Special Article

The role of recombinant factor VIIa in on-pump cardiac surgery: Proceedings of the Canadian Consensus Conference

[Le rôle du facteur VIIa recombinant dans la chirurgie cardiaque avec circulation extra-corporelle : Rapport de la Conférence canadienne de consensus]

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Purpose: Recombinant activated factor VII (rFVIIa) is currently not approved by Health Canada or the Food and Drug Administration for treating excessive blood loss in non-hemophiliac patients undergoing on-pump cardiac surgery, but is increasingly being used "off-label" for this indication. A *Canadian Consensus Conference* was convened to generate recommendations for rFVIIa use in on-pump cardiac surgery. **Methods**: The panel undertook a literature review of the use of rFVIIa in both cardiac and non-cardiac surgery. Appropriateness, timing, and dosage considerations were addressed for three cardiac surgery indications: prophylactic, routine, and rescue uses. Recommendations were based on evidence from the literature and derived by consensus following recognized grading procedures. **Results:** The panel recommended against prophylactic or routine use of rFVIIa, as there is no evidence at this time that the benefits of rFVIIa outweigh its potential risks compared with standard hemostatic therapies. On the other hand, the panel made a weak recommendation (grade 2C) for the use of rFVIIa (one to two doses of 35–70 $\mu g \cdot kg^{-1}$) as rescue therapy for blood loss that is refractory to standard hemostatic therapies, despite the lack of randomized controlled trial data for this indication. **Conclusions:** In cardiac surgery, the risks and benefits of rFVIIa are unclear, but current evidence suggests that its benefits may outweigh its risks for rescue therapy in selected patients. Methodologically rigorous studies are needed to clarify its risk-benefit profile in cardiac surgery patients.

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***Objectif** : Le facteur VII activé recombinant (rFVIIa) n'est actuellement approuvé ni par Santé Canada ni par la Food and Drug Administration (FDA) pour le traitement du saignement excessif chez les patients non-hémophiles subissant une chirurgie cardiaque avec circulation extra-corporelle (CEC) ; néanmoins, il est de plus en plus utilisé de manière 'non conforme' pour cette indication. Une Conférence canadienne de consensus s'est réunie afin de rédiger des recommandations quant à l'utilisation du rFVIIa lors de la chirurgie cardiaque avec CEC.*

***Méthode** : Le panel a entrepris une revue de la littérature traitant de l'utilisation du rFVIIa en chirurgies cardiaque et non cardiaque. Des considérations quant à la justification, au moment de l'administration et à la posologie ont été évaluées pour trois indications en chirurgie cardiaque : les utilisations prophylactique, de routine ou de sauvetage. Les recommandations, basées sur des*

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données probantes tirées de la littérature, ont été interprétées par un consensus suivant des procédures de gradation reconnues.

***Résultats** : Le panel s'est prononcé contre une utilisation prophylactique ou de routine du rFVIIa, étant donné qu'il n'existe actuellement pas de preuve que les bienfaits du rFVIIa l'emportent sur les risques potentiels encourus en comparaison des thérapies hémostatiques standard. En revanche, le panel a énoncé une recommandation faible (note 2C) en faveur de l'utilisation du rFVIIa (une à deux doses de 35–70 $\mu g \cdot kg^{-1}$) comme thérapie de sauvetage en cas de saignement réfractaire aux thérapies hémostatiques standard et ce, malgré le manque de données d'études randomisées contrôlées concernant cette indication.*

***Conclusion** : En chirurgie cardiaque, les risques et bienfaits du rFVIIa ne sont pas clairs ; toutefois, les données actuelles suggèrent que ses bienfaits pourraient contrebalancer ses risques dans les cas de thérapie de sauvetage chez certains patients. Des études méthodologiquement rigoureuses sont nécessaires afin de clarifier le profil risque/bénéfice du rFVIIa pour les patients de chirurgie cardiaque.*

DESPITE major advances in the field of cardiac surgery, excessive blood loss necessitating large-volume fluid and blood product resuscitation, surgical re-exploration, or both, remains an important complication of on-pump cardiac surgery. While the reported incidence of excessive blood loss varies based on the definition used, there is increasing evidence that it is one of the most common complications of cardiac surgery. In a recent survey of seven Canadian hospitals, the rate of transfusion of five or more units of red blood cells (RBCs) or surgical re-exploration in on-pump cardiac surgery ranged from 11% to 22% (personal communication by Keyvan Karkouti). There is also evidence that excessive blood loss, rather than simply being a marker for surgical misadventure as it is often presumed, is independently associated with both morbidity and mortality.[1–4]

