



## ADULT CARDIAC SURGERY:

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# Recombinant Activated Factor VII in Cardiac Surgery: Experience From the Australian and New Zealand Haemostasis Registry

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**Background.** Data from the Australian and New Zealand Haemostasis Registry (ANZHR) were used to report on the efficacy, mortality, and outcomes of a cohort of cardiac surgical cases receiving recombinant activated factor VII (rFVIIa).

**Methods.** The ANZHR collects retrospective and contemporaneous data on the use of rFVIIa in patients with critical bleeding from hospitals throughout Australia and New Zealand. Participating centers commit to the collection of data on all patients without hemophilia treated with rFVIIa, which limits bias and prevents the reporting of only positive or anecdotal experiences.

**Results.** At September 2006, the cardiac surgical cohort comprised 304 patients (43%) of a total of 695 cases reported to the ANZHR from 46 hospitals. The 304 cases date from January 2001. The median patient age was 66 years (interquartile range [IQR], 53 to 75 years), and 73% were men. After administration of rFVIIa, all blood product usage was significantly reduced. Patients received a median dose of 93  $\mu\text{g}/\text{kg}$  (IQR, 82 to 102), and 85% of patients received a single dose. The documented response rate to a single dose of rFVIIa was 84%, of which 23% reported cessation of bleeding and 61% reported a reduction in bleeding. Patients received a median volume of 6 U of red blood cells before rFVIIa treatment. The median reduction in red blood cells

after the rFVIIa dose compared with before was 4 U. Response was reduced in patients with a lower baseline hemoglobin, coagulopathy (determined by international normalized ratio, fibrinogen, and platelets), the number of red blood cell units transfused before rFVIIa, advanced age, more complex operations, hypothermia, and acidosis. Responders had a significantly reduced mortality ( $p < 0.001$ ). The percentage of patients alive at 28 days was 95% if bleeding ceased after rFVIIa, 86% if bleeding reduced, and 60% for nonresponders. A 7% adverse event rate attributed as "probably" or "possibly" associated with rFVIIa was reported with a 4% reported thromboembolic event rate.

**Conclusions.** Recombinant FVIIa is a potential rescue therapy in severe uncontrollable critical bleeding after cardiac operations. The observed response rate was high, and response was associated with improved mortality. There was an observed reduction in blood product usage after rFVIIa. The adverse event rate reported was similar to documented adverse event rates in complex cardiac surgical patients. In the absence of randomized controlled trials, this registry provides a basis for understanding current clinical practice with rFVIIa in cardiac surgical procedures.

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Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is effective for the prevention or treatment of bleeding in patients with coagulation inhibitors [1–3]. In Australia and New Zealand

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land, rFVIIa is licensed for this indication and congenital factor VII deficiency. It has been extensively used amongst patients with hemophilia [2, 3]. Its mechanism of action is complex, but the supraphysiologic levels of FVIIa can act in a tissue factor (TF)–dependent manner, forming TF:rFVIIa complexes at the site of injury, activating coagulation factors and platelets, and ultimately, the generation of a “burst” of thrombin and fibrin deposition, or to a lesser extent in a TF independent manner, by directly binding platelets and generating thrombin by direct activation of factor X [4, 5].

In recent years, an increasing number of case reports [6–8] and case series [9–15] have reported on the use of rFVIIa in salvage situations associated with persistent bleeding in cardiac operations. In many cases, control of critical bleeding is possible with surgical hemostasis and the replacement of blood products to support the underlying coagulopathy. In a small number of cases (< 3.5%) [16], this is not possible despite appropriate surgical intervention.

Patients with uncontrolled critical bleeding and coagulopathy have significant mortality, despite standard replacement of coagulation factors and surgical intervention [17, 18]. The transfusion of blood and blood products has been correlated with increased morbidity, including multiorgan failure, acute respiratory distress syndrome (ARDS), transfusion-related acute lung injury (TRALI), immune modulation, and infection [19, 20], as well as death [21]. This cohort of patients is often associated with increased costs to the health care system in the form of excessive blood and blood products and extended stays in the intensive care unit (ICU) and hospital [22, 23].

To date, reports of use of rFVIIa in cardiac surgical procedures are mostly case reports or series or retrospective chart reviews [24]. Only two randomized controlled studies have been published in cardiac surgery. The first was a pilot study that explored prophylactic use in adults undergoing complex cardiac operations [25], and the second examined prophylactic use in neonates [26]. Novo Nordisk is currently conducting a phase 2 randomized controlled study in adults, and an investigator-led study investigating salvage use of rFVIIa in complex cardiac operations is also ongoing.

