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REPORTS OF ORIGINAL INVESTIGATIONS

Off-label use of recombinant activated factor VII in surgical and non-surgical patients at 16 Canadian hospitals from 2007 to 2010 (Canadian Registry Report)

Utilisation hors indication d'un facteur VII activé recombinant chez des patients chirurgicaux et non chirurgicaux dans 16 hôpitaux canadiens de 2007 à 2010 (Rapport du Registre canadien)

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Abstract

Purpose *Recombinant activated factor VII (rFVIIa) is a pro-hemostatic drug that is approved for treatment of bleeding in hemophilia patients, but it is frequently used off-label in non-hemophiliacs. The purpose of this study was to determine if the off-label use of rFVIIa is expanding and whether this poses a net harm to patients.*

Methods *For this historical cohort study, data were collected on all non-hemophilia patients who received rFVIIa from 2007 to 2010 at 16 Canadian centres, and the pattern of use was examined. Logistic regression was used to determine the prognostic importance of severity of bleeding and the presence of an rFVIIa dose-effect relationship with major adverse events.*

Results *One thousand three hundred seventy-eight patients received rFVIIa off-label, and 987 (72%) of*

Author contributions All authors have made substantial contributions to the conception and design of the study as well as to the acquisition and interpretation of data. *Keyvan Karkouti* conducted the analysis and wrote the first draft of the manuscript. All authors took part in manuscript revision.

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these patients underwent cardiac surgery. The median [interquartile range] dose was 57 [36-85] μg·kg^{-1}. Usage increased from 2007 to 2008 (n = 341 and 380, respectively) but decreased in 2009 and 2010 (n = 350 and 307, respectively). Dose of rFVIIa and bleeding severity were associated with measured adverse events (P < 0.05). After adjusting for bleeding severity, dose was not associated with any of the adverse events.

Conclusions *The off-label use of rFVIIa in Canada remains stable. Since severity of bleeding is prognostically important, the benefits of rapidly gaining control of bleeding that is non-responsive to conventional therapies may at times warrant the use of potent hemostatic drugs with established risk profiles, such as rFVIIa.*

Résumé

Objectif *Le facteur VII activé recombinant (rFVIIa) est un médicament prohémostatique approuvé pour le traitement des saignements chez les patients hémophiles, mais qui est fréquemment utilisé hors indication chez des patients non-hémophiles. L'objectif de cette étude était de déterminer si l'utilisation hors indications du rFVIIa est en progression et si cela pose un risque net pour les patients.*

Méthodes *Pour cette étude de cohorte historique, des données ont été collectées sur tous les patients non-hémophiles qui ont reçu du rFVIIa entre 2007 et 2010 dans 16 centres canadiens et le profil d'utilisation a été examiné. Une régression logistique a servi à déterminer l'importance pronostique de la sévérité du saignement et la présence d'une relation dose effet du rFVIIa avec les principaux événements indésirables.*

Résultats *Mille trois cent soixante-dix-huit patients ont reçu du rFVIIa hors indication et 987 d'entre eux (72 %) ont subi une chirurgie cardiaque. La dose médiane [intervalle interquartile] était de 57 [36-85] μg·kg^{-1}. L'utilisation a augmenté de 2007 à 2008 (respectivement, n = 341 et 380), mais a diminué en 2009 et 2010 (respectivement, n = 350 et 307). La dose de rFVIIa et la sévérité des saignements ont été associées aux événements indésirables mesurés (P < 0,05). Après ajustement pour la sévérité des saignements, la dose n'était associée à aucun des événements indésirables.*

Conclusions *L'utilisation hors indication du rFVIIa au Canada reste stable. Dans la mesure où la sévérité des saignements a une importance pronostique, les avantages qu'apporte le contrôle rapide d'une hémorragie qui ne répond pas aux traitements conventionnels peuvent, occasionnellement, justifier l'utilisation de médicaments hémostatiques puissants avec des profils de risque connus, tels que le rFVIIa.*

