¹ infusion), three received aminocaproic acid (5 g load, 5 g in bypass circuit, 1 g·hr⁻¹ infusion), and two received aminocaproic acid and aprotinin. In Australia, during the audit period, the manufacturer withdrew aminocaproic acid and tranexamic acid had limited availability.

Anesthetic techniques comprised a variety of drugs, including propofol, fentanyl, isoflurane, and sevoflurane, often in combination. Patients were anticoagulated with approximately 300 units·kg⁻¹ of heparin before bypass, aiming to provide a cellite activated clotting time of greater than 480 sec. After bypass, heparin was reversed with protamine titrated to an activated clotting time of less than 150 sec. Cardiopulmonary bypass used centrifugal pumps with 1800 mL prime of Plasmalyte (Baxter, Sydney, Australia). Both antegrade and retrograde blood cardioplegia were used. Cooling was passive to around 34°C, or active to 20°C during deep hypothermic arrest. Acid-base management was alpha-stat.

Transfusion of blood products was at the discretion of treating physicians although a more formal hospital guideline (Table III) was introduced during the second half of the audit period. Adherence to this protocol was encouraged but was not mandatory. Some patients still received transfusion in excess of the amount required for authorization to use rFVIIa. Packed red cells were administered depending on the degree of anemia. Platelets, fresh frozen plasma, and cryoprecipitate were administered in batches of four to five units. Laboratory investigations and or thromboelastography were used at clinician discretion. With the exceptions of thromboelastography, activated clotting time, and hemoglobin level, hematology assays were performed in a central laboratory rather than at point of care. The decision to administer rFVIIa was based largely on the assessment of the surgical, anesthesia, and perfusion teams that, despite apparently adequate conventional treatment, bleeding was at least severe enough to prevent chest closure. Authority to use rFVIIa (Table III) was given only if the patient in the operating room, either at primary operation or re-exploration, with his/her chest open, had surgical causes of bleeding rectified both before and after introducing the guideline. Surgeons graded the improvement in hemostasis after administration of rFVIIa as excellent, moderate, mild, or no response (non-responders). Details of adverse events were specifically sought from both the history and hospital discharge codes.

TABLE I Characteristics and operative course of 53 patients

Age (yr)	68 (IQR: 55 to 75)
Male, <i>n</i> (%)	35 (66%)
Type of surgery*, <i>n</i> (%)	
Aortic + valve	24 (44%)
Aortic	12 (22%)
Complex valve†	14 (25%)
Single valve	3 (5%)
Coronary grafts	2 (4%)
Bleeding risk factors, <i>n</i> (%)	
Deep hypothermic arrest	12 (22%)
Redo surgery	10 (18%)
Endocarditis	7 (13%)
Bypass time (min)	266 (IQR: 221 to 346)
Lowest bypass temperature (°C)	29.6 (IQR: 22.1 to 31.8)
Re-exploration post rFVIIa, <i>n</i> (%)	
All	7 (13%)
Responders	3 (5%)
ICU ventilation (hr)	20 (IQR: 14 to 58)
ICU duration (days)	4 (IQR: 2 to 8)
Surgery to discharge time (days)	10 (IQR: 7 to 20)

IQR = interquartile range; rFVIIa = recombinant activated factor VII; ICU = intensive care unit. *Two patients received rFVIIa twice for two stage aortic surgery. †Multiple valves and/or endocarditis

TABLE II Hematology before and after rFVIIa

Variable*	Before	After	Reference range
Prothrombin time (sec)	17.5 (12.0–22.0)	11.5 (8.7–13.0)	11–15
INR	1.4 (1.2–1.8)	1.0 (0.8–1.2)	0.9–1.2
aPTT (sec)	55 (38–71)	52 (35–68)	25–38
Fibrinogen (g·L ⁻¹)	3.1 (2.2–4.1)	3.1 (2.3–3.4)	2.0–4.0
Platelets (<i>n</i> × 10 ⁹ ·L ⁻¹)	139 (108–169)	136 (112–150)	150–400
Hemoglobin (g·L ⁻¹)	85 (73–92)	87 (83–94)	115–180

rFVIIa = recombinant activated factor VII; INR = international normalized ratio; aPTT = activated partial thromboplastin time; *Median (interquartile range).

