

# Use of rFVIIa for critical bleeding in cardiac surgery: dose variation and patient outcomes

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## Vox Sanguinis

**Background and Objectives** Recombinant activated factor VIIa (rFVIIa) is increasingly being used in non-haemophiliac patients for the treatment of severe bleeding refractory to standard interventions. Optimal dosing regimens remain debated in cardiac surgery. Therefore, this study investigated the use of different rFVIIa dosing practices on response to bleeding and patient outcomes in cardiac surgery patients using data from the Haemostasis Registry.

**Methods** Data were extracted from the Haemostasis Registry that records cases of off-licence rFVIIa use in participating institutions. Univariate analyses compared patients receiving  $\leq 40$   $\mu\text{g}/\text{kg}$ , 41–60  $\mu\text{g}/\text{kg}$ , 61–80  $\mu\text{g}/\text{kg}$ , 81–100  $\mu\text{g}/\text{kg}$  and  $>100$   $\mu\text{g}/\text{kg}$  of rFVIIa on key parameters. Logistic regression models investigated the relationship between independent variables and 28-day mortality.

**Results** Complete data was available on 804 cardiac surgery patients who received rFVIIa. Of these, 42 (5.2%) were treated with doses  $\leq 40$   $\mu\text{g}/\text{kg}$ , while the dose group containing the most patients was 81–100  $\mu\text{g}/\text{kg}$  (368, 45.77%). Results demonstrated no significant differences in the rate of thromboembolic adverse events, response to bleeding or 28-day mortality.

**Conclusions** These findings raise the important question of whether lower doses of rFVIIa may be as effective as higher doses in the treatment of severe bleeding in cardiac surgery patients.

**Key words:** cardiac surgery, dose, factor VIIa, haemostasis, NovoSeven.

Received: 17 July 2009,  
revised 30 September 2009,  
accepted 3 October 2009

## Introduction

Blood loss following cardiac surgery that is refractory to standard interventions, including blood and blood product replacements, has been reported as a major source of patient mortality and morbidity [1,2]. Return to theatre for mediastinal exploration occurs in approximately 3–5% of patients [3], therefore considerable interest exists in identifying alternative, non-surgical treatments that are useful for restoring haemostasis. Recombinant activated factor VII

(rFVIIa) (NovoNordisk Pharmaceuticals Pty Ltd) is currently licensed for use in the treatment of Haemophilia A and B with inhibitors, as well as Glanzmann's thrombasthenia. Use of rFVIIa for the treatment of uncontrolled bleeding in cardiac surgery patients therefore constitutes an 'off-label' application [4]. Reported reduction in blood loss, transfusion requirements and need for surgical revision following rFVIIa administration have added to its appeal as a haemostatic agent for cardiac surgery patients [1,4–7].

While some have suggested a dose-dependent relationship between rFVIIa and the development of TAEs [8], recent results from the single RCT in cardiac surgery by Gill *et al.* do not provide definitive evidence of the optimal dose regimen for use in this population. For on-licence use of rFVIIa, recommendations of an initial dose ranging from

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35 µg/kg to 90 µg/kg were originally derived from a single, small sample study [9], whereas reported doses in cardiac surgery vary widely, ranging from 17 µg/kg to 180 µg/kg [10,11]. With evidence of a possible dose-dependent increase in TAEs seen in a randomized, placebo-controlled clinical trial in acute intracerebral haemorrhage [8], recommendations for the lowest effective dose have been made [12]. In Australia, Queensland Health has responded by introducing a state-wide protocol that recommends an off-licence dose of 50 µg/kg. As other Australian states have not formally adopted this 'low-dose' protocol, this study aimed to explore the current variation in rFVIIa dosing practices in cardiac surgery settings and investigate the relationship between dosing regimens and response to treatment and mortality. We hypothesized that there would be no significant difference in outcome for patients receiving different dose levels of rFVIIa.

## Methods

Data were extracted from the Haemostasis Registry, which captures all cases of off-label use of rFVIIa in patients treated at participating hospitals in Australia and New Zealand. The Haemostasis Registry was established in the Department of Epidemiology and Preventive Medicine, Monash University in 2005. Ethics approval has been obtained from the Standing Committee on Ethical Research involving Humans of Monash University as well as all participating hospitals. The Registry collects de-identified information and does not require informed patient consent.