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In 1999, Health Canada approved the use of recombinant activated factor VII (rFVIIa; Niastase; Novo Nordisk, Mississauga, ON, Canada), a hemostatic drug, for the treatment of bleeding episodes in hemophilia patients with inhibitors to factor VIII or IX.[A] It was soon found to be useful for controlling bleeding in non-hemophilia patients,[1,2] and since approval, it has been increasingly used off-label in various clinical settings, e.g., for refractory bleeding in cardiac surgery.[3-5] A recent review of its use in hospitals across the United States found that the off-label use of rFVIIa increased by approximately 140-fold from 2000 to 2008, whereas its use for approved indications increased by only fourfold.[3]

This off-label use has been the focus of some controversy. On the one hand, although rFVIIa may decrease blood loss and blood transfusion, opponents emphasize that there is no evidence of a mortality benefit and its administration carries thrombotic risks, possibly in a dose-dependent manner. Thus, they have proposed that its off-label use should be confined to clinical trials.[6-9] On the

[A] See product monograph. Available from URL: http://www.novonordisk.ca/PDF_Files/NiaStase.pdf (accessed April 2014).

other hand, proponents counter that judicious use of rFVIIa outside hemophilia is warranted when the risk-benefit profile is favourable, such as in life-threatening coagulopathy after surgery or trauma.[10-15] In either case, the "runaway" increase in the off-label use of rFVIIa in United States hospitals is disconcerting, as it would suggest that the drug is being used outside the select group of patients in whom its benefits may potentially outweigh its thrombotic risks. Whether the pattern of off-label use is similar in Canada, however, is not known. A focused review of the off-label use of rFVIIa in cardiac surgery at 18 Canadian hospitals found that its off-label use nearly doubled from 2003 to 2007. This increase was attributed to the late adoption at some centres for treatment of refractory hemorrhage.[4] To determine the general pattern of off-label use in Canada since 2007, we conducted a comprehensive patient-level review of *all* off-label use of rFVIIa in non-hemophilia patients in surgical and non-surgical settings at 16 Canadian hospitals from 2007 to 2010. Additional objectives of this observational study were to explore the relationship between rFVIIa dose response and severity of bleeding and their relationships with major adverse events.

Methods

This was a historical cohort study. Investigators at 25 large Canadian hospitals were approached for participation; 16 agreed to participate and were included (Appendix). Institutional research ethics board approval was obtained at each participating hospital, all of which waived the need for informed consent. The blood bank or pharmacy database at each hospital was used to obtain a list of every patient who had received rFVIIa from January 1, 2007 to December 31, 2010.

Using a standardized data collection form, detailed data were retrospectively collected from medical records for all patients who had received rFVIIa while in hospital. Patients with hemophilia were excluded. Data were entered directly into a web-based database with built-in logic controls. Variables collected included patient demographics, comorbidities, hemodynamic and laboratory data, blood product transfusions (up to 24 hr before and after first dose of rFVIIa), indications for and dose of rFVIIa, as well as in-hospital (up to 30 days after therapy) major adverse events. Adverse events were obtained from patients' clinical notes, discharge forms, death certificates, and autopsy reports where available. Major adverse events were divided into those likely to be thrombotic or non-thrombotic in nature. Stroke, deep vein thrombosis, pulmonary embolism, gut ischemia, limb ischemia, and myocardial infarction were classified into the thrombotic adverse events subgroup for analysis. Renal failure requiring dialysis, sepsis, disseminated intravascular coagulopathy, multi-organ failure, and cardiac arrest were classified into the non-thrombotic adverse events subgroup for analysis. Mortality was analyzed separately. The total number of red blood cells transfused within 24 hr of rFVIIa therapy was used as a surrogate measure for overall bleeding severity.

Statistical analysis

SAS^{TM} version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analysis. Categorical variables were summarized as frequencies and percentages and continuous variables as medians and interquartile ranges. As an indirect measure of effectiveness, the Wilcoxon signed-rank test was used to compare the amount of transfusions before and after rFVIIa therapy (data were collected for up to 24 hr before and after therapy). Only patients who underwent cardiac surgery were used in this analysis to provide for a more homogeneous sample of patients in whom rFVIIa was administered in response to postoperative bleeding.

