

Comprehensive Canadian Review of the Off-Label Use of Recombinant Activated Factor VII in Cardiac Surgery

Keyvan Karkouti, MD; W. Scott Beattie, MD; Ramiro Arellano, MD; Tim Aye, MD; Jean S. Bussieres, MD; Jeannie L. Callum, MD; Davy Cheng, MD; Lee Heinrich, MD; Blaine Kent, MD; Trevor W.R. Lee, MD; Charles MacAdams, MD; C. David Mazer, MD; Brian Muirhead, MD; Antoine G. Rochon, MD; Fraser D. Rubens, MD; Corey Sawchuk, MD; Shaohua Wang, MD; Terrence Waters, MD; Bill I. Wong, MD; Terrence M. Yau, MD

Background—This observational study sought to identify the off-label use pattern of recombinant activated factor VII (rFVIIa) in cardiac surgery and to identify predictors of its effectiveness and risk.

Methods and Results—At 18 Canadian centers, 522 nonhemophiliac cardiac surgical patients received rFVIIa during the period 2003 through 2006; data were available, and retrospectively collected, on 503 patients. The median (quartile 1, quartile 3) units of red blood cells transfused from surgery to therapy and in the 24 hours after therapy were 8 (5, 12) and 2 (1, 5), respectively ($P < 0.0001$). Mortality rate was 32%, and mortality or major morbidity rate was 44%. These rates were within expected ranges (mortality, 27% to 35%; mortality or morbidity, 39% to 48%), which were calculated with a separate cohort of cardiac surgical patients who did not receive rFVIIa used as reference. Independent predictors of complications included instability before therapy (multiple inotropes or intra-aortic balloon pump) and increasing red blood cell units transfused before and after therapy. Variables independently associated with nonresponse included abnormal coagulation parameters and >15 red blood cell units transfused before therapy.

Conclusions—In Canada, rFVIIa is used primarily when standard interventions have failed to control bleeding. In this setting, rFVIIa is associated with reduced blood product transfusions and, after risk adjustment, does not appear to be associated with increased or decreased complication rates. The effectiveness of the drug may be enhanced if it is given early in the course of refractory blood loss in the setting of adequate amounts of circulating coagulation factors. (*Circulation*. 2008;118:331-338.)

Key Words: cardiopulmonary bypass ■ coagulation ■ drugs ■ pharmacology ■ thrombosis

Despite major advances in the field of cardiac surgery, excessive blood loss necessitating large-volume fluid and blood product resuscitation, surgical reexploration, or both remains a serious complication that is directly linked to increased morbidity and mortality.¹ Recombinant activated factor VII (rFVIIa) is a hemostatic agent that may be effective in preventing or treating excessive blood loss in cardiac surgery, but it is currently not approved for this indication in any jurisdiction. In most countries, rFVIIa is only approved for hemophiliac patients with inhibitors against factors VIII and IX. In some countries, it is also approved for factor VII deficiency and Glanzmann's thrombasthenia. Whether rFVIIa is safe and effective outside these approved indications in adult cardiac surgery has not yet been elucidated by large-scale, randomized, placebo-controlled clinical trials; current best evidence is limited primarily to case-control studies.² Nevertheless, owing to the heavy burden of excessive blood

loss, current recommendations are that it is reasonable to consider rFVIIa therapy in cases of excessive blood loss that is unresponsive to standard interventions,^{3,4} and as a result the drug is being increasingly used in this setting.⁵ Given the unresolved safety and effectiveness issues, however, some have questioned the appropriateness of the off-label use of the drug in cardiac surgery and other settings.⁶ Safety is of particular concern because of reports of thrombotic complications associated with its off-label use in various settings.⁷

Clinical Perspective p 338

To address some of these unresolved issues, we undertook this retrospective, observational, multicenter review to (1) identify the emerging off-label use pattern of this drug in cardiac surgery across Canada during the period 2003 through 2006; (2) identify the determinants of its effectiveness and risk in cardiac surgery; and (3) determine whether it is associated with increased risk of adverse events in this setting.

Received January 2, 2008; accepted May 23, 2008.

From the University Health Network, Toronto General Hospital, Department of Anesthesia, Toronto, Ontario, Canada (K.K.). For affiliations of other authors, please see the Disclosures Table.

Correspondence to Keyvan Karkouti, MD, University Health Network, Toronto General Hospital, Department of Anesthesia, EN 3-402, 200 Elizabeth St, Toronto, Ontario, Canada M5G 2C4. E-mail keyvan.karkouti@uhn.on.ca

© 2008 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.108.764308

Methods

All major centers across Canada that perform adult cardiac surgery were approached for the study. Twenty-one centers agreed to participate, but 3 centers that had not used any rFVIIa in cardiac surgery during the study period were excluded. Institutional research ethics approval was obtained at each participating center.

The blood bank (or, when applicable, pharmacy) database at each center was used to obtain a list of every cardiac surgical patient who had received rFVIIa from January 1, 2003, to December 31, 2006. With the use of a standardized data collection form and trained data abstractors, detailed perioperative data were then collected retrospectively from hospital records for all patients who had undergone surgery with cardiopulmonary bypass (CPB). Patients with hemophilia were excluded. Variables collected included patient demographics, comorbidities, and operative information; dose and timing of rFVIIa therapy; hemodynamic, laboratory, and transfusion data before and after rFVIIa therapy (Tables 1 and 2); and postoperative outcomes.