## Patients

Eighty-seven hospitals across Australia and New Zealand contribute data to the Haemostasis Registry. Audits of rFVIIa inventory, issue and usage are performed annually to ensure complete data capture at all participating sites. Clinical and laboratory data before and after rFVIIa administration are collected, along with outcome data. In the present study patients aged more than 15 years who received rFVIIa from September 2005 to November 2008 for the treatment of bleeding associated with cardiac surgery were included. In the Haemostasis Registry, cardiac surgery includes all surgical interventions on the heart or on major thoracic vessels that require cardiopulmonary bypass.

## Dose categories

Patients were divided into five dose categories based on the initial rFVIIa dose volume: ≤40 µg/kg, 41–60 µg/kg, 61–80 µg/kg, 81–100 µg/kg and >100 µg/kg.

## Statistical analysis

Baseline patient characteristics (including age, weight, gender, place of administration, pH, temperature, case complexity and medications, products administered and coagulation parameters prior to rFVIIa) were compared between groups using chi-squared for categorical data, one-way ANOVA for normally distributed continuous data and the non-parametric Kruskal–Wallis test for non-normally distributed continuous variables. Response in bleeding to treatment (a clinical judgment made at the time of administration), mortality and TAEs were compared by dosage group using chi-squared. Multivariate analyses modelled the relationship between covariates and mortality using a backward step-wise approach. A multilevel model was used as patients were clustered by hospital to account for institutional dosing practices. Values  $P < 0.05$  were considered statistically significant. All analyses were conducted using Stata v. 9.2 (Stata Corp, TX).

## Results

The final dataset included 859 cases. Fifty-five patients had missing information relating to dose, reducing the total sample to 804 patients. Of these, 42 (5.22%) patients received doses of 40 µg/kg or less, while 368 (45.77%) received a dose between 81 and 100 µg/kg (Table 1).

Table 1 reports baseline patient characteristics by dose category. Predose INR values varied from 1.4 to 1.6, with the highest dose and lowest dose groups both recording an INR of 1.5. Patients receiving ≤40 µg/kg of rFVIIa recorded the highest fibrinogen levels (2.7 g/l), while the lowest fibrinogen levels were seen in the highest dose group (2.0 g/l,  $P = 0.049$ ). Of the patients receiving ≤40 µg/kg, 38% reported taking aspirin pre-dose compared to 28% in the highest dose category ( $P = 0.046$ ).

Case complexity did not differ statistically between the five dose categories (Fig. 1). The largest differences between dose categories appeared to be in the proportion of isolated valve procedures and 'other surgeries'; interventions that comprise the most complex cardiac procedures including heart transplants and aortic surgery. Approximately 66% of patients in the ≤40 µg/kg category were classified as 'other surgeries', compared to 49% in the 81–100 µg/kg and 50% in the >100 µg/kg dose categories ( $P = 0.132$ ).

Patients in the ≤40 µg/kg dose category received fewer predose units of cryoprecipitate (one unit) when compared to patients in all other dose categories (Table 1). Patients receiving >100 µg/kg received the highest median number of units of cryoprecipitate (eight units,  $P = 0.001$ ).