The association between dose of rFVIIa (per kg) and severity of bleeding was measured with the Spearman's rank correlation coefficient. For missing weight values, the gender-specific sample mean value was used. Dose of rFVIIa and severity of bleeding were categorized into quartiles, and their relationships with measured adverse events were assessed using the Mantel-Haenszel Chi square test. Multivariable logistic regression that controlled for severity of bleeding was used to determine the dose effect of rFVIIa on adverse events. The dose analyses were repeated after excluding patients with missing weight values, after excluding patients who received rFVIIa for non-surgical indications, and using the total dose rather than the weight-based dose.

Results

At the 16 participating hospitals, 1,378 patients received rFVIIa (median 87 patients, range 4-245 patients). Dosing data were missing in 11 patients, and these patients were excluded from the relevant analyses. The median [interquartile range] dose of rFVIIa (after imputing missing weight data in 106 patients) was 57 [36-85] $\mu g \cdot kg^{-1}$. Based on this distribution, patients were classified into quartiles as follows: $< 36\ \mu g \cdot kg^{-1}$ ($n = 352$), 36-57 $\mu g \cdot kg^{-1}$ ($n = 329$), > 57 and $< 85\ \mu g \cdot kg^{-1}$ ($n = 352$), and $\geq 85\ \mu g \cdot kg^{-1}$ ($n = 334$). Overall, 906 patients (66%) received a single dose of rFVIIa, 369 (27%) received two doses, 70 (5%) received three doses, 19 (1%) received four doses, and five (0.4%) received more than four doses.

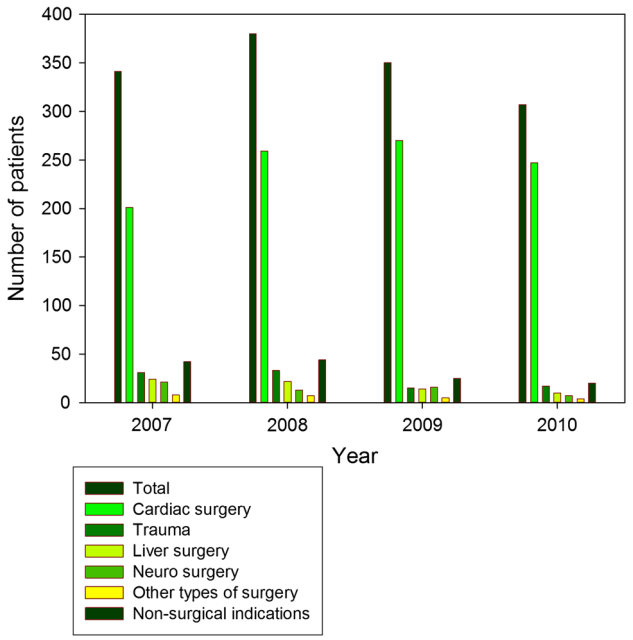


Fig. 1 Number of patients treated with rFVIIa per year rFVIIa = recombinant activated factor VII

There was no discernible change in the amount or number of doses administered during the study period (data not shown).

The number of patients who received rFVIIa increased slightly from 2007 to 2008 but decreased thereafter (Fig. 1). Cardiac surgery was the indication for 72% of the cases ($n = 987/1,378$), increasing from 60% of the cases in 2007 ($n = 201/341$) to 81% in 2010 ($n = 247/307$) (Fig. 1). Of the 131 patients (10%) who received rFVIIa for non-surgical indications, 58 (44%) received it for intra-cerebral hemorrhage, 26 (20%) for reversal of warfarin, 24 (18%) for gastrointestinal bleed, and 12 (9%) for disseminated intravascular coagulation. Overall, the cohort consisted of high-risk patients (older, multiple comorbidities, high rate of catastrophic events, and requiring hemodynamic support prior to rFVIIa therapy) who had major blood loss (as measured by number of transfusions) and a high rate of adverse events (Table 1). There were no discernible changes in patient characteristics during the study period (data not shown). Coagulation tests conducted during the hour before rFVIIa therapy were, on average, not severely deranged, but test results were not available for many of the patients (Table 1). Comparing the amount of transfusions before and after rFVIIa therapy in patients who underwent cardiac surgery, we found that transfusions were substantially lower after rFVIIa therapy (Table 2).