Groups from both the United States [27] and Europe [28] have published recommendations on the use of rFVIIa in perioperative coagulopathic bleeding in cardiothoracic surgical procedures. Although some individual centers in Australia have described guidelines that are specific for cardiac surgery [14], consensus guidelines in Australia focus on the surgical management of persistent hemorrhage, the medical management of coagulopathy, and the salvage use of rFVIIa in general and are not specific for cardiac operations [29, 30]. Inadequate hemostasis in cardiac operations is inherently different (eg, due to cardiopulmonary bypass and the ability to directly observe the bleeding source) from other areas of critical bleeding, such as from trauma or obstetric bleeding, and thus requires a different approach [14].

The Australian and New Zealand Haemostasis Registry (ANZHR) was established by the Department of Epidemiology and Preventive Medicine at Monash University, Melbourne, Australia to collect information on patients without hemophilia treated with rFVIIa throughout Australia and New Zealand. The development of the ANZHR has enabled the systematic collection of data from a large cohort of patients undergoing cardiac operations complicated by critical bleeding and treated with rFVIIa. This article describes the safety, indications, dosing, reported efficacy, mortality and outcomes from cardiac surgical cases included in the Haemostasis Registry in the period January 2001 to September 2006 from institutions across Australia and New Zealand.

## Material and Methods

### *The Haemostasis Registry*

The Haemostasis Registry collects data from patients without hemophilia treated with rFVIIa at participating hospitals throughout Australia and New Zealand. The Haemostasis Registry has been established by Monash University, Melbourne, Australia with financial support in the form of an unrestricted educational grant from Novo Nordisk Pharmaceuticals Pty Ltd. The Haemostasis Registry has obtained ethics approval from the Human Research Ethics Committees of Monash University and all participating hospitals to collect information without patient consent, which is then forwarded to the ANZHR in a deidentified form.

### *Patients*

The Haemostasis Registry began receiving data in May 2005 but includes cases dating back to January 2001. Forty-six hospitals from all states and territories of Australia and from New Zealand are currently contributing data to the registry, of which there are 21 cardiac surgery centers. Participating hospitals undertake to provide information to the registry on all patients without hemophilia treated with rFVIIa at that hospital, and compliance is audited to ensure that complete data sets are received. Local investigators identify eligible patients after treatment with rFVIIa through pharmacy or blood bank records, depending on the protocol at each hospital. Patients were included in this study if the primary cause of bleeding was associated with cardiac operations as reported by the local investigator. In this registry, “cardiac surgery” includes all surgical procedures on the heart or on major thoracic vessels requiring cardiopulmonary bypass.

### *Data*

Standardized data forms were completed by trained ANZHR coordinators at each center. The following data were obtained for the Haemostasis Registry:

- patient demographics—age, sex, country, state;
- type of cardiac operation;
- blood test results before and after each rFVIIa dose—prothrombin time (PT), international nor-

malized ratio (INR), activated partial thromboplastin time (APTT), hemoglobin, hematocrit, fibrinogen, and platelet count;

- blood products use in the 24 hours before and 24 hours after the rFVIIa dose—red blood cells (RBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate;
- dose event—actual dosage, time elapsed since onset of bleeding, and place of administration; for example, operating theater or ICU;
- pH, and temperature;
- concomitant use of procoagulant (eg, aprotinin) or anticoagulant medication (eg, aspirin); and
- 28-day mortality.

In addition, prescribing clinicians were asked to assess patient response by indicating whether bleeding had stopped or decreased (responders), or was unchanged or had increased (nonresponders) after the use of rFVIIa. Clinicians were also asked to report all adverse events within 28 days of treatment with rFVIIa and to give an assessment of the probability that these events were linked to the administration of rFVIIa by assigning one of the following relationships: not linked, unlikely to be linked, possibly linked, probably linked, or definitely linked. The ANZHR data collection forms and the Data Dictionary containing definitions are available at the Haemostasis Registry Web site ([www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html](http://www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html)).