Statistical analysis

The primary endpoint in the audit was use of blood products before and after administering rFVIIa.^{5,9} We used GraphPad Prism Version 4 software (GraphPad Software, San Diego, CA, USA). Data were tested for normality, and because the majority of data sets did not pass normality, non-parametric statistics were applied. Data are expressed as medians with the range or interquartile (25% to 75%) range. Wilcoxon rank sign and Mann-Whitney U tests were used to compare variables. Spearman correlation was performed between time to rFVIIa administration and pre- and

post-transfusion requirements. A *P* value < 0.05 was considered statistically significant.

Results

Data were collected from 53 patients who received rFVIIa for bleeding after cardiopulmonary bypass for complex cardiac or thoracic aortic surgery (Table I). Patients were consecutive, and no patient was excluded from the analysis. Two patients had planned two-stage aortic repairs and received rFVIIa at two operations more than one month apart. The patients had surgery over a three-year period between December 2002 and August 2005. Six primary surgeons performed a total of 55 initial procedures. Thirty-nine (71%) patients received rFVIIa at primary sternotomy, 13 (24%) at second sternotomy (re-exploration), and two (4%) at third sternotomy. Three patients received rFVIIa at both primary sternotomy and at subsequent re-exploration for bleeding. Therefore, rFVIIa was given on a total of 58 occasions. The average dose was 90 µg·kg⁻¹ (standard deviation: 15 µg·kg⁻¹), rounded up to the nearest ampoule. Ten patients (19%) died in hospital (Table III) and nine survivors (17%) suffered major morbidity (Table IV).

Between the end of bypass and administering rFVIIa patients received the following median doses of donor blood products (Figure): packed red cells four units; platelets 15 units; fresh frozen plasma eight units; and cryoprecipitate ten units. Eight patients received washed red cells from a cell saver. Six patients received neither donor red cells nor cell saver blood. Adequacy of heparin reversal was monitored by frequent measurement of activated clotting time and administration of protamine as required. After administration of rFVIIa there was a marked reduction in blood product administration (Figure). The median doses of donor blood products after rFVIIa, up to 12 hr after ICU admission were: packed red cells one unit; platelets zero units; fresh frozen plasma zero units; and cryoprecipitate zero units. The reduction in dose of blood products was significant for each type of blood product (*P* < 0.001, Figure). Overall, patients received 34 units of blood products [interquartile range (IQR): 26–37 units] before rFVIIa and two units afterwards (IQR: 0.5–9.5 units). This represented a median difference of 31 units [95% confidence interval (CI): 26–37 units, *P* < 0.001].

The six surgeons were asked to rate the improvement in hemostasis after rFVIIa administration. After 58 administrations of rFVIIa the improvement in hemostasis was graded as excellent in 11 (19%) cases, moderate in 35 (64%), mild in five (9%), and no apparent response in four (7%) administrations. All

TABLE III Austin Hospital rFVIIa cardiac surgery guideline

If bleeding persists after bypass

1. Exclude surgical cause.
2. Optimize physiology; particularly temperature, hemodynamics, and pH.
3. Consider antifibrinolytic therapy, if not already used.
4. Administer blood products up to:
 - a. Platelets: 5 units if < 70 kg, 10 units > 70 kg;
 - b. Cryoprecipitate: 1 unit/10 kg body weight;
 - c. Fresh frozen plasma: 5mL·kg⁻¹ (rounded to nearest unit).
5. Order coagulation and TEG studies.
6. If ongoing bleeding prevents chest closure:
 - Confirm with surgeon that the patient has reasonable chance of survival;
 - Contact director of anesthesia or director of medical perfusion for authority to use rFVIIa.
7. Optimize local surgical control of bleeding with swabs/packs. Reduce blood pressure to lower range acceptable for patient. Administer rFVIIa 90 µg·kg⁻¹ *iv*.
8. If bleeding continues despite rFVIIa
 - a. Exclude surgical cause
 - b. Check coagulation study and TEG results
 - c. Transfuse blood products as required
 - d. Remember dilutional coagulopathy and anemia now more likely.
 - e. If second rFVIIa is dose considered, repeat step 6.

rFVIIa = recombinant activated factor VII; TEG = thromboelastography.

four non-responders³ underwent surgical re-exploration. One patient had ongoing surgical bleeding requiring revision of his distal aortic anastomosis,

and one patient had evacuation of periaortic hematoma without ongoing bleeding being identified. The other two patients had ongoing microvascular bleeding. One responded to a second dose of rFVIIa and coagulation factors; the other did not respond to a second dose of rFVIIa and required further coagulation factors. This patient had a subsequent operation for control of bleeding.