The total dose of rFVIIa and bleeding severity in the entire cohort were correlated with each other (Spearman

Table 1 Patient variables

	Total
rFVIIa usage	
Number of patients treated	1,378
Number of doses per patient	1 [1, 2]
Total dose per patient (mg)	4.8 [2.4-6.0]
Primary indication	
Cardiovascular surgery	985 (71.5%)
Trauma surgery	96 (7.0%)
Liver / abdominal surgery	70 (5.1%)
Neurosurgery	57 (4.1%)
Thoracic surgery	15 (1.1%)
Obstetrical surgery	11 (0.8%)
Orthopedic / spine surgery	7 (0.5%)
Other surgery	6 (0.4%)
Non-surgical	131 (9.5%)
Demographics and comorbidities	
Female sex	423 (30.7%)
Age (yr) (1 missing)	62 [50, 73]
Weight (kg) (108 missing)	77 [66, 89]
Pulmonary disease	189 (13.7%)
Diabetes	254 (18.4%)
Myocardial infarction	257 (18.6%)
Peripheral Vascular Disease	86 (6.2%)
Deep vein thrombosis, pulmonary embolism, or other thromboembolic event	79 (5.7%)
Stroke; transient ischemic event; or carotid disease	173 (12.6%)
Congestive Heart Failure	388 (28.2%)
Liver disease	107 (7.8%)
Dialysis	57 (4.1%)
Endocarditis	100 (7.3%)
Sepsis	53 (3.8%)
Baseline laboratory values	
Hemoglobin ($g \cdot L^{-1}$) (16 missing)	122 [101-138]
Platelet count ($\times 10^9 \cdot L^{-1}$) (24 missing)	188 [139-243]
Creatinine ($\mu mol \cdot L^{-1}$) (54 missing)	97 [76-131]
Condition and laboratory values prior to treatment (within one hour)	
Shock	91 (6.6%)
Catastrophic event*	341 (25.0%)
Hemodynamic support (medication or mechanical)	1,037 (75.0%)
Temperature (Celsius) (373 missing)	36.0 [35.3-36.7]
pH (237 missing)	7.34 [7.26-7.39]
Ionized Calcium ($mmol \cdot L^{-1}$) (608 missing)	1.03 [0.91-1.16]
Hemoglobin ($g \cdot L^{-1}$) (184 missing)	84 [74-98]
Platelet count ($\times 10^9 \cdot L^{-1}$) (408 missing)	104 [74-137]
INR (410 missing)	1.5 [1.3-1.8]
Partial thromboplastin time (453 missing)	38 [33-51]
Fibrinogen ($g \cdot L^{-1}$) (671 missing)	2.0 [1.6-2.5]

Table 1 continued

	Total
Total Transfusions (units)	
Red blood cells	13 [7-22]
Platelets	15 [10-25]
Plasma	10 [6-18]
Adverse events	
Thrombotic†	233 (16.9%)
Non-thrombotic†	505 (36.7%)
Mortality	460 (33.4%)

rFVIIa = recombinant activated factor VII; INR = international normalized ratio

*Any event deemed to be catastrophic by data abstractors, including but not limited to cardiac arrest and multi-organ failure; †Composite outcome – see text for definitions

Continuous variables are shown as median [interquartile range], and categorical variables are shown as counts (%)

Table 2 Transfusions before and up to 24 hr after first dose of rFVIIa in the subgroup of patients who received rFVIIa due to bleeding after cardiac surgery

Product	Before rFVIIa	Up to 24 hr after rFVIIa	*P* value
Red blood cells	7 [4-11]	2 [1-5]	< 0.0001
Platelets	10 [10-15]	5 [0-10]	< 0.0001
Plasma	8 [5-11]	2 [0-4]	< 0.0001

rFVIIa = recombinant activated factor VII. Variables are shown as median [interquartile range]