Outcomes

The numbers of units of blood products transfused before rFVIIa therapy (from initiation of surgery) and after rFVIIa therapy (24 hours after the first dose) were compared as a measure of effectiveness. Patients were classified as responders or nonresponders on the basis of the number of red blood cell (RBC) units that they received after rFVIIa therapy to allow us to identify which variables were associated with better response.

The following in-hospital postoperative adverse outcomes were analyzed: mortality, stroke (defined as documented new postoperative, persistent neurological deficit), renal failure (defined as documented postoperative institution of dialysis), myocardial infarction (if documented in the medical records), and the composite outcome of any of the above. With recognition of the limitations of retrospective reviews, myocardial infarction was not defined formally; rather, data abstractors were instructed to document it if it was noted on the clinical notes, discharge forms, death certificates, or autopsy reports. Data on other ischemic events (eg, pulmonary embolism, deep vein thrombosis, limb ischemia) were also collected.

Data were entered centrally into a database (with built-in logic controls); out of range or missing data were queried and verified or obtained when possible.

Statistical Analyses

Statistical analyses were performed with the use of SAS version 9.1 (SAS Institute, Inc, Cary, NC). Descriptive data were used to examine the yearly use of rFVIIa, as well as patient characteristics and outcomes. Blood product transfusions before and after rFVIIa therapy were compared with the Wilcoxon signed rank test.

Multivariable logistic regression was used to identify the independent predictors of (1) response to rFVIIa, (2) in-hospital mortality, and (3) composite outcome of in-hospital mortality or major morbidity (stroke, renal failure, or myocardial infarction). First, the bivariate associations between the potential predictor variables and the 3 outcome variables were determined with appropriate tests (χ^2 or Fisher exact tests for categorical variables and unpaired *t* test or Wilcoxon rank sum test for continuous variables). These relationships guided any simplifications of categorical variables in the multivariable analyses. When appropriate, continuous variables were divided into clinically sensible categories on the basis of their association with the outcome in restricted cubic spline plots regression.⁸ All potential predictor variables for each outcome ($P < 0.3$ in the bivariate analyses or based on clinical judgment) were next fitted into multivariable logistic regression models.⁹ The models were constructed with the use of backward stepwise variable selection, and a probability value of ≤ 0.05 was used as the criterion for variable retention. Model discrimination was assessed by the *c* index, and calibration was assessed by the Hosmer-Lemeshow test.⁹ Bootstrap resampling¹⁰ was used to assess the stability of the models as follows: 100 computer-generated samples, each including 500 patients, were derived from the study cohort by random selection with replacement, and the models were refitted for each sample. The number of times each predictive variable remained in the bootstrap samples was measured.

To determine whether rFVIIa therapy is associated with increased adverse event rates, the expected rates for mortality and the composite adverse outcome in the study cohort were calculated from a risk model constructed on a separate cohort of patients who underwent cardiac surgery during 2004 at 7 of the centers that participated in the present study. Details of this comparison cohort, which consisted of 500 consecutive patients from each participating center ($n = 3500$), have been described previously.^{11,12} Because the comparison cohort included consecutive patients, it is expected to be representative of the general cardiac surgery population. Importantly, data fields, definitions, and collection processes for the comparison cohort were similar to those used for the present study. The risk model was constructed on the comparison cohort with the same methodology as described above, with the following modifications: total RBC transfusion during hospital stay was used instead of number of units before and after rFVIIa surgery, post-CPB variables were not included (because they were not available in the comparison cohort), and patients in the comparison cohort who had received rFVIIa ($n = 28$) were excluded. The risk models developed on the comparison cohort were then used to calculate the adjusted probability of the occurrence of the outcomes for each individual patient in both cohorts. The sums of the adjusted probabilities for patients in the cohorts were calculated to obtain the expected number of events in the cohorts. The 95% confidence intervals (CIs) around the estimates (ie, range of expected events) were then calculated.¹³ For sensitivity analysis, the same analyses were performed in 2 subgroups: (1) patients who received > 5 RBC units and (2) those who underwent surgery at the 7 hospitals that were used to obtain the comparison cohort.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The 18 participating centers performed between 500 and 1800 cardiac surgical cases annually. The 21 evaluated centers perform $\approx 26\,000$ cardiac surgery cases per year, which represents $\approx 90\%$ of adult cardiac surgery cases performed in Canada. (The cardiac surgery rate in Canada is $\approx 30\,000/y$ according to the Canadian Institute for Health Information.) During 2003–2006, 522 nonhemophiliac patients who underwent cardiac surgery with CPB at these centers received 1 or more doses of rFVIIa. No data were available for 19 patients (3 of whom died); thus, 503 patients were included in the study cohort. Missing data for included patients were not imputed; consequently, some of the descriptive statistics include < 503 patients.

The number of patients who received rFVIIa at each center ranged from 8 to 158 (median, 17). In 2 of the centers, rFVIIa was used in $\approx 2\%$ of cases (high-user centers), whereas in the other 16 rFVIIa was used in $\approx 0.5\%$ of cases (low-user centers). Overall, rFVIIa use increased slightly from 2003 to 2005 but almost doubled in 2006, primarily because of increased usage in the low-user centers (Figure 1).