Excessive blood loss after cardiac surgery can be due to incomplete surgical hemostasis, coagulopathy, or most often, a combination of the two. Along with surgical re-exploration to correct or rule out incomplete surgical hemostasis, management of patients with excessive blood loss is essentially supportive, being limited to blood component therapy to replenish RBCs, platelets, and coagulation factors. In a substantial proportion of coagulopathic bleeding patients, however, blood component therapy as a sole intervention is ineffective, leading to massive blood loss and poor outcomes. Approved pharmaceutical options in Canada for the management of excessive bleeding are limited to antifibrinolytic drugs such as aprotinin and lysine analogues. These drugs, however, are often only partially effective as manifest by the high incidence of excessive blood loss despite their use.[5]

Recombinant activated factor VII (rFVIIa) is a hemostatic agent that may be effective in preventing or treating excessive blood loss in on-pump cardiac surgery. It is currently not approved for this indication in any jurisdiction. This drug was developed as an alternative therapy for hemophiliac patients with inhibitors against factors VIII and IX, and it is currently approved in most countries only for this indication. 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 has not been elucidated by large-scale, randomized, placebo-controlled clinical trials. Nevertheless, rFVIIa is being increasingly used 'off-label' in cardiac surgery (as well as other types of surgery), a practice that has generated controversy.[A] At the same time, several groups have recommended guidelines for the 'off-label' use of rFVIIa in certain non-hemophiliac patients.[6–11] In none of these, however, was the focus cardiac surgery.

Consequently, we convened the *Canadian Consensus Conference on the Emerging Role of rFVIIa in On-pump Cardiac Surgery* to address the lack of recommendations for the use of rFVIIa in this setting. Our panel members focused on specific considerations. First, we limited our discussion to on-pump cardiac surgery because of the frequency of this off-label use, but reviewed the literature on rFVIIa as it pertained to other off-label uses and weighed whether extrapolating data from non-cardiac studies was appropriate in the cardiac surgery setting. Second, treatment benefits were debated against the risks of reported adverse events with consideration of the mechanism of action and interactions with other relevant agents. Third, we addressed the timing and dosage of rFVIIa for three indications in cardiac surgery: prophylactic therapy, as part of routine therapy of bleeding patients, and as rescue therapy in patients with refractory blood loss. Our recommendations, therefore, addressed all possible uses of rFVIIa in on-pump cardiac surgery and were based on results of both cardiac and non-cardiac surgery rFVIIa studies.

Methods

The consensus panel met in June 2006 to review the literature and to formulate their recommendations.

A *Little R*. Dangerous Remedy. Baltimore Sun 2006 (11-19-2006).

TABLE I Grading recommendations

Grade of recommendation	*Description*	*Quality of supporting evidence*
1A	Strong recommendation based on high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies
1B	Strong recommendation based on moderate quality evidence	RCTs with important limitations or exceptionally strong evidence from observational studies
1C	Strong recommendation based on low quality evidence	Observational studies or case series
2A	Weak recommendation based on high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies
2B	Weak recommendation based on moderate quality evidence	RCTs with important limitations or exceptionally strong evidence from observational studies
2C	Weak recommendation based on low quality evidence	Observational studies or case series

RCTs = randomized clinical trials.

Before the meeting, the chair (K.K.) undertook a systematic literature search. A PubMed database search was performed using all permutations of the following Medical Subject Heading terms: Factor VII and Factor VIIa / Surgery / Hemorrhage; with no restrictions. The titles and abstracts of retrieved articles were reviewed to identify those relevant to the perioperative use of rFVIIa in non-hemophiliacs, which were distributed to the panel members. Each relevant topic was reviewed by one of the members, who then presented the review at the meeting. The recommendations were derived by consensus. The panel's report was finalized and approved by all members in January 2007. To supplement the report, relevant articles published up to December 2006 were retrieved and reviewed by the chair, and where appropriate, were incorporated in the report.