### Statistical Analysis

Because almost none of the variables measured conformed to normal distributions, nonparametric statistics were used throughout for consistency of reporting and analysis. Coagulation indicators and blood product usage before and after rFVIIa dose were compared in individuals by using Wilcoxon matched-pairs signed ranks tests. Univariate and multivariate analyses were performed to assess the relationship between the outcomes of interest (response and mortality, or both) and age, sex, patient weight, size of dose, temperature, pH, hemoglobin, hematocrit, platelet and fibrinogen levels, PT/INR, APTT, type of operation; number of RBCs, FFP, cryoprecipitate, and platelet units before dose; time to dose from bleeding onset, and place of administration. Where necessary, continuous variables were categorized according to clinical indicators. Analysis by  $\chi^2$  was used to identify associations between categorical baseline variables and the outcomes. Multivariate analysis was used to identify significant associations with each outcome. A binary logistic regression procedure was used. Variables demonstrating a univariate association of  $p \leq 0.10$  with either outcome were included in the multivariate models. For each model, the odds ratio and 95% confidence interval (CI) are provided.

### Results

As of September 2006, the Haemostasis Registry database included 695 cases, of which 302 patients (43%) were

Table 1. Overview of Cardiac Surgery Types in Patients Included in the Haemostasis Registry

Types of Surgery	Patients, No. (%)
Patients, No. <sup>a</sup>	293 (100)
CABG only	42 (14)
Valve only	56 (19)
Aortic valve only	29 (10)
Mitral valve only	8 (3)
Multiple valves	19 (6)
CABG and valve	35 (12)
Aorta and valve	107 (37)
Aortic valve + ascending aorta only	65 (22)
Aortic valve, ascending aorta, aortic arch	25 (9)
Including other valves or aortic areas	17 (6)
Other	53 (18)
Cardiac transplant	13 (4)

<sup>a</sup> Nine pediatric cases have been excluded from the analyses.

CABG = coronary artery bypass grafting.

recorded where the primary cause of bleeding was associated with the cardiac operation. The rest of the registry consists of patients with critical bleeding as a result of (in descending frequency) other operations (including liver transplantation), trauma, medical bleeding (including coagulopathy), oncology, obstetric, and intracranial hemorrhage. The cardiac surgical cases were from 21 hospitals, including 16 of 26 (61%) major cardiac centers in Australia. For 41 patients (13%), the data collection was within 30 days of treatment. Data for the remaining patients were collected retrospectively.

### Demographics

Most patients were male (73%). The median age of patients was 66 years (range, 0 to 89). Nine patients were younger than 17 years old and for this study were excluded from all subsequent analyses. The mean (SD) age of the remaining patients was 63 (15) years. Most patients were treated at hospitals in the states of New South Wales (47%) or Victoria (45%).

### Type of Operation

A description of the types of cardiac operations involved in registry cases is summarized in Table 1. A total of 48 (15%) patients had redo operations.

The rFVIIa was administered in the operating theater in 57% of patients or the ICU in 34%. All patients treated in the operating theater received rFVIIa after removal from cardiopulmonary bypass, with the exception of 1 patient who had isolated coronary artery bypass grafting (CABG) that was done off-pump. This patient received the rFVIIa dose during a return to the operating theater.

### Dose

The 293 patients received 343 doses of rFVIIa: 6 patients received three consecutive doses, 38 patients received two doses, and the remaining patients (85%) receiving a single dose. The median dose was 92.3  $\mu\text{g}/\text{kg}$  (interquar-

**Table 2. Blood Product Usage in the 24 Hours Before and After Administration of the Initial Dose of Activated Recombinant Factor VII**

Blood Product	Time Relative to Initial rFVIIa Dose	Number of Units Median (IQR)	Range	<i>p</i> Value <sup>a</sup>
RBC	Before	6 (3–9)	0–44	<0.001
	After	2 (0–4)	0–23	
FFP	Before	6 (4–10)	0–43	<0.001
	After	0 (0–4)	0–40	
Platelets	Before	5 (2–10)	0–32	<0.001
	After	0 (0–3)	0–30	
Cryoprecipitate	Before	8 (1–10)	0–46	<0.001
	After	0 (0–1)	0–30	
Total blood products	Before	25 (17–39)	0–115	<0.001
	After	4 (1–13)	0–99	

<sup>a</sup> Values for *p* relate to Wilcoxon matched-pairs signed ranks tests of individual values before and after initial dose of rFVIIa.