Of the 503 patients, 378 (75%) received a single dose, 99 (20%) received 2 doses, 19 (4%) received 3 doses, and 7 (1%) received > 3 doses of rFVIIa. The median total dose received was 62 $\mu\text{g/kg}$ (quartile 1 [Q1], quartile 3 [Q3], 40, 89 $\mu\text{g/kg}$); the median first dose received was 49 $\mu\text{g/kg}$ (Q1, Q3, 35, 72 $\mu\text{g/kg}$). The median elapsed time from end of CPB to first dose of rFVIIa therapy was 280 minutes (Q1, Q3, 154, 556 minutes). There were no material changes in the yearly patterns of dosage and timing of rFVIIa during the study (data not shown).

Patients' characteristics and health status before rFVIIa therapy in the entire cohort and in relation to mortality are shown in Table 1. As can be seen, patients had many

Table 1. Patient Characteristics and Bivariate Relationships With In-Hospital Mortality

Variable*	Total Sample (n=503)	Survivors (n=344)	Nonsurvivors (n=159)	P
Preoperative variables				
Age, y	62±15	61±16	64±14	0.1
Weight, kg	76±18	76±18	77±19	0.5
Female	154 (31)	97 (28)	57 (37)	0.06
Diabetes mellitus (type 1 or 2)	104 (21)	59 (17)	45 (28)	0.004
Hypertension (on treatment with medications)	295 (59)	188 (55)	107 (67)	0.007
Left ventricular dysfunction (ejection fraction <40%)	121 (25)	79 (24)	42 (28)	0.3
Peripheral vascular disease (claudication or previous surgery on peripheral vessels)	53 (11)	32 (9)	21 (13)	0.2
Cerebrovascular disease (stroke, transient ischemic event, or carotid artery disease)	77 (15)	49 (14)	28 (18)	0.3
Shock (requiring hemodynamic support)	89 (18)	39 (11)	50 (32)	<0.0001
Antiplatelet or anticoagulant drugs at time of surgery (not including acetylsalicylic acid)	196 (39)	123 (36)	73 (46)	0.03
Renal dysfunction (creatinine >100 μmol/L in women or >110 μmol/L in men; or on dialysis)	184 (36)	105 (31%)	79 (50%)	<0.0001
Operative variables				
Urgent surgery	232 (50)	153 (48)	79 (53)	0.3
Redo surgery	165 (35)	107 (33)	58 (41)	0.1
Complex surgery (other than isolated aortocoronary bypass or single-valve surgery)	388 (77)	256 (74)	132 (83)	0.03
Aortocoronary bypass (±other procedures)	227 (45)	140 (41)	87 (55)	0.003
Valve repair or replacement (±other procedures)	278 (55)	194 (56)	84 (53)	0.4
Aortic repair or replacement (±other procedures)	132 (26)	90 (26)	42 (27)	0.9
Aprotinin	263 (55)	169 (52)	94 (61)	0.03
CPB duration, min	203±110	185±90	243±137	<0.0001
Deep hypothermic circulatory arrest	112 (22)	74 (21)	38 (24)	0.5
Reexploration	259 (53)	184 (55)	75 (49)	0.2
Condition before rFVIIa therapy*				
Unstable (requiring >2 inotropes or IABP)	180 (36)	88 (26)	92 (58)	<0.0001
Hemoglobin, g/dL	8.5±1.6	8.6±1.5	8.5±1.9	0.7
Platelet count, 10 ⁶ /L	115±50	119±50	106±48	0.004
International normalized ratio	1.7±0.9	1.6±0.5	2.0±1.6	0.002
Abnormal coagulation tests (international normalized ratio >2.0, partial thromboplastin time >60 s, fibrinogen <1.0 g/L, or platelets <80×10 ⁶)	254 (55)	155 (48)	99 (70)	<0.0001
Temperature, °C	36.0±1.4	36.0±1.3	36.0±1.4	0.5
pH	7.4±0.1	7.4±0.1	7.3±0.1	<0.0001

Values are mean±SD or n (%). IABP indicates intra-aortic balloon pump.

*Last available before rFVIIa.

Table 2. Blood Product Transfusions

Variable	Total in Hospital	Before rFVIIa (From Surgery to First Dose)	After rFVIIa (Within 24 h After First Dose)	<i>P</i>	No. With Missing Pre- or Post-rFVIIa Data
RBCs	13 (8, 20)	8 (5, 12)	2 (1, 5)	<0.0001	18
Platelets	20 (10, 25)	10 (10, 15)	5 (0, 10)	<0.0001	42
Fresh frozen plasma	12 (8, 20)	8 (5, 12)	2 (0, 6)	<0.0001	39
Cryoprecipitate	10 (0, 20)	0 (0, 10)	0 (0, 10)	<0.0001	39
Total products	55 (40, 84)	33 (22, 50)	9 (2, 22)	<0.0001	62

Values are median (Quartile 1, Quartile 3).

high-risk characteristics, and many of them underwent high-risk surgical procedures. Moreover, many patients required hemodynamic support or had other signs of instability by the time they received rFVIIa.