The median time from the end of bypass to administration of rFVIIa was 102 min (IQR: 60–431 min). During the three-year audit period, the time from the end of bypass to administering rFVIIa decreased. For the first nine patients the median time to administration was 118 min (range: 60–1231 min); while for the last nine patients the median time was 74 min (range: 21–102 min). This represented a decrease of 44 min ($P = 0.03$). There was a moderately strong correlation between the length of time to administration of rFVIIa and the total amount of blood product administered before administering rFVIIa (spearman $r = 0.52$, $P < 0.001$). The rFVIIa guideline was introduced after 28 of the 53 patients had received rFVIIa. Comparing the first and last 20 patients there was a trend towards decreased blood product utilization before rFVIIa administration; the median blood product use in the first 20 patients was 40.5 units and in the last 20 patients was 30.5 units. This represented a median decrease of eight units, 95% CI: 16 unit decrease to one unit increase ($P = 0.096$). While the laboratory clotting profiles were not available when the decision to administer rFVIIa was made, the profiles were within 50% of the limits of the reference range⁵ in the

TABLE IV Mortality and morbidity

Patient	Primary surgery	Cause of death
4	Mitral + tricuspid repair	Multiorgan failure
14	Redo aortic homograft for endocarditis	Hypoxic brain injury
17	Redo mitral valve replacement for endocarditis	Septic shock
18	Repair ascending aortic aneurysm	Cardiogenic shock
21	Aortic valve replacement/ascending + arch aortic repair	Right heart failure
29	Mitral valve replacement for endocarditis + grafts	Multiorgan failure
30	Grafts + repair ruptured pulmonary artery	Air embolism
32	Third set grafts	Multiorgan failure
43	Aortic valve replacement	Cardiogenic shock
49	Repair descending aorta	Hypoxic brain injury
<i>Major morbidity</i>		
2	Thoracoabdominal aortic repair	Pulmonary embolism, day 6
6	Aortic homograft for endocarditis	Renal failure*
10	Ascending + arch aortic repair	Basal ganglia stroke
15	Mitral and aortic valve replacement, coronary grafts	Renal failure*
40	Aortic valve replacement and tricuspid repair	Respiratory failure
41	Redo mitral valve replacement	Multiorgan failure
42	Redo aortic valve replacement and tricuspid repair	Multiorgan failure
51	Ascending + arch + descending aortic repair	Cerebellar stroke

*Requiring renal replacement therapy.

FIGURE Blood product utilization

Box and whisker plot of blood product utilization before recombinant activated factor FVII administration (grey boxes) and for 12 hr after intensive care unit admission (white boxes). The boxes represent the 25% to 75% interquartile ranges, the lines in the boxes display median values, and the whiskers reflect ranges. The blood products were platelets (Plts), fresh frozen plasma (FFP), cryoprecipitate (cryo), and red blood cells (RBCs). The decrease in product use for each product type was significant ($P < 0.001$).

majority of patients (Table II). Both the prothrombin time and the related international normalized ratio decreased significantly after rFVIIa ($P < 0.001$). Other hematologic variables were unchanged (Table II).

After administering rFVIIa, the median time to chest closure was 60 min (IQR: 30–90 min). The median chest drainage one hour after arriving in the ICU was 100 mL (IQR: 50–255 mL). The median chest drainage at 12 hr after arriving in the ICU was 440 mL (IQR: 250–775 mL). Including the four non-responders, seven patients (12%) were returned to the operating room for re-exploration. Finally, overall outcomes are presented in Table IV. In this sample, 19% of patients died and 17% of the survivors experienced significant morbidity.