FFP = fresh frozen plasma; IQR = interquartile range; RBC = red blood cells; rFVIIa = activated recombinant factor VII.

tile range [IQR], 82 to 103  $\mu\text{g}/\text{kg}$ ; range, 9 to 141  $\mu\text{g}/\text{kg}$ ). The median time from onset of bleeding to dose administration was 4 hours (IQR, 1 to 8 hours; range, 0 to 66 hours). Before treatment with rFVIIa, 35% of patients were returned to the operating theater in an attempt to control blood loss, including 12 patients who were returned more than once before treatment with rFVIIa. After treatment with an initial dose of rFVIIa, 35 patients were returned to the operating theater for bleeding control.

#### Blood Products

Transfusion of all blood products was significantly reduced (Table 2). A comparison of units of RBCs received before and after the initial dose of rFVIIa in each individual showed a significant reduction ( $p < 0.001$ ). Similar significant reductions were seen in individuals in the amount of FFP ( $p < 0.001$ ), platelets ( $p < 0.001$ ), cryoprecipitate ( $p < 0.001$ ), and total blood products ( $p < 0.001$ ). After the administration of rFVIIa, most patients (88%) received less than 6 U of RBCs. The median reduction in RBC transfusion was 4 U (IQR, 0 to 8 U; range, –21 to 40).

Before the administration of rFVIIa, 142 (49%) received 5 U or fewer of packed RBCs, 246 (83%) received 10 U or fewer, and 17 (6%) received 0 U. Two of these patients received no blood products because of religious beliefs. The remaining patients had received other blood products (FFP, platelets, or cryoprecipitate, or a combination) before rFVIIa was used. There was no statistical difference between this group and the remainder of the cohort with regards to type of operation, efficacy, or mortality. No patients were identified as receiving rFVIIa prophylactically.

#### Temperature and pH

Temperature was not recorded for 83 patients at the time of the initial rFVIIa dose. Of the remaining 210 cases, 36 (17%) were hypothermic (temperature  $< 35.0^\circ\text{C}$ ). The pH was not documented for 84 patients at the time of the initial rFVIIa dose. Of the remaining 209 patients, 109

(52%) were acidotic (pH  $< 7.35$ ) at the time of the initial rFVIIa dose, including 18 patients (10%) who were moderately acidotic (pH, 7.2 to 7.05) and 2 patients who were severely acidotic (pH  $< 7.05$ ).

#### Laboratory Indicators

Details of coagulation indicators before and after the initial dose of rFVIIa are provided in Table 3. Prothrombin time was prolonged ( $>15.5$  seconds) in 156 of 214 patients (73%) before administration of rFVIIa. Similarly, INR was prolonged ( $>1.5$ ) in 118 of 235 patients (50%) before administration of rFVIIa.

Most coagulation indicators exhibited statistically significant changes in individuals after the initial dose of rFVIIa compared with before the administration of rFVIIa (Table 3). Fibrinogen ( $p = 0.002$ ) levels were significantly higher after the initial dose of rFVIIa. Reductions were significant in PT ( $p < 0.001$ ), INR ( $p < 0.001$ ), and APTT ( $p < 0.001$ ) after the initial dose of rFVIIa. Platelet levels did not exhibit a statistically significant change ( $p = 0.113$ ). The hemoglobin level ( $p = 0.011$ ) and hematocrit ( $p = 0.024$ ) increased significantly after rFVIIa.

#### Response and Outcome

Recombinant FVIIa was considered to have decreased or stopped bleeding in 245 of 297 (82%) of uses where efficacy was reported. Of the 256 first doses of rFVIIa where efficacy was reported, 215 doses (84%) resulted in the reduction or cessation of bleeding. The reported response rate for the second rFVIIa dose was 25 of 35 doses (71%) and for the third dose, 5 of 6 patients (83%) responded to treatment. In the 41 patients reported as not responding to the initial dose of rFVIIa, 6 later had surgical bleeding identified in a return to the operating room.

Patients whose bleeding was considered to have stopped or decreased were less likely to die than those whose bleeding was unchanged ( $\chi^2_2 = 22.3$ ;  $p < 0.001$ , see Figure 1). Patients undergoing re-do operations showed no significant difference in the rate of response

Table 3. Coagulation Indicators Before and After Administration of the Initial Dose of Activated Recombinant Factor VII