Table 2 shows the blood product transfusion data from time of surgery to discharge and in relation to rFVIIa therapy. In general, patients received large amounts of blood products before rFVIIa therapy, and they received substantially fewer blood products after rFVIIa therapy. Of note, 6 patients received rFVIIa without any blood products being transfused. In all but 23 other patients, rFVIIa therapy was preceded by both platelet and plasma transfusions. On response to rFVIIa therapy, 380 patients (78%) received ≤ 5 RBC units during the 24 hours after rFVIIa therapy. Yearly blood product usage patterns were similar (data not shown).

The adverse event rates in the study cohort were as follows: mortality, 32% ($n=159$); stroke, 12% ($n=58$); renal failure, 12% ($n=59$); myocardial infarction, 9% ($n=45$); composite outcome of mortality, stroke, renal failure, or myocardial infarction, 44% ($n=222$). Other ischemic events were documented in 20 patients (4%).

Table 3 shows the independent predictors of mortality (the model for the composite outcome of mortality or major morbidity was similar and is not presented). The model was highly discriminative (*c* index of 0.84), reliable (Hosmer-Lemeshow $P=0.2$), and stable (all variables remained in all 100 bootstrap-sample models). Of note, aortocoronary bypass surgery did not remain in the model. (Antifibrinolytic drug

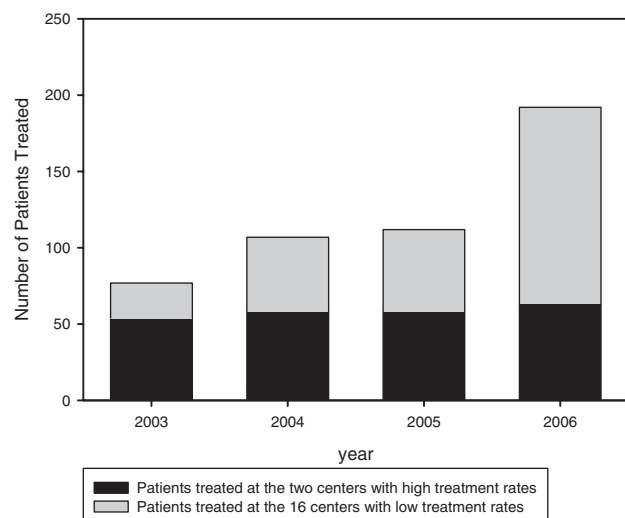


Figure 1. Yearly usage of rFVIIa.

type, year of surgery, and dose of rFVIIa were not included in the models because they were strongly related to the site.)

Figure 2 shows the observed and expected rates of mortality and the composite outcome of mortality or morbidity in the comparison and study cohorts. The models constructed on the comparison cohort for calculating expected rates were discriminative (*c* index >0.80) and reliable (Hosmer-Lemeshow test $P>0.2$). The top 4 predictive variables in both models were RBC units transfused, preoperative shock, CPB duration, and preoperative renal dysfunction. As can be seen in Figure 2, although the observed adverse event rates were markedly higher in the study cohort, they were within the 95% CI of the calculated expected rates (which were 27% to 35% for mortality and 39% to 48% for mortality or morbidity). In the study cohort, the ratios of observed to expected numbers of mortalities and the composite outcomes of mortality or morbidity were 1.04 (95% CI, 0.90 to 1.16) and 1.01 (95% CI, 0.92 to 1.12), respectively. Similarly, in the subgroups analyzed, the observed adverse event rates in the study cohort were well within the range of expected adverse event rates (results not shown).

Independent predictors of failure to respond (when defined as transfusion of >5 RBC units within 24 hours of therapy) were pretreatment abnormal coagulation tests (presence of 1 or more of the following: international normalized ratio >2.0 , partial thromboplastin time >60 seconds, fibrinogen <1.0 g/L, or platelet count $<80 \times 10^6$) (odds ratio, 3.1; 95% CI, 1.8 to 5.3; $P<0.0001$); salvage therapy (defined as >15 units of RBCs transfused before rFVIIa therapy) (odds ratio, 2.0; 95% CI, 1.1 to 3.6; $P=0.03$); and CPB duration >150 minutes (odds ratio, 1.8; 95% CI, 1.0 to 3.0; $P=0.04$). Because the definition of response was based on the number of posttreatment RBC transfusions, adjustment was made for pretreatment hemoglobin by forcing it into the model ($P=0.9$). The model's *c* index was 0.70, and its Hosmer-Lemeshow test probability value was 0.4. The results were not materially different if different posttherapy RBC transfusion thresholds (2, 3, or 4 units) were used to define response to therapy.

Discussion

This comprehensive evaluation of the off-label use of rFVIIa in cardiac surgery addresses several important issues relating to appropriateness, effectiveness, and safety of rFVIIa in this setting.