**Table 1** Cardiac surgery patient characteristics (*n* = 804)

Variable	≤40 µg/kg ( <i>n</i> = 42)	41–60 µg/kg ( <i>n</i> = 107)	61–80 µg/kg ( <i>n</i> = 104)	81–100 µg/kg ( <i>n</i> = 368)	>100 µg/kg ( <i>n</i> = 183)	<i>P</i>
Age (years) <sup>a</sup>	63 (48–74)	68 (58–75)	67 (59–78)	67 (54–74)	67 (54–75)	0.273
Weight, mean (SD), (kg)	81.4 (15.5)	79.9 (15.3)	77.6 (17.8)	78.5 (15.8)	69.2 (14.5)	0.001
Female, <i>n</i> (%)	12 (28.6)	27 (25.2)	26 (25.0)	98 (26.6)	59 (32.0)	0.548
Medications prior to FVIIa <sup>a</sup>						
Aspirin	16 (38.1)	42 (39.3)	27 (26.0)	140 (38.0)	52 (28.4)	0.046
Anti-platelet	2 (4.8)	9 (8.4)	7 (6.7)	39 (10.6)	12 (6.6)	0.392
Low molecular weight heparin	4 (9.5)	10 (9.4)	7 (6.7)	33 (9.5)	17 (9.3)	0.953
Warfarin	6 (14.3)	14 (13.1)	19 (18.3)	58 (15.8)	29 (15.9)	0.888
Laboratory results prior <sup>a</sup>						
INR	1.5 (1.3–1.8)	1.4 (1.3–1.6)	1.5 (1.3–1.9)	1.6 (1.3–1.9)	1.5 (1.3–1.8)	0.008
Platelets (10 <sup>9</sup> /l)	163 (94–208)	133 (98–193)	115 (85–163)	116 (88–152)	118 (89–153)	0.203
Haemoglobin (g/l)	84 (72–108)	84 (73–104)	82 (72–101)	83 (72–96)	83 (69–99)	0.775
Fibrinogen (g/l)	2.7 (1.8–3.8)	2.2 (1.7–3.1)	2.2 (1.7–2.8)	2.1 (1.7–2.6)	2.0 (1.7–2.7)	0.049
Products prior (units) <sup>a</sup>						
Packed cells	6 (3–10)	5 (2–10)	6 (4–9)	6 (3–9)	7 (4–10)	0.106
FFP	8 (6–12)	6 (4–10)	6 (4–10)	6 (4–10)	7 (4–10)	0.149
Cryoprecipitate	1 (0–10)	5 (0–10)	5 (0–8)	8 (0–10)	8 (0–10)	0.001
Platelets	4 (2–8)	2 (2–5)	3 (2–5)	3 (2–5)	3 (2–6)	0.243
Total blood products post-dose 1 (units) <sup>a</sup>						
Packed cells	2 (1–4)	2 (1–3)	2 (1–5)	2 (1–5)	2 (1–6)	0.913
FFP	0 (0–4)	2 (0–4)	2 (0–5)	2 (0–4)	2 (0–5)	0.970
Cryoprecipitate	0 (0–5)	0 (0–1)	0 (0–2)	0 (0–5)	0 (0–6)	0.338
Platelets <sup>b</sup>	0 (0–1)	0 (0–2)	1 (0–2)	1 (0–2)	1 (0–3)	0.566
Case complexity, <i>n</i> (%)						
Isolated CABG	9 (21.4)	19 (17.8)	21 (20.2)	65 (17.7)	39 (21.3)	0.132
Isolated valve	2 (4.8)	24 (22.4)	18 (17.3)	71 (19.3)	26 (14.2)	
Valve & CABG	3 (7.1)	11 (10.3)	6 (5.8)	151 (41.3)	26 (14.2)	
Other	28 (66.7)	53 (49.5)	59 (56.7)	181 (49.2)	92 (50.3)	
Place of administration, <i>n</i> (%)						
Theatre	26 (61.9)	68 (63.6)	60 (57.7)	238 (65.0)	99 (54.4)	0.158
ICU	16 (38.1)	39 (36.4)	44 (42.3)	128 (35.0)	83 (45.6)	
pH <sup>a</sup>	7.33 (7.25–7.38)	7.38 (7.33–7.41)	7.36 (7.30–7.41)	7.30 (7.27–7.41)	7.34 (7.28–7.40)	0.157
Temperature <sup>a</sup>	36.0 (35.3–36.9)	36.3 (35.3–37.0)	36.3 (35.1–37.0)	36.2 (35.3–36.8)	36.1 (35.2–37.0)	0.966
Dose in mg <sup>a</sup>	2.4 (1.2–2.4)	4.8 (3.6–4.8)	4.8 (4.8–6.0)	7.2 (6.0–8.4)	7.2 (7.2–9.6)	0.001
Size of dose 1 (µg/kg) <sup>a</sup>	27.0 (16–35)	54.0 (48.0–56.0)	72.0 (66.0–77.0)	92 (88–96)	109 (103–120)	0.001
Size of total dose (µg/kg) <sup>a</sup>	32 (25–40)	56 (51–92)	75 (67–80)	84 (89–99)	111 (104–128)	0.009
Two or more doses, <i>n</i> (%)	10 (23.8)	32 (29.9)	22 (21.2)	54 (14.7)	23 (12.6)	0.001