Indicator	Time Relative to Initial rFVIIa Dose	Patients, No. <sup>a</sup>	Median (IQR)	Range	<i>p</i> Value <sup>b</sup>
PT, sec	Before	214	18.5 (15.0–21.5)	8.5–100.0	<0.001
	After	204	12.3 (10.8–14.5)	5.0–40.4	
INR	Before	235	1.6 (1.3–1.8)	0.8–5.4	<0.001
	After	227	1.0 (0.9–1.2)	0.6–10.0	
APTT, sec	Before	262	51.0 (40.9–70.0)	25–300	<0.001
	After	257	46.0 (38.0–60.0)	22–215	
Hemoglobin, g/L	Before	271	85.0 (73.0–99.0)	7–196	0.011
	After	258	91.5 (81.0–101.0)	9–144	
Hematocrit, %	Before	250	25 (22–29)	14–60	0.024
	After	240	27 (24–30)	10–88	
Fibrinogen, g/L	Before	159	2.1 (1.7–2.8)	0.6–8.8	0.002
	After	153	2.2 (1.7–2.9)	0.2–5.1	
Platelet count, $\times 10^9/L$	Before	272	118.0 (92.0–157.8)	7–500	0.113
	After	255	114.0 (91.0–146.0)	25–320	

<sup>a</sup> Patients with missing values have been excluded from these analyses. The impact of these cases may influence the significance of the findings. <sup>b</sup> Values for *p* relate to Wilcoxon matched-pairs signed-ranks tests of individual values before and after initial dose of rFVIIa. Only individuals with values for both before and after are included in this analysis.

APTT = activated partial thromboplastin time; INR = international normalized ratio; IQR = interquartile range; rFVIIa = activated recombinant factor VII; PT = prothrombin time.

to rFVIIa, but were more likely to die (OR, 2.1; 95% CI, 1.0 to 4.4).

The observed mortality for all patients at 28 days was 49 of 293 (17%). The percentage of patients alive at 28 days was 97% if bleeding ceased after rFVIIa, 87% if bleeding reduced, and 63% for nonresponders. Thirteen deaths occurred within 24 hours of rFVIIa administration all as a direct result of an underlying condition or the operation, and 33 deaths occurred after 24 hours. Causes were cardiac in 13 patients, ischemic brain/spine injury (subsequent to procedure) in 7, infectious complications in 8, and multiorgan failure in 7. The difference in the cause of death of patients who responded to rFVIIa vs those who did not respond was not significant.

#### Adverse Events

Details of adverse events are given in Table 4. A total of 161 adverse events were reported in 130 (44%) patients within 28 days of receiving rFVIIa. Of these 161, 127 (79%) were considered to be unlikely to be linked (*n* = 53) or not linked (*n* = 74) to the administration of rFVIIa. A total of 22 (7%) were considered to be either probably or possibly linked to the administration of rFVIIa, of which 13 were thromboembolic in nature. No patients were considered to have died of adverse events related to the use of rFVIIa.

#### Univariate Analyses

Of the variables considered, advancing age (*p* = 0.056), higher number of units of RBCs transfused before the dose (*p* = 0.002), abnormal PT/INR (*p* = 0.037), place of administration (operating theater vs ICU; *p* = 0.085), low hemoglobin (*p* = 0.076), or hematocrit (*p* = 0.003), were associated with a lower response rate. Sex, size of dose,

patient weight, temperature, pH, platelet level, fibrinogen level, type of operation, APTT, and time to dose were not associated with response.

Mortality demonstrated an association with female sex (*p* = 0.020), low pH (*p* < 0.001), type of cardiac operation (other type vs CABG or valve, or both; *p* = 0.011), place of administration (operating theater vs ICU; *p* = 0.096), and high APTT (> 80 seconds; *p* = 0.004).

#### Multivariate Analyses

Variables showing a univariate association (*p* < 0.1) with either of the outcome variables were entered into the multivariate analyses, the results of which are provided in Table 5. Hematocrit level was not included because it showed a strong colinearity with hemoglobin level (Spearman correlation *p* = 0.981). Sex, age, hemoglobin level, category of cardiac operation, and pH were all found to be associated with death when taking into account place of administration, PT/INR, APTT, and number of RBC units. Women were more likely to die (OR, 3.23; 95% CI, 1.05 to 9.90) than men.

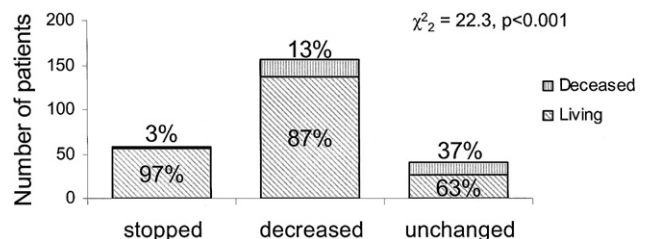


Fig 1. Effect of activated recombinant factor VII on bleeding versus outcome (deceased, vertical pattern; living, diagonal pattern) at 28 days ( $\chi^2_2 = 22.3$ ; *p* < 0.001).