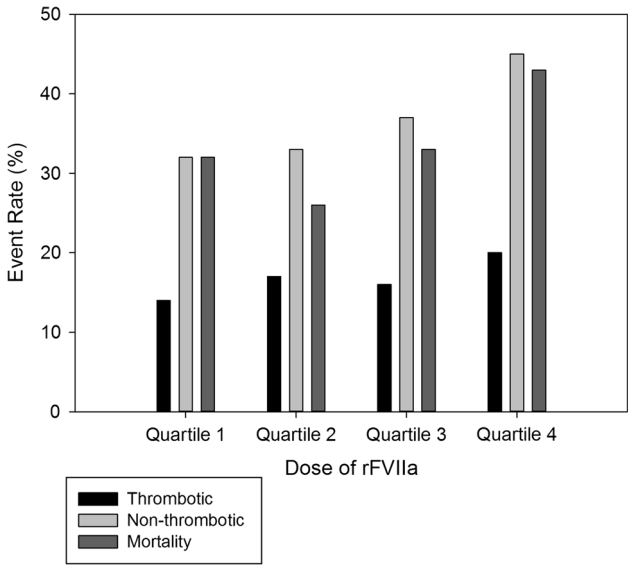


Fig. 2 Relationship between total rFVIIa dose and adverse events Dose of rFVIIa quartiles are as follows: Quartile 1 is < 36 μg·kg^{-1} (n = 352); Quartile 2 is 36-57 μg·kg^{-1} (n = 329); Quartile 3 is > 57 and < 85 μg·kg^{-1} (n = 352); and Quartile 4 is ≥ 85 μg·kg^{-1} (n = 334). rFVIIa = recombinant activated factor VII

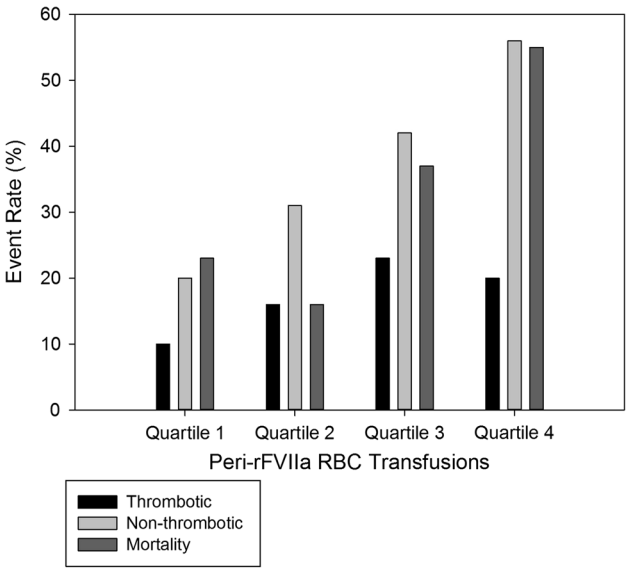


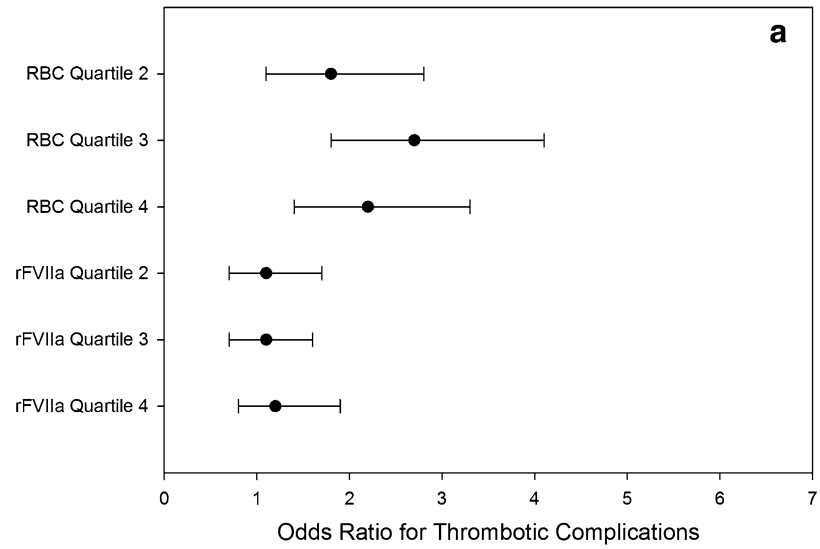
Fig. 3 Relationship between bleeding severity and adverse events Peri-rFVIIa red blood cell (RBC) transfusion includes all transfusions up to 24 hr before and after rFVIIa therapy: Quartile 1 is ≤ 6 units (n = 410); Quartile 2 is 7-10 units (n = 307); Quartile 3 is 11 to 17 units (n = 308); and Quartile 4 is > 17 units (n = 353). rFVIIa = recombinant activated factor VII