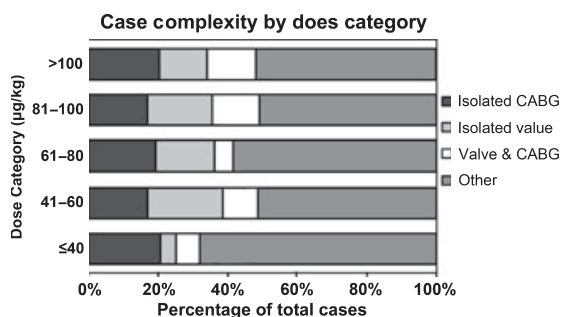
<sup>a</sup>Values represent Median (IQR).<sup>b</sup>Platelets comprise whole blood derived and apheresis platelets.**Fig. 1** Case complexity by dose category.

Figure 2 demonstrates mean patient weight for each dose category along with dose information. Patients in the ≤40, 41–60, 61–80 and 81–100 µg/kg dose categories had mean weights ranging from 77.6 kg to 81.4 kg while those in the highest dose category weighed on average approximately 10 kg less, at 69.2 kg (*P* < 0.001). The median initial rFVIIa dose differed significantly between dose category, with the lowest dose category receiving a median dose of 27 µg/kg, and the highest dose category 109 µg/kg (Table 1 and Fig. 2). While fewer patients in the two highest dose categories received second doses of rFVIIa (14.7% in

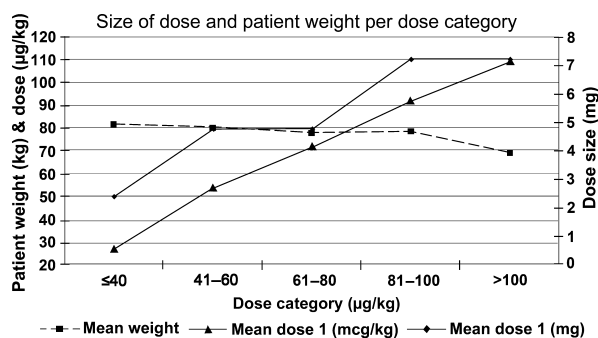


Fig. 2 Size of dose and patient per dose category.

81–100 µg/kg and 12.6% in >100 µg/kg, compared to 23.8% in ≤40 µg/kg group), the cumulative total dose of rFVIIa remained significantly lower for the lowest dose group (32 µg/kg) than for any other dose category, and considerably lower than the highest dose category (111 µg/kg) (Table 1).

Neither reported bleeding response to initial ( $P = 0.664$ ) or total ( $P = 0.368$ ) rFVIIa dose, nor 28-day mortality ( $P = 0.788$ ) varied significantly between the five dosage categories (Table 2). Of patients judged to have responded to rFVIIa, 33.73% required >2 RBC units following dose 1, compared to 60.98% in the non-response category

( $P < 0.001$ ). TAEs (Table 3) were subdivided into cerebrovascular accident (CVA), transient ischemic attack (TIA), deep vein thrombosis (DVT), pulmonary embolus (PE) and arterial thrombosis. Due to the low number of events, tests of statistical significance were considered inappropriate. However, CVAs were the most frequently occurring adverse event (40 events across the dose categories), while TIAs were the least common event (two across dose categories).

The results from the logistic regression model described in Table 4 are presented in Table 5. Isolated valve and combined valve and coronary artery bypass graft surgeries (CABG) demonstrated the strongest relationship with mortality (OR 3.48 and 5.56 respectively). In addition, pH demonstrated a strong relationship with mortality (OR 2.15), while platelet count prior to rFVIIa demonstrated a weak positive relationship with mortality (OR 1.01). Size of rFVIIa dose was not found to demonstrate a statistically significant relationship with mortality and was therefore dropped from the model.