The system of scoring recommendations followed the grading system described by Guyatt *et al.*[12] (Table I). If the panelists were certain about the balance of the benefits vs the risks of rFVIIa therapy for a particular indication, they made a strong (grade 1) recommendation for or against the use of rFVIIa for that indication; otherwise, they made a weak (grade 2) recommendation. Factors that were considered in making the recommendations included varying burden of illness of blood loss and blood product transfusions for specific patient populations, varying patients' values on receiving blood products, expected magnitude of treatment effect, and risks of rFVIIa therapy. The strength of the recommendations was further modulated by adding an A, B, or C amendment depending upon the methodological quality of the data sources (Table I).

TABLE II Summary of recommendations

Type of use of rFVIIa	*Recommendations*	*Suggested dosing rFVIIa*
Prophylactic use	No – grade 1B	Not applicable
Routine use	No – grade 2C	Not applicable
Rescue use	Yes – grade 2C	35-70 $\mu g \cdot kg^{-1}$ *iv* push, repeat once if no response

rFVIIa = recombinant activated factor VII.

Definitions, rationale, and recommendations

A summary of the panel's recommendations is shown in Table II. An overview of the clinical studies of rFVIIa in cardiac surgery that were considered by the panel is shown in Table III.

Recombinant factor VIIa as prophylaxis for excessive blood loss in cardiac surgery

DEFINITION

Prophylactic use of rFVIIa in cardiac surgery was defined as administration soon after termination of cardiopulmonary bypass (CPB) and reversal of anticoagulation, in the early stages of microvascular bleeding. Two scenarios were considered. One was its general use in all patients (as antifibrinolytic drugs are often currently used). Another was its limited use in patients deemed to be at high risk for excessive blood loss or for those who refuse blood products.

TABLE III Summary of clinical studies of rFVIIa in cardiac surgery considered by the panel

Study	*Design*	*Indication*	*n*	*Dose*	*Comments and key findings*
Ekert *et al.* 2006[14]	RCT Pediatrics	Prophylactic	40 treatment 36 placebo	40 $\mu g \cdot kg^{-1}$	One to three doses of rFVIIa/placebo; first dose given after protamine administration. No antifibrinolytics were given. Blood products were administered if bleeding was excessive 30 min after protamine. All efficacy and safety outcomes were comparable between the two groups.
Diprose *et al.* 2005[13]	RCT	Prophylactic	10 treatment 10 placebo	90 $\mu g \cdot kg^{-1}$	One dose given after protamine administration. Blood products permitted 10 min after intervention. All patients received antifibrinolytic drugs (aprotinin). There was a trend towards reduced transfusion needs in the treatment group. Adverse events were comparable.
Karkouti *et al.* 2006[41]	Case-control (concurrent)	Refractory hemorrhage	114 cases 541 controls	56 $\mu g \cdot kg^{-1}$ (mean)	Patients were treated either in the operating room or in the intensive care unit. All patients also received antifibrinolytic drugs (tranexamic acid or aprotinin). Risk-adjusted adverse event rates were comparable among cases and controls. Early rFVIIa therapy in the course of blood loss was associated with better outcomes than late therapy.
Romagnoli *et al.* 2006[42]	Case-control (historical)	Refractory hemorrhage	15 cases 15 controls	17 $\mu g \cdot kg^{-1}$ (median)	Patients were treated either in the operating room or in the intensive care unit. All patients also received antifibrinolytic drugs (tranexamic acid or aprotinin). Treated patients had reduced blood loss, blood-product transfusion, and length of stay. The control group had three deaths and zero strokes *vs* zero deaths and two strokes in the rFVIIa group.
Von Heymann *et al.* 2005[43]	Case-control (historical)	Refractory hemorrhage	24 cases 24 controls	187 $\mu g \cdot kg^{-1}$ (median)	All patients received antifibrinolytic drugs (aprotinin). Median treatment time was 14 hr after surgery. Hemostatic response was noted in 18 patients. Eight of 24 treated patients died; none were deemed to be related to rFVIIa. Effectiveness and safety were comparable to the control group.
Karkouti *et al.* 2005[44]	Case control (concurrent)	Refractory hemorrhage	51 cases 51 controls	62 $\mu g \cdot kg^{-1}$ (mean)	These cases were also included in the 2006 article by the same authors.[42] All patients received antifibrinolytic drugs. Most patients responded to rFVIIa. Risk-adjusted complication rates were comparable between cases and controls. There were, however, four strokes in cases and only one stroke in controls.
McCall *et al.* 2006[27]	Case series	Refractory hemorrhage	53	90 $\mu g \cdot kg^{-1}$ (mean)	Patients were treated only in the operating room, either at primary operation or re-exploration. All but one of the patients received antifibrinolytic drugs (ε-aminocaproic acid, tranexamic acid, aprotinin, or a combination). Four patients did not respond to their initial dose of rFVIIa. Ten patients died and eight others had major morbidity (four strokes).
Filsoufi *et al.* 2006[29]	Case series	Refractory hemorrhage	17	103 $\mu g \cdot kg^{-1}$ (mean)	Patients were treated either in the operating room or in the intensive care unit. All patients also received antifibrinolytic drugs (ε-aminocaproic acid or aprotinin). Hemostasis obtained in all treated patients and no complications related to rFVIIa occurred. Five patients, however, died (two had stroke, two had multi-system organ failure, and one had heart failure).
Brandsborg *et al.* 2006[30]	Case series	Refractory hemorrhage	5	29 $\mu g \cdot kg^{-1}$ (median)	Hemostasis obtained in most treated patients. One patient died. No serious adverse reactions occurred. Indicates that rFVIIa more effective when adequate hemostatic constituents were present, and a dose-effect response was observed.
Walsham *et al.* 2006[31]	Case series	Refractory hemorrhage	6	85 $\mu g \cdot kg^{-1}$ (median)	Most patients had a surgical source of bleeding identified after rFVIIa therapy. High complication rates: two died and three others had thromboembolic complications.