Discussion

We conducted an audit of the effect of rFVIIa, used in the operating room, at primary operation (71%) or re-exploration, on blood product requirements and apparent bleeding in 53 cardiac surgical patients. These cases involved complex cardiac procedures, with a risk of significant post bypass bleeding, based

on both the type of surgery and prolonged cardiopulmonary bypass (median 266 min). Further, half the patients were 70 yr or older, 12 patients (22%) underwent deep hypothermic cardiac arrest, and six patients (11%) had active endocarditis. Factor VIIa was used for bleeding that prevented chest closure despite administration of blood products, protamine and surgical attempts to secure hemostasis. We found rFVIIa effective in most cases.

Our finding of decreased blood product utilization after rFVIIa is consistent with other recent studies of rFVIIa use for bleeding after cardiac surgery.^{3,5,7} Further, as with these studies^{3,5,7} we found significant mortality and morbidity (Table IV), and were unable to distinguish possible side effects of rFVIIa from patient comorbidities and complications of the procedures. Unlike these studies,^{3,5,7} however, we had a policy of using rFVIIa in the operating room with the chest open rather than in the ICU,⁷ or both the operating room and the ICU.^{3,5}

The Australian drug regulator has yet to approve rFVIIa for bleeding in patients without hemophilia. However, in several Australian hospitals, including ours, rFVIIa has been used (“off label”)¹⁰ to treat bleeding in cardiac surgery unresponsive to conventional therapy. As experience with rFVIIa increased at our hospital, anesthesiologists and surgeons had fewer concerns regarding the safety and effectiveness of appropriate rFVIIa use in cardiac surgery. Further, we had growing concerns about the limitations and side effects of conventional therapy.^{11,12} Therefore, with the approval of the Austin Health Drugs and Therapeutics Committee, we developed a guideline for the use of rFVIIa in cardiac surgery (Table III) which was applied to the last 25 patients in this series. Our guideline has much in common with a recent Israeli guideline for rFVIIa use in uncontrolled bleeding, including trauma.¹³

Limited evidence to guide blood product utilization exists for cardiac surgery.^{14,15} The pathophysiology of post bypass bleeding, particularly in complex cardiac surgery, is incompletely understood, but appears to be multifactorial, with platelet dysfunction and decreased fibrinogen concentrations playing important roles.^{15–17} Australian transfusion guidelines¹⁴ suggest that cryoprecipitate may be indicated when bleeding is associated with decreased fibrinogen, and that fresh frozen plasma may be indicated for bleeding after cardiac surgery. Our guideline recommends platelet and cryoprecipitate transfusion in response to decreases in platelets and fibrinogen concentrations in lieu of using fresh frozen plasma alone.¹⁸ British¹⁹ and Israeli¹³ guidelines suggest that the platelet count should be at least $50 \times 10^9 \text{ L}^{-1}$

(reference range: $150\text{--}400 \times 10^9\text{L}^{-1}$) and fibrinogen $1\text{ g}\cdot\text{L}^{-1}$ (reference range: $2\text{--}4\text{ g}\cdot\text{L}^{-1}$).²⁰ To establish the effectiveness of conventional therapy we aim to achieve suggested platelet and fibrinogen targets^{13,19,20} (Tables II and III). A further advantage of giving adequate, but not excessive doses of blood products, is that when rFVIIa is administered, adequate circulating concentrations of platelets and clotting factors should be present to act as substrate for optimal rFVIIa effect.^{2,21} We found that delay in administration of rFVIIa was associated with patients receiving more blood products. Anecdotally, as each surgeon gained more experience with rFVIIa, the decision to administer rFVIIa was made earlier in relation to the timing of separation from cardiopulmonary bypass. This impression is supported by the finding that, on average, the last nine patients received rFVIIa 45 min earlier than the first nine.