## Discussion

The relatively high cost, possible safety risks and ill-defined effectiveness of off-licence rFVIIa administration, have been reported as major barriers to the early use of rFVIIa in settings of uncontrolled bleeding associated with cardiac

Table 2 Response to rFVIIa and mortality by dose category

		No. patients (%)					
		≤40 µg/kg (n = 42)	41–60 µg/kg (n = 107)	61–80 µg/kg (n = 104)	81–100 µg/kg (n = 368)	>100 µg/kg (n = 183)	P
Effect on bleeding	Effect recorded	35 (83)	94 (88)	90 (87)	335 (91)	161 (88)	
	Responded to dose 1	27 (77)	75 (80)	67 (74)	273 (81)	127 (79)	0.664
	Responded to final dose*	29 (81)	85 (91)	76 (85)	283 (86)	134 (83)	0.368
28-Day outcome	Deceased	7 (17)	15 (14)	17 (16)	67 (18)	36 (20)	0.788

\* Response to final dose equals response to dose 1 in patients only receiving a single dose.

Table 3 Thromboembolic adverse events by dose category

		No. patients (%)					
		≤40 µg/kg (n = 42)	41–60 µg/kg (n = 107)	61–80 µg/kg (n = 104)	81–100 µg/kg (n = 368)	>100 µg/kg (n = 183)	P
CVA		3 (7)	5 (5)	8 (8)	16 (4)	8 (4)	0.643 <sup>a</sup>
TIA		0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	–
DVT		2 (5)	0 (0)	0 (0)	1 (0)	1 (1)	–
PE		1 (2)	2 (2)	1 (1)	0 (0)	0 (0)	–
Arterial thrombosis		0 (0)	2 (2)	0 (0)	5 (1)	1 (1)	–

<sup>a</sup>Statistical test:  $\chi^2$ , remaining P-values not appropriate for calculation.

CVA, cerebrovascular accident; TIA, transient ischemic attack; DVT, deep vein thrombosis; PE, pulmonary embolism.

**Table 4** Regression model covariates

Parameters	Entered in model	Details
Dose	Dose	µg/kg
Patient factors	Age	Years
	Gender (Male = 1)	Male = 1
Surgical factors	Procedure type	Isolated CABG = 1
		Isolated valve = 2
		Valve and CABG = 3
		Other = 4
	Urgency of surgery	Elective = 1
		Emergency = 2
		Salvage = 3
		Continuous
Laboratory results	INR before dose	Continuous
	Platelet count before dose	10 <sup>9</sup> /l
	Fibrinogen result before dose	g/l
	pH	Continuous (in 0.1 units)
Transfusion requirements	Temperature	Celsius
	Packed red cells before dose	Units
	FFP before dose	Units
	Cryoprecipitate before dose	Units
	Platelets before first dose	Units

CABG, coronary artery bypass graft surgery; INR: international normalized ratio; FFP, fresh frozen plasma.

**Table 5** Regression model for mortality

Dependent variable	Variable	OR	SE	P	95% CI
Mortality	Procedure type: Isolated valve	3.48	1.731	0.012	1.31, 9.23
	Procedure type: CABG and valve	5.56	3.636	0.009	1.55, 20.03
	pH	2.15	0.828	0.001	1.60, 2.88
	Platelet count before dose	1.01	0.004	0.001	1.01, 1.02

$n = 344$ , C-statistic = 0.81, H-L = 4.81 ( $P = 0.778$ ).

CABG, coronary artery bypass graft surgery.

surgery [13]. Recent results from the first randomized placebo-controlled trial of rFVIIa in cardiac surgery reported a non-significant association between rFVIIa given at two dose levels (40 µg/kg and 80 µg/kg) and critical serious adverse events [14]. While the study reported a reduced rate of bleeding, reduced transfusion requirement and reduced need for re-operation in patients receiving 80 µg/kg of rFVIIa versus placebo, no such differences were identified between patients receiving 80 µg/kg and 40 µg/kg of rFVIIa. The study was limited by a small sample size ( $n = 172$ ), which resulted in significant group imbalances on key covariates such as age, CPB time and

predose transfusion rates. The investigation was further restricted by a cumulative end point that combined mortality, acute myocardial infarction and thromboembolic adverse events (TAEs), along with stringent exclusion criteria that excluded patients receiving rFVIIa in operating theatres (a group that constituted 61% of patients in the present study). Therefore, results from the present investigation highlight the relationship between different dosing levels of rFVIIa and patient outcomes using the largest and most inclusive sample to date of cardiac surgery patients receiving rFVIIa.