Bishop *et al.* 2006[32]	Case series	Refractory hemorrhage	12	100 μg·kg^{-1} (mean)	Eleven of the patients were treated in the operating room during the initial surgery. All but one of the patients received antifibrinolytic drugs (aprotinin). Hemostasis obtained in all treated patients and no complications related to rFVIIa occurred. There were no thrombotic complications and no deaths.
Hyllner *et al.* 2005[33]	Case series	Refractory hemorrhage	24	60 μg·kg^{-1} (median)	All patients received antifibrinolytic drugs (tranexamic acid or aprotinin). Hemostasis obtained after therapy in all but two of the patients. Seven patients died (cardiac or multi-system organ failure). No adverse events were deemed to be related to rFVIIa therapy.
Raivio *et al.* 2005[34]	Case series	Refractory hemorrhage	16	65 μg·kg^{-1} (mean)	All patients received antifibrinolytic drugs (tranexamic acid or aprotinin). Most patients responded to therapy. Four patients died and another four had thromboembolic complications.
Halkos *et al.* 2005[35]	Case series	Refractory hemorrhage	9	68–120 μg·kg^{-1}	All patients received antifibrinolytic drugs (aprotinin). All patients responded to treatment. Two patients died. There were no thromboembolic complications.
Aggarwal *et al.* 2004[36]	Case series	Refractory hemorrhage	24	90 μg·kg^{-1}	Treatment effective in the majority of cases; however, mortality was extremely high at 75%.
Herbertson 2004[37]	Case series	Refractory hemorrhage	17	13–90 μg·kg^{-1}	All patients received antifibrinolytic drugs. Treatment was effective and no thrombotic complications occurred.
Eikelboom *et al.* 2003[38]	Case series	Refractory hemorrhage	5	100 μg·kg^{-1} (median)	Patients received antifibrinolytic drugs (aprotinin). Most patients responded to treatment and there were no thromboembolic complications.
Egan *et al.* 2003[39]	Case series Pediatrics	Refractory hemorrhage	6	180 μg·kg^{-1} starting dose	All patients received antifibrinolytic drugs (aprotinin). All patients responded well with no adverse events.
Al Douri *et al.* 2000[40]	Case series	Refractory hemorrhage	5	30 μg·kg^{-1}	Treatment was effective in all cases. One patient died of right ventricular failure.

rFVIIa = recombinant activated factor VII.

RATIONALE

The prophylactic use of rFVIIa in surgery has been assessed by randomized clinical trials (RCTs) in cardiac,[13,14] orthopedic,[15] urologic,[16] and hepatic surgeries,[17–20] with varying results. There are also isolated published[21] and unpublished (personal communication of panel members) reports of its prophylactic use in cardiac surgery.