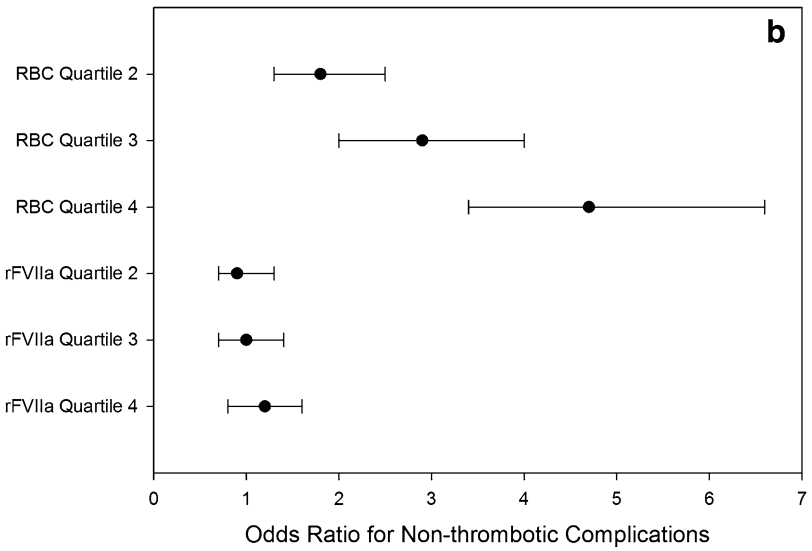
correlation coefficient 0.24; $P < 0.0001$), and adverse events generally increased in direct proportion to the increasing dose and bleeding severity (Figs. 2 and 3). After adjusting for bleeding severity, which remained directly related to adverse events, there was no dose-effect relationship between rFVIIa and any of the major adverse events (Fig. 4). The results were similar when patients with missing weight were excluded, when patients who received rFVIIa for non-surgical indications were excluded, or when total rather than weight-based dosing was used in the analyses (data not shown).

Discussion

In this comprehensive four-year Canadian review, we found that the overall off-label use of rFVIIa in non-hemophilia patients remained relatively stable over the study period. We also found that rFVIIa was primarily and increasingly used in the setting of bleeding after cardiac surgery. The absolute use of rFVIIa for cardiac surgery increased to such an extent during the study period that it represented over 80% of usage during the last year of the study. We also found that major adverse events in the entire cohort were strongly related to the severity of bleeding rather than to the dose of rFVIIa.

One of the main concerns about rFVIIa are reports that its off-label use has been rapidly expanding since initial approval for treatment of bleeding episodes in hemophilia