Appropriateness

One important issue in cardiac surgery is whether rFVIIa is being used appropriately in clinically reasonable settings or inappropriately in questionable settings.⁶ Current recommen-

Table 3. Independent Predictors of Mortality

Variable	Unit or Classification	Wald χ^2	P	Odds Ratio	95% CI	Bootstrap Retention, %
Age	1: >50 years old	7.2	0.007	2.6	1.3–5.4	100
Preoperative shock	1: See Table 2	11.0	0.0009	2.7	1.5–4.9	100
Renal dysfunction	1: See Table 2	4.5	0.03	1.7	1.1–2.8	100
CPB duration	Continuous (minutes)	8.0	0.005	1.003	1.001–1.006	100
Unstable before rFVIIa therapy	1: >2 inotropes or IABP	9.3	0.002	2.2	1.3–3.6	100
pH before rFVIIa therapy	3: pH <7.2			7.9	2.7–23.3	
	2: 7.2 ≤ pH <7.3			3.1	1.5–6.3	
	1: 7.3 ≤ pH <7.4			2.0	1.1–3.6	
RBC units before rFVIIa therapy	1: >10 units	11.2	0.0008	2.4	1.4–4.0	100
RBC units after (24 h) rFVIIa therapy		27.0	<0.0001			100
	2: >10 units			8.9	3.6–22.0	
	1: 6 to 10 units			2.6	1.3–5.1	

IABP indicates intra-aortic balloon pump.

dations are that the off-label use of rFVIIa be considered only in cases of excessive blood loss that is unresponsive to standard interventions,^{2–4} a complication that by some estimates occurs in only ≈2% of cases.¹⁴ Our findings suggest that, for the most part, clinicians are following these recommendations. None of the participating centers, which together perform ≈90% of adult cardiac surgery in Canada, used rFVIIa in >2% of their cases, and in all but 5% of cases patients received both platelet and plasma transfusions before rFVIIa therapy. On the other hand, approximately one half of patients had abnormal coagulation parameters before rFVIIa therapy (Table 1), which indicates that patients had not received sufficient blood products before rFVIIa therapy. Given the long turnaround time for these tests, however, many of these patients may have received additional blood products from the time samples were collected for measuring coagulation to the time when rFVIIa was administered. Of note, 6 patients received rFVIIa without any blood products being transfused, presumably because they did not wish to

receive blood transfusions (data on transfusion preferences were not collected).

Of possible concern is the nearly 2-fold increased usage in the final year of the study, which may herald “indication creep” (or inappropriate expansion of indications).⁶ This, however, does not seem to be the case because time to therapy, as measured by both elapsed time from end of CPB to therapy and number of RBC units transfused before therapy, was constant during the 4 years of the study. Our data suggest, rather, that the increased usage is due to low-use centers adopting the therapy later than high-use centers (Figure 1).

Effectiveness and Predictors of Response

Another issue addressed here is whether rFVIIa effectively reduces or stops hemorrhage after cardiac surgery in patients without hemophilia. To date, randomized clinical trials aimed at assessing the efficacy of rFVIIa in various surgical and trauma settings have found it to be no more effective than placebo in preventing or reducing bleeding in patients without hemophilia.¹⁵ None of these studies, however, assessed the efficacy of rFVIIa when it is used as rescue therapy in patients with refractory hemorrhage after cardiac surgery.¹⁵ On the other hand, numerous observational studies have found a strong temporal relationship between rFVIIa use in this setting and reduced blood loss or blood product transfusions.² This finding is consistent with the results of our study, in which patients received substantially fewer blood product transfusions in the 24 hours after rFVIIa therapy than they did from surgery to rFVIIa therapy. Even though observational studies cannot prove causation, the strength, consistency, and temporality of this observed association in this and many other observational studies suggest the presence of a cause-and-effect relationship.¹⁶

Previous studies have suggested that response to rFVIIa is adversely affected by pretreatment acidosis and hypothermia,^{5,17} but in this study these factors were not independently associated with the amount of RBC transfusions after therapy. Generally, however, patients in this study were not severely acidotic or hypothermic before rFVIIa therapy. Variables that were independently associated with increasing RBC transfusions after

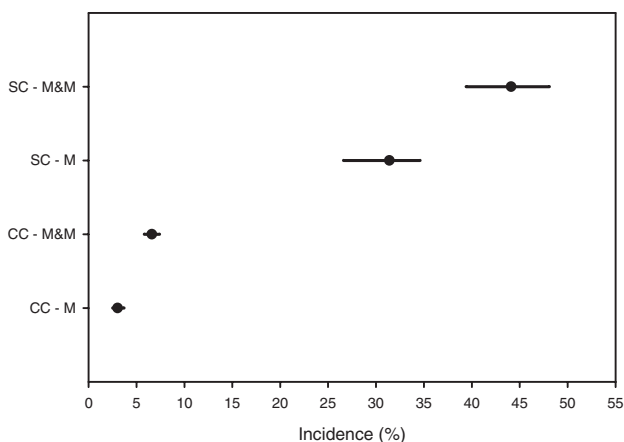


Figure 2. Observed and expected adverse event rates in the study and comparison cohorts. CC indicates comparison cohort; SC, study cohort; M, mortality; M&M, composite outcome of mortality or morbidity; ●, observed event rate; and black line, range of expected event rates.

therapy (ie, lack of response) included abnormal coagulation parameters before therapy and transfusion of >15 units of RBCs before therapy. This is consistent with the emerging understanding that rFVIIa may be more effective when it is administered early in the course of refractory blood loss in the setting of adequate amounts of circulating coagulation factors.^{17–19} It may also explain why rFVIIa was not efficacious in existing randomized controlled clinical trials in bleeding patients, many of which did not stipulate the presence of adequate amounts of coagulation factors before rFVIIa therapy.