Table 4. Details of Adverse Events Within 28 Days of Administration of Activated Recombinant Factor VII

Adverse Events	Adverse Events, No.	Patients Living at 28 Days, No.	Link With rFVIIa, No. <sup>a</sup>
Thromboembolic			
CVA	20	15	6
TIA	1	1	1
DVT	4	2	2
PE	2	1	1
AMI	5	1	0
Arterial	4	4	0
Other	5	4	3
DIC	5	3	1
MOF	29	9	0
ARDS	8	5	0
Infection <sup>b</sup>	15	14	1
ARF	8	6	0
Atrial fibrillation	12	11	0
Other	43	38	7
Total	161	114 (71%)	22

<sup>a</sup> Adverse events considered “possibly” or “probably” linked with rFVIIa administration. <sup>b</sup> Patients with known infection prior to administration of rFVIIa are not included here.

AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; ARF = acute renal failure; CVA = cerebrovascular accident; DIC = disseminated intravascular coagulopathy; DVT = deep venous thrombosis; MOF = multisystem organ failure; PE = pulmonary embolism; TIA = transient ischemic attack.

Patients aged 75 years or older were more likely to die than those younger than 35 years (OR, 35.4, 95% CI, 2.49 to 503.74). Patients with a pH < 7.20 were significantly more likely to die (OR, 7.33, 95% CI, 1.61 to 33.55) than those with higher pH. Patients undergoing operations in the “other” category were more likely to die than those undergoing isolated CABG (OR, 7.03, 95% CI, 1.04 to 47.41).

Number of units of RBCs received was associated with patient response when all the other variables were taken into account. Patients receiving more than 10 U of RBCs before treatment were significantly less likely to respond than patients receiving no RBCs (OR, 0.15; 95% CI, 0.03 to 0.68).

### Comment

This report of a large case series provides a unique insight into the real-world experience with rFVIIa in perioperative cardiac bleeding across Australia and New Zealand. An important aspect in this series is that submitting hospitals are required to commit to supplying complete data sets. This commitment, which is audited by Monash University Department of Epidemiology and Preventive Medicine, limits bias and prevents the reporting of only positive or anecdotal experiences. The subjective reporting of response rate is a potential area of weakness but is unavoidable, and indeed, a similar practice has been adopted for an ongoing phase 3 trial in

cardiac surgery. It is reassuring that the subjective efficacy assessment correlated with both transfusion requirements and hemoglobin and, ultimately, with mortality.

One of the real difficulties with this project was the lack of truly objective measures of efficacy that are applicable to the wide variety of situations in which rFVIIa is used. Chest tube output, although applicable to those patients who have left the operating theater, is not universally applicable to all cardiac surgical cases. Return to the operating theater, likewise, is not a universal outcome measure, although returns to the operating theater may indicate some instances of lack of effect. The number of units of blood products is unreliable due to inconsistencies in practice across hospitals and because of issues such as refilling after bleeding has ceased. The measure of response we used is subjective, but it is highly reproducible, and the strong correlation between this measure and mortality, although obvious, goes against any suggestion of systematic bias in the subjective measure of efficacy used.

Incomplete data records remain an issue in some areas; however, all patients had data on outcomes, blood products, dosage information, age, and sex. The percentage of missing data values ranges from 0% to 48% (fibrinogen level after dose 1) and was particularly evident in laboratory results: 31 patients had no laboratory results for the period after treatment with rFVIIa. Some hospitals regularly report only PT or INR (and not both). Temperature and pH at the time of dose were missing in 28% and 29% of cases, respectively. Laboratory results were not taken at all after rFVIIa treatment in some patients, particularly if bleeding had ceased or if the patient had died or was close to death.

The patients recorded in the Haemostasis Registry are reflective of typical cardiac surgical patients, frequently older men, who are undergoing a wide range of cardiac procedures ranging from simple revascularization to more complex valvular and aortic procedures. Before the use of rFVIIa, patients had received blood product support in an attempt to control hemorrhage, and 102 (35%) had already had surgical reexploration.

This group had a high response rate of 84% and, more important, responders had an improved mortality. The bleeding response rate after cardiac operations is higher than that seen in other critical bleeding settings (data submitted for publication), emphasizing the potential value of rFVIIa in this group. Why this is so is open to speculation.