Previous reports of rFVIIa in cardiac surgery have described a range of dose categories. Comparison of two dose regimens (70 and 35 µg/kg) in cardiac patients reported clinically effective results following low dose administration [1]. The authors concluded that an initial low dose of rFVIIa was favourable to treatment with higher doses, despite an increased likelihood for low dose patients to require a second dose [1]. Even lower doses (11.1–21.5 µg/kg) have been reported as beneficial in cardiac surgery patients for reducing bleeding, transfusion requirements and normalizing coagulation [10]. Similarly, investigations of rFVIIa doses ranging from 18 to 65 µg/kg have all reported decreased bleeding and reduced transfusion needs following rFVIIa administration [5,13,15]. The potential effectiveness of low dose treatment in non-cardiac settings, such as trauma, has added to the appeal of administering small initial doses in cardiac surgery patients [16]. The high cost of rFVIIa and the potential risk for TAEs, has highlighted the need for further dose related investigations to determine both safety and efficacy.

Other than in Queensland, there are no formal state-wide guidelines for dose and timing of rFVIIa administration. Patients receiving low dose therapy may be expected to present with less severe coagulation profiles and a reduced transfusion requirement compared to patients receiving higher rFVIIa doses. These data demonstrate statistically significant differences in the baseline characteristics of patients receiving different doses of rFVIIa. The lowest-dose category patients presented with similar INR values to patients receiving higher doses of rFVIIa, while fibrinogen values for patients receiving ≤40 µg/kg were significantly higher than patients in other dose categories, however results for all were still within normal ranges. The significant difference in the use of cryoprecipitate prior to rFVIIa may be reflective of the slightly elevated fibrinogen levels in the ≤40 µg/kg dose category or regionally based differences in the use of blood products. As this study is non-randomized, statistically different baseline characteristics are not unexpected. Despite the statistical differences between dose groups on a number of baseline characteristics, the clinical significance of differences in INR of 0.1–0.2 is uncertain. Some of the difference in baseline characteristics

can be accounted for by the statistical model. It is uncertain whether these differences constitute clinically relevant variations in underlying patient condition.

Patients receiving lower initial doses were more likely to receive multiple doses of rFVIIa than patients receiving higher initial doses [1]. Despite this, the cumulative total dose in the lowest dose category remained significantly lower than the total dose administered to patients in other dose categories. The decision to deliver a second dose of rFVIIa suggests a lesser response to the primary dose, which may relate to the source of bleeding or variation in individual patient response to treatment [17]: 74–81% of patients were judged to have responded to treatment across the dose categories. Due to the multiple, and often simultaneous interventions received by these patients, it is difficult to ascribe reductions in bleeding to specific interventions such as rFVIIa. Therefore it is possible that this judgment is an overestimate of the effectiveness of rFVIIa. Alternative markers of treatment effectiveness have been documented by others such as need for reoperation and blood transfusion post-dose [14]. While repeat operation for surgical bleeding was not analysed in the present analysis, the reduced need for large blood transfusions (>2 units) post-dose in those judged to have responded to treatment compared to non-responders ( $P < 0.001$ ), suggests clinical judgement may be useful. Moreover, the lack of statistical variation across dose categories in response to treatment according to clinical judgment indicates similar effects attributable to rFVIIa regardless of dose amount. Therefore, despite a greater likelihood of receiving a second dose of rFVIIa, lower dose administrations (40 µg/kg or 41–60 µg/kg) appear to be associated with similar bleeding responses to treatment as medium (61–80 µg/kg or 81–100 µg/kg) and high doses (100 µg/kg).