Timely use of rFVIIa in the cardiac operating room for bleeding resistant to conventional therapy may prevent massive transfusion, and possibly reduce morbidity and mortality.^{11,22} One study of 50 medical and surgical patients found that rFVIIa was more effective in mild to moderate coagulopathy than severe coagulopathy.²³ If used, rFVIIa should be administered in a timely manner, not as a “last ditch option”.²³ At both our hospitals, coagulation studies are performed in central laboratories. Point-of-care measurements of hemoglobin concentrations and activated clotting time are available at both institutions, and thromboelastography at one (Austin). The central laboratory turnaround time for coagulation studies is too long (about 60 min) for these studies to guide decisions in the cardiac operating room. Therefore, the decision to administer rFVIIa was based upon clinical assessment that bleeding prevented chest closure, and that adequate blood component therapy had been given (Table III). However, retrospective analysis of the central laboratory tests (Table II) suggests that the majority of our patients fulfilled the clotting requirements for rFVIIa use of other groups using point-of-care coagulation testing.⁵ Further, significant bleeding after complex cardiac surgery requires prompt coagulation product transfusion, but often only limited red cell transfusion is required in contrast to situations such as trauma.²⁴ Therefore in cardiac surgery, unlike trauma, red cell use may not be an indicator of the severity of coagulation defect.^{3,13} If, however, a superimposed dilutional coagulopathy occurs due to inadequate surgical hemostasis, a situation similar to trauma, then red cell and volume replacement is required along with coagulation products.²⁵

In our series, patients received an initial dose of rFVIIa of about $90\text{ }\mu\text{g}\cdot\text{kg}^{-1}$, similar to that used in

most anecdotal reports.² Three patients received a second dose within 30 min because of inadequate clinical response. Response to administration varied. Some patients had a dramatic improvement in hemostasis; some patients had a moderate improvement that allowed for surgical closure to proceed both with and without additional coagulation factors. In some patients the resolution of coagulopathic bleeding revealed previously unidentified surgical bleeding. Four patients (7%) were considered non-responders on clinical grounds. This is similar to other reported series.³ A possible explanation for failure to respond to rFVIIa includes unrecognized surgical bleeding. There may also be varying dose requirements due to the degree of hemostatic challenge or dose-response between individuals. Some studies of patients with hemophilia demonstrate varying dose requirements between patients.¹ Some hemostatic lesions may be resistant to rFVIIa irrespective of dose.

The prophylactic use of rFVIIa has several potential problems: 1) lack of effectiveness; 2) possible side effects; and 3) cost. First, the effectiveness of prophylactic rFVIIa has been inconsistent in randomized trials in non-cardiac surgery.^{2,26,27} The only published randomized trial of prophylactic rFVIIa in cardiac surgery⁸ was a pilot study of 20 patients that found a significant reduction in transfusion associated with rFVIIa in the per-guideline analysis, but found that prophylactic rFVIIa use was not cost-effective. Second, possible side effects of rFVIIa include an increased risk of thrombosis^{2,10} and sepsis.^{10,28} Prophylactic use of rFVIIa may expose patients without coagulopathy to a higher incidence of these possible side effects. Third, the high cost of rFVIIa is a problem in many countries, including Australia. A $90\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ dose of rFVIIa costs approximately (AUS) \$100/kg of body weight. Given the current evidence, cost, and lack of regulatory approval, it is our view that rFVIIa be considered for the bleeding cardiac surgery patient only when conventional therapy appears to have failed.

This study has several limitations, including its retrospective nature, absence of a control group, heterogeneity of bleeding (ranging from persistent to life threatening) and a hemostatic endpoint which was subject to interpretation. Despite the limitations, given the clinical response, it appears that rFVIIa may be efficacious for refractory bleeding in cardiac surgery, including complex surgery with a significant bleeding risk. Recombinant factor VIIa may, however, be associated with complications which need to be weighed against the morbidity of escalating transfusion of blood products. The current role of rFVIIa is limited to the relatively rare situation in cardiac

surgery where bleeding persists despite conventional therapy.^{10,29} Our guideline (Table III) incorporates recommendations from existing guidelines (recognizing that evidence is limited)^{13,14,30} and our own clinical experience with use of rFVIIa. Further research is warranted to establish the optimal timing and dose of rFVIIa. Large international trials will be needed to determine the effects of rFVIIa on postoperative mortality, morbidity, and health care economics in the setting of cardiac surgery.

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