Most patients received a single rFVIIa dose of about 90 µg/kg, consistent with the most commonly used dose in patients with hemophilia with inhibitors. No specific guidelines exist in Australia for dosing in bleeding after cardiac operations. Given the heterogeneity in cases, treatment protocols, blood products, and the triggers for treatment, it is difficult to compare outcomes among patient groups. The patients who received rFVIIa before RBC transfusion are an interesting group, but the lack of difference between this group and the cardiac group in

Table 5. Multivariate Analyses

Variable	Mortality OR (95% CI)	p Value	Response OR (95% CI)	p Value
Sex				
Female	3.23 (1.05–9.90)	0.04	0.89 (0.26–3.05)	0.86
Age, years				
<35 (ref)		0.03		0.57
35–44	18.50 (0.84–406.82)	0.06	0.20 (0.01–4.12)	0.30
45–54	5.96 (0.39–91.51)	0.20	1.99 (0.07–60.65)	0.69
55–64	4.23 (0.28–64.27)	0.30	1.02 (0.07–14.35)	0.99
65–74	6.32 (0.49–81.12)	0.16	0.50 (0.04–6.49)	0.60
75+	35.40 (2.49–503.74)	0.01	0.70 (0.05–10.18)	0.80
Hemoglobin level				
Normal-high (ref)		0.03		0.09
Low	0.25 (0.05–1.15)	0.07	0.96 (0.13–7.01)	0.97
Very low	1.24 (0.23–6.70)	0.81	0.25 (0.03–2.21)	0.21
Place of administration				
Operating theater (ref)		0.86		0.13
Intensive care unit	1.38 (0.44–4.38)	0.58	0.33 (0.10–1.09)	0.07
Other	0.00 (0.00–0.00)	1.00	0.24 (0.04–1.66)	0.15
pH				
Normal-high >7.369 (ref)		0.03		0.28
Low 7.2–7.369	2.72 (0.91–8.15)	0.07	0.49 (0.16–1.49)	0.21
Very low < = 7.2	7.34 (1.61–33.55)	0.01	2.22 (0.17–29.89)	0.55
PT/INR				
Normal-low(ref)		0.83		0.35
Prolonged	1.45 (0.38–5.57)	0.59	0.95 (0.19–4.74)	0.95
Very prolonged	1.83 (0.16–21.06)	0.63	0.13 (0.01–2.67)	0.19
APTT				
Normal-low (ref)		0.69		0.69
Prolonged	0.62 (0.13–2.94)	0.55	1.86 (0.41–8.52)	0.42
Very prolonged	0.97 (0.15–6.30)	0.97	2.41 (0.24–24.23)	0.45
Cardiac surgery category				
CABG only (ref)		0.05		0.74
Valve only	0.39 (0.05–3.15)	0.38	0.38 (0.05–2.66)	0.33
CABG and Valve	1.38 (0.20–9.40)	0.74	0.48 (0.05–4.36)	0.51
Ascending aorta only	2.50 (0.51–12.27)	0.26	0.30 (0.05–1.90)	0.20
Other	7.03 (1.04–47.41)	0.05	0.56 (0.07–4.73)	0.59
RBC units, No.				
<5 (ref)		0.66		0.04
6–10	0.75 (0.24–2.34)	0.62	0.32 (0.09–1.12)	0.07
11–20	0.50 (0.12–2.22)	0.37	0.15 (0.03–0.68)	0.01

APTT = activated partial thromboplastin time; CABG = coronary artery bypass grafting; CI = confidence interval; INR = international normalized ratio; OR = odds ratio; PT = prothrombin time; RBC = red blood cell.

general probably simply reflects a growing awareness of the importance of early control of excessive hemorrhage.

Recent evidence has suggested efficacy with lower doses in bleeding after cardiac operations [31, 32], but the number of patients who received lower doses in our sample was too small to provide meaningful data. Our findings demonstrate a statistically significant decrease in the number of all types of blood products received after the administration of rFVIIa.

It has been shown both theoretically [33] and clinically in this study, that low pH is associated with a reduction in response to rFVIIa. Ideally, rFVIIa should be given before

patients become acidotic. Further work is necessary to enable prediction of which patients are likely to become acidotic and to determine whether a reversal of acidosis relates to improved response to rFVIIa.