The incidence of TAEs is routinely used as a marker of the safety of rFVIIa in off licence settings. While the present analysis has been unable to identify any major differences in the rate of TAEs between dose categories, these results may be difficult to interpret due to the low number of TAEs reported for all dose groups. Taken in aggregate, the total TAE rate in this study (7.2%) is marginally higher than results of a systematic review of rFVIIa in cardiac surgery that suggested a TAE rate of 5.3% [18]. Similar figures have been reported in populations with critical bleeding due to anti-coagulation, cirrhosis or trauma [19]. As noted by Bowman *et al.* the possible link between rFVIIa and the development of TAEs is difficult to establish due to the action of confounding factors such as medications and coexisting medical conditions [20]. Further investigation of the relationship between dose and TAEs is therefore warranted.

The overall mortality rate in this study was 18%. While mortality rates appeared to be higher in larger dose groups

(excluding the lowest dose category), these results were not statistically significant. Furthermore, logistic regression analysis did not identify dose category as an independent predictor of mortality. Other reports on the use of rFVIIa in cardiac surgery patients have reported mortality rates ranging from 9% to 32% [4,5,14,17,21,22]. While the mortality rate in the present study is considerably higher than the 9% mortality rate reported by Gill *et al.*, differences in underlying patient populations may explain this finding. For example, in the present study cardiopulmonary transplant patients (3.6% of patients) and aortic arch/descending thoracic aorta patients (32% of patients), were found to carry mortality rates of 89% and 76% respectively. As both surgical groups were excluded in the RCT by Gill *et al.*, differences in outcome between these studies may not be unexpected.

Surprisingly a higher platelet count prior to rFVIIa, was a weak predictor of increased mortality in the present analysis. As this finding is unexpected and difficult to rationalize, further investigation of the relationship between platelet count and mortality is required, and may benefit from including hemodynamic data and variables known to determine cardiac surgical outcomes such as cardiopulmonary bypass time and ventricular function. As expected, pH demonstrated a strong link to mortality, but remains a poorly documented parameter in the medical record, with data missing from many Haemostasis Registry submissions. As hypothesized, results from the multivariate analysis adjusting for key parameters, suggest that size of dose may not be an independent predictor of mortality in this clinical context.

This study had a number of limitations. Due to the registry based nature of the data collected, no control group was present. Moreover, factors influencing patient outcomes not routinely collected on the registry but which may differ between dose categories are unknown. As dose was not normally distributed it was necessary to use dose categories in this analysis. As these dose categories were based on clinical grounds, different results using alternative dose ranges may be possible.

The present study reports on the largest series of off-label administrations of rFVIIa in cardiac surgery patients and suggests that considerable variation exists in the off-licence dosing practices across hospitals in Australia and New Zealand. Approximately 5% of patients in the present study received a dose of rFVIIa  $\leq 40$  µg/kg. These patients did not appear to differ clinically from other patients receiving higher doses in terms of complexity or transfusion requirements. Patients receiving lower dose therapy did not demonstrate significantly different outcomes from medium and higher dose patients, as measured by the rate of TAEs. Moreover, multivariate analyses suggested that dose was not an independent predictor of mortality in these

patients. These findings raise the important question of whether lower doses of rFVIIa may be as effective and efficacious as higher doses in the treatment of severe bleeding in cardiac surgery patients.

## Acknowledgement

The Haemostasis Registry is supported by an unrestricted educational grant from Novo Nordisk Pharmaceuticals Pty Ltd.