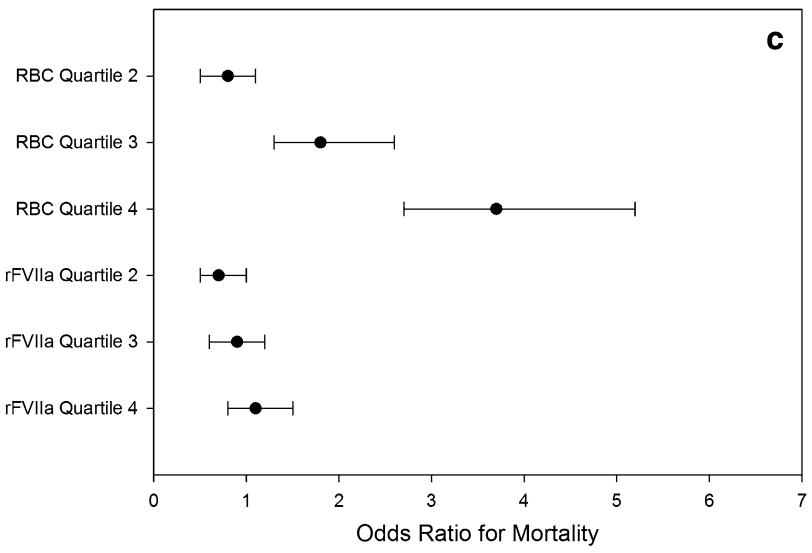


Fig. 4 Relationship between total rFVIIa dose and adverse events, adjusted for bleeding severity See Figs. 2 and 3 for quartile ranges. For both variables, Quartile 1 is the reference category. rFVIIa = recombinant activated factor VII; RBC = red blood cell

patients. This has led to calls for its manufacturer to be investigated for promoting the misuse of the drug.[7] Our study, however, found that the overall off-label use of rFVIIa from 2007 to 2010 did not expand in Canada (although there was a change in pattern of usage with increased use in cardiac surgery). This finding is not consistent with the experience in United States hospitals where there was a 140-fold increase in the off-label use of rFVIIa from 2000 to 2008, with no indication of abatement in the latter years.[3] While our study did not capture all rFVIIa use across Canada, the results are corroborated by the reduction in rFVIIa issued by the Canadian Blood Services (CBS; the supplier of the drug to all Canadian provinces except Quebec) from 2008 to 2011.[8] As reported in the recent review by Lin *et al.*,[8] the total amount of rFVIIa issued by the CBS reached a plateau of just over 32,000 mg during 2007 and 2008 and then gradually declined to about 27,000 mg in 2011. Assuming that the on-label use remained constant, this would imply that the off-label use decreased from 2008 to 2011. Our finding of reduced off-label use is not unique. A large ($n = 3{,}314$) registry that reported on all off-label use of rFVIIa at Australian and New Zealand hospitals from 2000 to 2009 also found a slight reduction in the use of the drug from 2006 to 2009.[B] It seems, therefore, that the concern about the "runaway" use of rFVIIa in off-label settings[7] is not warranted, at least outside of the United States.

Another important finding of our study is that rFVIIa was primarily and increasingly used in the setting of severe bleeding in cardiac surgery where, in many cases, the bleeding was not responsive to standard therapy (as reflected by the relatively normal coagulation tests before rFVIIa therapy). Unlike most other off-label settings, cardiac surgery is an area for which the use of rFVIIa is supported by several observational studies and recommended in the setting of non-responsive bleeding.[4,12,16-19] As in previous studies in cardiac surgery where the amount of transfusions before and after rFVIIa therapy was used as an indirect measure of effectiveness,[4] we also found that the amount of transfusions in cardiac surgical patients was substantially lower after therapy than before therapy (Table 2). While this analysis is confounded by time (i.e., all bleeding eventually stops) and cannot prove causation, it is suggestive that rFVIIa may contribute to this bleeding cessation.

Another major concern with the off-label use of rFVIIa is its propensity to increase the risk of thrombotic adverse events in non-hemophilia patients without any clear benefit in reducing mortality. This has led to the recommendation that its off-label use be curtailed.[8] It has also been argued, however, that the judicious off-label use of rFVIIa may be reasonable in patients who develop severe coagulopathic bleeding that is non-responsive to conventional therapies.[10-15,18,19] The basis for this argument is primarily because rapid control of bleeding is crucial for reducing poor outcomes in this setting and because there is increasing evidence (albeit primarily from observational studies) that rFVIIa may achieve this objective.[4,11] This latter argument is supported by this study's finding that the rate of adverse events in the entire cohort was strongly related to bleeding severity, to such an extent that the relationship dwarfed any potential risks attributable to the dose of rFVIIa. Further in support of this argument, the Australian and New Zealand registry on the off-label use of rFVIIa found a clear relationship between lack of response to rFVIIa and mortality. Specifically, analyzing data from over 2,500 patients, they found that 62% ($n = 479/771$) of patients who did not respond to rFVIIa died, whereas only 20% ($n = 363/1{,}818$) of those who did respond died ($P < 0.001$).[A]