Safety and Predictors of Adverse Events

Perhaps the most important unresolved issue in cardiac surgery is whether rFVIIa is safe. After cardiac surgery with CPB, there is upregulation of tissue factor expression both locally in areas of tissue injury and systemically.^{20,21} Given that the mechanism of action of rFVIIa in part involves binding to tissue factor,²² increased tissue factor expression may lead to more local and systemic clot formation.²³ This is of particular concern in patients with excessive blood loss, in whom organ hypoperfusion and reperfusion injury resulting from inadequate or delayed resuscitation may lead to disseminated intravascular coagulation,²⁴ which can increase systemic tissue factor expression²⁵ and may therefore further increase the risk of thrombotic complications with rFVIIa therapy. Furthermore, rFVIIa therapy may increase the incidence of acute coronary events in patients undergoing coronary artery bypass grafting or in those who have vulnerable atherosclerotic plaques in their coronary vasculature.²³ It has also been postulated that rFVIIa may contribute to multiorgan failure by modulating the inflammatory response in the setting of systemic inflammatory response syndrome,^{26,27} which commonly occurs after cardiac surgery with CPB.²⁸ In addition, antifibrinolytic drugs that are frequently used to preserve the hemostatic system during CPB may further increase the risk of thrombotic complications with rFVIIa.²⁹

Consistent with several previous reports,^{5,7,30–32} we found an alarmingly high unadjusted rate of mortality and morbidity in the study cohort. Because they lacked control patients, however, these previous studies could not determine whether this high rate was due to rFVIIa therapy or patients' underlying medical status. In this study, we used a large multicenter cohort of cardiac surgical patients who did not receive rFVIIa and were representative of the general cardiac surgery population as a reference and found that the observed adverse event rates in the study cohort were neither increased nor decreased compared with expected rates based on patients' underlying risk status and RBC transfusion rate. This finding is consistent with several smaller studies in cardiac surgery that have found that patients who receive rFVIIa have risk-adjusted complication rates similar to those who do not receive rFVIIa.^{14,33–35} Importantly, by adjusting for RBC transfusions in this analysis, we have discounted the potential benefits of rFVIIa in reducing blood loss, thereby enhancing our ability to detect the risks of rFVIIa. It is important to note, however, that the severity of patients' underlying risk status and the high complication rates in this and most other studies may mask clinically important modulations in risk caused by rFVIIa therapy. Thus, although our results are reassuring, it is important that the observed versus expected

adverse event rates in the study cohort not be interpreted or inferred to be an indication of safety of rFVIIa. Adequately powered randomized controlled clinical trials are required to settle the safety issue in cardiac surgery.

Important independent predictors of mortality and morbidity in this study were unstable status at the time of rFVIIa therapy (as measured by the need for hemodynamic support and level of acidosis) and failure to respond to rFVIIa (as measured by number of RBC units transfused after therapy) (Table 3). This finding, together with our finding that rFVIIa may be more effective if it is given early in the course of refractory blood loss, supports the hypothesis that the early (rather than late) use of rFVIIa in patients with refractory bleeding may be preferable because it may prevent massive blood loss and the resultant hemodynamic instability.^{17,36} Future randomized clinical trials should be designed to allow the testing of this hypothesis.

Study Strengths and Limitations

The strengths of this study are its comprehensiveness (all patients who received rFVIIa at the participating centers were identified, and >95% of them were included in the study), which limited reporting bias; its large sample size, which allowed for robust multivariable analyses; and its use of an independent cohort representative of the general cardiac surgery population to assess the expected adverse event rates in the study cohort.

The primary limitations of the study are that, as in any other observational study, it can only identify associations rather than cause-and-effect relationships and cannot exclude the role of unmeasured confounders in the observed associations (eg, surgical source of bleeding as a cause of lack of response). Moreover, because at most of the centers the dose of rFVIIa used was directly related to the severity of patients' blood loss, the relationships between dose and effectiveness and risk of rFVIIa could not be determined.

Another limitation is that adverse outcomes were not prospectively evaluated; thus, many complications may have been missed. To minimize this problem, we limited our analyses to serious complications that were expected to be accurately recorded in patients' hospital records. Moreover, because the methodology used to identify complications in the comparison cohort was similar to that used in this study, our calculation of expected adverse event rates should be valid. Nevertheless, this study cannot exclude the possibility that rFVIIa is associated with increased risk of serious adverse events.

Finally, the study could only assess effectiveness by measuring changes in transfusion rates before and after rFVIIa therapy and could only assess safety by comparing adverse event rates with a reference cohort of patients who did not receive rFVIIa but received similar amounts of RBC transfusions. In effect, therefore, the latter analysis assumes that rFVIIa is not at all effective in reducing RBC transfusions. Consequently, the study could not assess whether rFVIIa improves clinical outcomes by reducing blood loss. A randomized controlled clinical trial is required to answer this important question.