## References

- Karkouti K, Beattie WS, Wijeyesundera DN, Yau TM, McCluskey SA, Ghannam M, Sutton D, van Rensburg A, Karski J: Recombinant factor VIIa for intractable blood loss after cardiac surgery: a propensity score-matched case-control analysis. *Transfusion* 2005; 45:26–34
- Loudon B, Smith MP: Recombinant factor VIIa as an adjunctive therapy for patients requiring large volume transfusion: a pharmacoeconomic evaluation. *Intern Med J* 2005; 35:463–467
- Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M: Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. *J Thorac Cardiovasc Surg* 1996; 111:1037–1046
- Karkouti K, Beattie WS, Arellano R, Aye T, Bussières JS, Callum JL, Cheng D, Heinrich L, Kent B, Lee TWR, MacAdams C, Mazer CD, Muirhead B, Rochon AG, Rubens FD, Sawchuk C, Wang S, Waters T, Wong BI, Yau TM: Comprehensive Canadian review of the off-label use of recombinant activated factor VII in cardiac surgery. *Circulation* 2008; 118:331–338
- Raivio P, Suojaranta-Ylinen R, Kuitunen AH: Recombinant factor VIIa in the treatment of postoperative hemorrhage after cardiac surgery. *Ann Thorac Surg* 2005; 80:66–71
- Tritapepe L, De Santis V, Vitale D, Nencini C, Pellegrini F, Landoni G, Toscano F, Miraldi F, Pietropaoli P: Recombinant activated factor VII for refractory bleeding after acute aortic dissection surgery: a propensity score analysis. *Crit Care Med* 2007; 35:1685–1690
- Bishop CV, Renwick WEP, Hogan C, Haeusler M, Tuckfield A, Tatoulis J: Recombinant activated factor VII: treating postoperative hemorrhage in cardiac surgery. *Ann Thorac Surg* 2006; 81:875–879
- Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *New Engl J Med* 2008; 358:2127–2137
- Lusher JM, Roberts HR, Davignon G, Joist JH, Smith H, Shapiro A, Laurian Y, Kasper CK, Mannucci PM: A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. rFVIIa Study Group. *Haemophilia* 1998; 4:790–798
- Romagnoli S, Bevilacqua S, Gelsomino S, Pradella S, Ghilli L, Rostagno C, Gensini GF, Sorbara C: Small-dose recombinant activated factor VII (NovoSeven) in cardiac surgery. *Anesth Analg* 2006; 102:1320–1326
- O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy DF, Laffan MA, Smith OP: Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion* 2003; 43:1711–1716
- Johnson SJ, Ross MB, Moores KG: Dosing factor VIIa (recombinant) in nonhemophiliac patients with bleeding after cardiac surgery. *Am J Health-Syst Ph* 2007; 64:1808–1812
- Gelsomino S, Lorusso R, Romagnoli S, Bevilacqua S, De Cicco G, Billè G, Stefano P, Gensini GF: Treatment of refractory bleeding after cardiac operations with low-dose recombinant activated factor VII (NovoSeven): a propensity score analysis. *Eur J Cardio-Thorac* 2008; 33:64–71
- Gill R, Herbertson M, Vuylsteke A, Skov Olsen P, von Heymann C, Mythen M, Sellke F, Booth F, Andersen Schmidt T: Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009; 120:21–28
- Karkouti K: Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. *Can J Anaesth* 2006; 53:802–809
- Harrison TD, Laskosky J, Jazaeri O, Pasquale MD, Cipolle M: "Low-dose" recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. *J Trauma* 2005; 59:150–154
- McCall P, Story DA, Karapillai D: Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery. *Can J Anaesth* 2006; 53:926–933
- Warren O, Mandal K, Hadjianastassiou V, Knowlton L, Panesar S, John K, Darzi A, Athanasiou T: Recombinant activated factor VII in cardiac surgery: a systematic review. *Ann Thorac Surg* 2007; 83:707–714
- Levy JH, Fingerhut A, Brott T, Langbakke IH, Erhardtson E, Porte RJ: Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: review of safety profile. *Transfusion* 2006; 46:919–933
- Bowman LJ, Uber WE, Stroud MR, Christiansen LR, Lazarchick J, Crumbley AJ, Kratz JM, Toole JM, Crawford FA, Ikonomidis JS: Use of recombinant activated factor VII concentrate to control postoperative hemorrhage in complex cardiovascular surgery. *Ann Thorac Surg* 2008; 85:1669–1676
- Hyllner M, Houlitz E, Jeppsson A: Recombinant activated factor VII in the management of life-threatening bleeding in cardiac surgery. *Eur J Cardio-Thorac* 2005; 28:254–258
- von Heymann C, Redlich U, Jain U, Kastrup M, Schroeder T, Sander M, Grosse J, Ziemer S, Koscielny J, Konertz WF, Wernecke K-D, Spies C: Recombinant activated factor VII for refractory bleeding after cardiac surgery—a retrospective analysis of safety and efficacy. *Crit Care Med* 2005; 33:2241–2246