An associated adverse event rate was reported in 7% of patients, of which 4% were thromboembolic in nature. This event rate is comparable with a recent systematic review of rFVIIa in cardiac surgery [24] and also to the adverse event rate reported in a meta-analysis of the first 13 Novo Nordisk-sponsored randomized controlled trials with rFVIIa in coagulopathic bleeding [34]. In addition, the adverse event rates do not appear higher than those

reported in other complex cardiac surgical procedures that require significant transfusion [24, 35] where rFVIIa was not used. Of importance was that no cases of microvascular graft stenosis occurred, a hypothetical complication that has been of concern to clinicians [36].

This large case series has limitations, which include the absence of a control group and the heterogeneity of bleeding contexts, but is strengthened by the intention to capture all patients at participating hospitals and data collection by a nonclinical independent research group.

Given the nature of the database, firm conclusions regarding patient selection, dosing guidelines, and adjuvant treatment cannot be drawn. Response to rFVIIa was improved in patients who had received less RBC transfusion. This study showed reduced pH was associated with death, but whether this identifies a poor risk group or highlights the need to attempt to normalize pH before treatment with rFVIIa is unclear.

In the absence of large, international, randomized controlled trials, this observational study provides insights into the current clinical practice of rFVIIa use in critical bleeding in cardiac surgery.

#### Participating Hospitals

Australia—Australian Capital Territory: The Canberra Hospital; New South Wales: Liverpool Hospital, Prince of Wales Hospital, Royal North Shore Hospital, Royal Prince Alfred Hospital, St Vincent's Private Hospital, and St Vincent's Public Hospital; Queensland: Princess Alexandra Hospital, and the Prince Charles Hospital; South Australia: Flinders Medical Centre; Tasmania: Royal Hobart Hospital; Victoria: Alfred Hospital, Austin Hospital, Geelong Hospital, Knox Private Hospital, Monash Medical Centre, and St Vincent's Hospital; Western Australia: Fremantle Hospital and Sir Charles Gairdner Hospital.

New Zealand—Auckland City Hospital and Wellington Hospital.

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## INVITED COMMENTARY

Level 1 evidence is seriously lagging behind the wide off-label use of recombinant activated factor VII (rFVIIa) in the control of massive or insurmountable bleeding. Dunkley and colleagues [1] have made a commendable effort in gathering and analyzing the data on nonhemophilia cardiac surgery cases with critical bleeding treated with rFVIIa from a large multicenter registry with financial support from Novo Nordisk. The study faces limitations, many of which are shared with other registries; lack of a control group is perhaps the biggest obstacle in interpreting the data, given the complicated nature of cardiac surgery and the numerous confounding variables and heterogeneous practices. For instance, 15 cases received platelets, fresh frozen plasma (FFP) or cryoprecipitate, but no red blood cells prior to rFVIIa. As an alternative to control, authors have resorted to comparing measurements before and after rFVIIa administration. However, observed improvements can be the result of collective salvage efforts rather than rFVIIa alone. In addition, data on 87% of the cases have been retrospectively collected, which raises the questions of accuracy, especially for response to treatment. With some cases dating back more than 4 years, the potential memory lapse combined with the possible bias toward the treatment can result in inaccuracies. Apart from the old cases, the subjective reporting of this outcome is of significant concern. Although the authors argue that this measure concurs with mortality rates, objective measurements (such as chest tube drainage) would have been more desirable. Finally, lack of set times for measuring blood parameters before and after giving rFVIIa could substantially obscure the causal relationship between the measured values and the treatment.

In a registry, bias can be introduced at many levels including data collection, submission, and analysis. The authors have taken appropriate countermeasures (ie, participating hospitals were required to submit all cases and their adherence was audited). The observed median dose in this study was very close to the dose used in

hemophilia patients as well as off-label cases. Interestingly, dose was not associated with outcomes, suggesting the possibility of lower doses being as effective (or less likely, the drug not being effective at all and all the observed improvements being due to other treatments). The observed thromboembolic adverse event rate of 7% in this study is close to the previously reported rates, which is of concern. This rare but significant complication would be acceptable providing rFVIIa had a demonstrable higher benefit. In summary and within constraints of a registry, this study serves to highlight some of the issues facing future trials on rFVIIa, such as defining outcomes and accounting for heterogeneity in practices while suggesting an acceptable safety profile. Although the present study provides a valuable insight, ongoing and future controlled trials will hopefully provide the much needed higher quality evidence for the "off-label" use of rFVIIa.

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