Conclusions

In this comprehensive review of the off-label use of rFVIIa in cardiac surgery in Canada, we found that rFVIIa is being used

primarily when standard interventions have failed to control blood loss. Moreover, as far as can be determined within the confines of an observational study, we found that rFVIIa is associated with a reduction in transfusion of blood products and, after adjustment for patients' underlying risk profile and RBC transfusion rate, does not appear to be associated with increased or decreased mortality or major morbidity. Finally, our data also suggest that the effectiveness of the drug may be enhanced if it

is given early in the course of refractory blood loss in the setting of adequate amounts of circulating coagulation factors. Adequately powered randomized clinical trials are needed to verify these findings.

Sources of Funding

This study was funded through an unrestricted grant from Novo Nordisk (Mississauga, Ontario, Canada).

Disclosures

Disclosures (In Alphabetical Order)

Author	Position	Disclosures
Ramiro Arellano	Department of Anesthesia, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada	None
Tim Aye	Cardiac Anesthesia, Intensive care, St Mary's Regional Cardiac Care Centre, Kitchener, Ontario, Canada	None
W. Scott Beattie	Department of Anesthesia, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada	R. Fraser Elliott Chair of Cardiac Anesthesia; has received research grants and honoraria from Novo Nordisk
Jean S. Bussieres	Department of Anesthesia, Laval University and University Heart and Lung Institute at Laval Hospital, Quebec City, Quebec, Canada	None
Jeannie L. Callum	Department of Clinical Pathology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada	None
Davy Cheng	Department of Anesthesia and Perioperative Medicine, University of Western Ontario, London Health Sciences Center and St Joseph's Health Care, London, Ontario, Canada	None
Lee Heinrich	Department of Anesthesia, Southlake Regional Health Centre, Newmarket, Ontario, Canada	None
Keyvan Karkouti	Department of Anesthesia and Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada	Funded in part by the Bristol Myers Squibb/Canadian Anesthesiologists Society Career Scientist Award; has received research grants, honoraria, and consultants' fees from Novo Nordisk
Blaine Kent	Department of Anesthesia, QEII Health Sciences Center, Dalhousie University; Halifax, Nova Scotia, Canada	Has received grants from Novo Nordisk
Trevor W.R. Lee	Department of Anesthesia and Perioperative Medicine, St Boniface General Hospital, University of Manitoba, Winnipeg, Manitoba, Canada	None
Charles MacAdams	Department of Anesthesia, University of Calgary and Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada	None
C. David Mazer	Department of Anesthesia, Keenan Research Centre in the Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada	Has received honoraria and consultants' fees from Novo Nordisk
Brian Muirhead	Department of Anesthesia, University of Manitoba Health Sciences Centre, Winnipeg, Manitoba, Canada	Has received honoraria from Novo Nordisk
Antoine G. Rochon	Department of Anesthesia, Montreal Heart Institute, Montreal, Quebec, Canada	Has received a research grant and honoraria from Novo Nordisk
Fraser D. Rubens	Department of Surgery, Division of Cardiac Surgery, University of Ottawa, Ottawa, Ontario, Canada	None
Corey Sawchuk	Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada	None
Shaohua Wang	Division of Cardiac Surgery, University of Alberta, Edmonton, Alberta, Canada	None
Terrence Waters	Department of Anesthesia, Pharmacology, and Therapeutics, University of British Columbia, Vancouver General Hospital, Vancouver, British Columbia, Canada	None
Bill I. Wong	Department of Anesthesiology, Trillium Health Centre, University of Toronto, Toronto, Ontario, Canada	Has received honoraria from Novo Nordisk
Terrence M. Yau	Division of Cardiovascular Surgery, Toronto General Hospital, Department of Surgery, University of Toronto, Toronto, Ontario, Canada	Has received honoraria from Novo Nordisk