Our study has several important limitations. First, a large number of data are missing for some variables, and there is the potential for inaccurate or incomplete data collection. To ensure that serious adverse events were accurately captured, we limited our data collection to adverse events that were expected to be recorded accurately in patients' records. Moreover, we had to use surrogate measures for some important variables, such as severity of bleeding, and could not capture some other important variables, such as the reasons for dose selection. Second, as this was a historical cohort study, causation cannot be proven. Third, as this was a registry, we had access only to data on patients who received rFVIIa. Lacking a control group, the study was not equipped to determine the association of rFVIIa therapy itself with outcomes. Thus, only the dose-response relationship between rFVIIa and measured outcomes could be explored. Fourth, the study was sponsored by the makers of rFVIIa, which may have introduced bias; however, the support was through an unrestricted grant and the sponsor had no input into the conduct of the study, the analysis of the results, or the writing of the manuscript.

In conclusion, this registry showed that the off-label use of rFVIIa in Canada remained relatively stable over a four-year period from 2007 to 2010 (although there was an absolute increase in its use in cardiac surgery). We also found that major adverse events in patients receiving rFVIIa were related to the severity of bleeding and not to the dose of rFVIIa. These findings add credence to the argument that use of potent hemostatic agents, such as rFVIIa, to gain rapid control of bleeding that is

[B] Haemostasis Registry Final Report. Ten years of data on the use of recombinant activated factor VII in Australia and New Zealand. Available from URL: http://www.calembeena.com.au/HR_Final%20Report.pdf (accessed April 2014).

non-responsive to conventional therapies may at times be warranted.

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Conflicts of interest None declared.

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Appendix: Participating sites and research ethics board (REB) identification number and approval date

Sites	REB Approval Date
Foothills Medical Centre Calgary, AB	Ethics ID: E-21780 July 17, 2008
Hamilton Health Sciences Hamilton, ON	Ethics ID: 08-333c July 14, 2008
Institut de Cardiologie de Montréal Montréal, QC	Ethics ID: NA September 8, 2008
Institut Universitaire de Cardiologie et de Pneumologie de Québec Québec City, QC	Ethics ID: 20408 March 31, 2009
Kingston General Hospital Kingston, ON	Ethics ID: ANAE-145-08 September 5, 2008
London Health Science Centre, University Hospital London, ON	Ethics ID: 15190E May 30, 2008
Queen Elizabeth II Health Science Centre Halifax, NS	Ethics ID: CDHA -RS/ 2011-057 June 30, 2010
St. Boniface General Hospital Winnipeg, MB	Ethics ID: H2008:227 October 7, 2008
St. Mary's Regional Cardiac Care Centre, Kitchener, ON	Ethics ID: 08-199 January 15, 2009
St. Michael's Hospital Toronto, ON	Ethics ID: 08-286c November 4, 2008
Sunnybrook Health Science Centre Toronto, ON	Ethics ID: 490-2008 January 30, 2009
Trillium Health Partners, Mississauga Hospital Mississauga, ON	Ethics ID: 420 April 16, 2010
University Health Network (Toronto General Hospital and Toronto Western Hospital) Toronto, ON	Ethics ID: 07-0890-BE January 30, 2008
University of Manitoba Health Sciences Centre Winnipeg, MB	Ethics ID: H2008:227 August 25, 2008
University of Ottawa Heart Institute Ottawa, ON	Ethics ID: 2008588-01H September 5, 2008
Vancouver General Hospital Vancouver, BC	Ethics ID: H08-02577 July 7, 2009

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