References

- Karkouti K, Wijeyesundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, Ghannam M, Yeo E, Djaiani G, Karski J. The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion*. 2004;44:1453–1462.
- Warren O, Mandal K, Hadjianastasiou 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.
- Karkouti K, Beattie WS, Crowther MA, Callum JL, Chun R, Fremes SE, Lemieux J, McAlister VC, Muirhead BD, Murkin JM, Nathan HJ, Wong BI, Yau TM, Yeo EL, Hall RI. The role of recombinant factor VIIa in on-pump cardiac surgery: proceedings of the Canadian Consensus Conference. *Can J Anesth*. 2007;54:573–582.
- Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding: a European perspective. *Crit Care*. 2006;10:R120.
- Isbister J, Phillips L, Dunkley S, Jankelowitz G, McNeil J, Cameron P. Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. *Intern Med J*. 2008;38:156–165.
- Hebert PC, Stanbrook M. Indication creep: physician beware. *CMAJ*. 2007;177:697–699.
- O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA*. 2006;295:293–298.
- Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY: Springer-Verlag; 2001.
- Feinstein AR. Multiple logistic regression. In: Feinstein AR, ed. *Multivariable Analysis: An Introduction*. New Haven, Conn: Yale University Press; 1996.
- Efron B, Tibshirani RJ. Estimates of bias. In: Cox DR, Hinkley DV, Reid N, Rubin DB, Silverman BW, eds. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall; 1993.
- Karkouti K, Wijeyesundera D, Beattie WS, Yau T. Variability and predictability of blood product use in cardiac surgery: a multicentre study. *Transfusion*. 2007;47:2081–2088.
- Karkouti K, Wijeyesundera DN, Beattie WS; RBC Investigators. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation*. 2008;117:478–484.
- Shwartz M, Ash AS, Iezzoni LI. Comparing outcomes across providers. In: Iezzoni LI, ed. *Risk Adjustment for Measuring Healthcare Outcomes*. Chicago, Ill: Health Administration Press; 1997.
- Karkouti K, Beattie WS, Wijeyesundera DN, Yau TM, McCluskey SA, Ghannam M, Sutton D, van Rensburg A, Karski J. Recombinant factor VIIa (rF-VIIa) for intractable blood loss after cardiac surgery: a propensity-score matched case-control analysis. *Transfusion*. 2005;45:26–34.
- Stanworth SJ, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev*. 2007;CD005011.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295–300.
- Stein DM, Dutton RP, O'Connor J, Alexander M, Scalea TM. Determinants of futility of administration of recombinant factor VIIa in trauma. *J Trauma*. 2005;59:609–615.
- Brandsborg S, Sorensen B, Poulsen LH, Ingerslev J. Recombinant activated factor VIIa in uncontrolled bleeding: a haemostasis laboratory study in non-haemophilia patients. *Blood Coagul Fibrinolysis*. 2006;17:241–249.
- Mayo A, Misgav M, Kluger Y, Geenberg R, Pauzner D, Klausner J, Ben Tal O. Recombinant activated factor VII (NovoSeven): addition to replacement therapy in acute, uncontrolled and life-threatening bleeding. *Vox Sang*. 2004;87:34–40.
- Ernoffsson M, Thelin S, Siegbahn A. Monocyte tissue factor expression, cell activation, and thrombin formation during cardiopulmonary bypass: a clinical study. *J Thorac Cardiovasc Surg*. 1997;113:576–584.
- Chung JH, Gikakis N, Rao AK, Drake TA, Colman RW, Edmunds LH Jr. Pericardial blood activates the extrinsic coagulation pathway during clinical cardiopulmonary bypass. *Circulation*. 1996;93:2014–2018.
- Hoffman M, Monroe DM, Roberts HR. Activated factor VII activates factors IX and X on the surface of the activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coag Fibrinol*. 1998;9(suppl 1):S61–S65.
- Dietrich W, Spannagl M. Caveat against the use of activated recombinant factor VII for intractable bleeding in cardiac surgery. *Anesth Analg*. 2002;94:1369–1370.
- Hardy J-F, De Moerloose P, Samama M. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anesth*. 2004;51:293–310.
- Carey MJ, Rodgers GM. Disseminated intravascular coagulation: clinical and laboratory aspects. *Am J Hematol*. 1998;59:65–73.
- 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.
- de Jonge E, Friederich PW, Vlasuk GP, Rote WE, Vroom MB, Levi M, van der Poll T. Activation of coagulation by administration of recombinant factor VIIa elicits interleukin 6 (IL-6) and IL-8 release in healthy human subjects. *Clin Diagn Lab Immunol*. 2003;10:495–497.
- Laffey JG, Boylan JF, Cheng DCH. The systemic inflammatory response to cardiac surgery. *Anesthesiology*. 2002;97:215–252.
- Despotis G, Avidan M, Lublin DM. Off-label use of recombinant factor VIIa concentrates after cardiac surgery. *Ann Thorac Surg*. 2005;80:3–5.
- McCall P, Story DA, Karapillai D. Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery. *Can J Anesth*. 2006;53:926–933.
- Filsoufi F, Castillo JG, Rahmanian PB, Scurlock C, Fischer G, Adams DH. Effective management of refractory postcardiotomy bleeding with the use of recombinant activated factor VII. *Ann Thorac Surg*. 2006;82:1779–1783.
- Aggarwal A, Malkovska V, Catlett JP, Alcorn K. Recombinant activated factor VII (rFVIIa) as salvage treatment for intractable hemorrhage. *Thromb J*. 2004;2:9.
- 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.
- 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.
- Gelsomino S, Lorusso R, Romagnoli S, Bevilacqua S, De Cicco G, Bille 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 Cardiothorac Surg*. 2007;33:64–71.
- Karkouti K, Yau TM, Riazi S, Dattilo KM, Wasowicz M, Meineri M, McCluskey SA, Wijeyesundera D, van Rensburg A, Beattie WS. Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. *Can J Anesth*. 2006;53:802–809.

CLINICAL PERSPECTIVE

In this comprehensive review of the use of recombinant activated factor VII in nonhemophilic patients who underwent cardiac surgery during the period 2003 through 2006 in Canada (n=503), we found that recombinant activated factor VII was used primarily when standard interventions had failed to control blood loss. Moreover, as far as could be determined within the confines of this observational study, we found that recombinant activated factor VII was associated with a reduction in transfusion of blood products and, after adjustment for patients' underlying risk profile and red blood cell transfusion rate, did not appear to be associated with increased or decreased mortality or major morbidity. Finally, our data also suggested that the effectiveness of the drug may be enhanced if it is given early in the course of refractory blood loss in the setting of adequate amounts of circulating coagulation factors. Adequately powered randomized clinical trials are needed to verify these findings.