Both cardiac surgery RCTs were small, preliminary studies. In the double-blinded study by Ekert *et al.*,[14] rFVIIa or placebo were administered to 76 infants (< one year old) soon after termination of CPB and reversal of heparin. There were no differences in any of the efficacy outcomes, including time to sternal closure, blood loss, or amount of blood products transfused. There were likewise no differences in adverse events. This trial, however, had limitations. The initial dose of rFVIIa (40 μg·kg^{-1}) was less than that used for other indications, which may have been insufficient given that rFVIIa has a shorter half-life and more rapid clearance in children than in adults.[22] Another limitation of the study is that blood product transfusions were delayed for at least 30 min from rFVIIa administration. Since children are particularly susceptible to CPB-related dilutional coagulopathy,[14] this delay may have prevented rFVIIa from generating adequate amounts of thrombin to restore hemostasis during its short circulating half-life.

Diprose *et al.*[13] carried out a similar study in adult patients undergoing on-pump cardiac surgery. In this study, 20 subjects who underwent complex on-pump cardiac surgery received 90 μg·kg^{-1} of rFVIIa and blood products were allowed after ten minutes from rFVIIa administration. While this study found a trend toward reduced blood product transfusion in the rFVIIa group, it was limited by its small sample size, presence of important prognostic imbalances between groups, and possibly inadequate blinding of physicians to treatment allocation.

Outside of cardiac surgery, double-blinded RCTs found prophylactic rFVIIa therapy to be effective in urological surgery (n = 36),[16] but not in orthopedic surgery (n = 48),[15] liver resection (n = 204 and 234),[18,19] or liver transplantation (n = 83 and 182).[17,20] In these studies rFVIIa was not associated with thromboembolic complications, but the number of such events was small, limiting the likelihood of finding such differences if they in fact were present.

Taken together these studies strongly suggest that the prophylactic use of rFVIIa for all patients under-

going on-pump cardiac surgery is not likely to reduce the risk of clinically important bleeding. Whether it is more effective in patient subgroups, such as those at high risk for massive blood loss, needs to be tested in a properly designed and powered randomized controlled trial.

RECOMMENDATIONS

For the general prophylactic use of rFVIIa, the panel made a strong recommendation against this practice based on moderate quality evidence (grade 1B). For its restricted prophylactic use in patient subgroups who are at high-risk for massive blood loss or refuse blood product transfusions, the panel was unable to make any recommendations owing to lack of data. The panel recommended that, owing to the heavy burden of illness of excessive blood loss,[4] and the ability to accurately predict patients who are at high-risk for excessive blood loss,[23] the prophylactic use of rFVIIa in high-risk cardiac surgical patients should be studied.

Recombinant factor VIIa as routine therapy for excessive blood loss in cardiac surgery

DEFINITION

'Routine use' refers to scenarios in which rFVIIa is used concurrently with, or in lieu of, standard hemostatic therapies in bleeding patients who have identifiable (e.g., elevated international normalized ratio, thrombocytopenia) or probable (e.g., post-CPB platelet dysfunction) coagulation defects. Standard therapy currently consists of surgical re-exploration, hemostatic drugs (antifibrinolytic drugs and 1-deamino-8-D-arginine vasopressin), and blood products (RBCs, plasma, platelets, and cryoprecipitate).

RATIONALE

The routine use of rFVIIa in bleeding patients has been assessed by RCTs in trauma (n = 301),[24] gastrointestinal (n = 245),[25] and post-transplant (n = 100)[26] bleeding scenarios. Although there are several case reports of its successful use in other clinical scenarios, these had limited influence on the panel's recommendations. While the RCTs did not find any increased risk of thromboembolic complications with rFVIIa use, they also did not find rFVIIa to be particularly efficacious on the primary endpoints. In fact, it was only in exploratory subgroup or post hoc analyses that the studies found rFVIIa to be efficacious.

RECOMMENDATIONS

Owing to the limited efficacy of rFVIIa reported in non-cardiac surgery RCTs, the panel concluded that potential benefits of rFVIIa do not appear to outweigh its potential risks in lieu of standard hemostatic therapies in cardiac surgery (grade 2C).

Recombinant factor VIIa as rescue therapy for refractory blood loss in cardiac surgery

DEFINITION

'Rescue use' refers to scenarios in which rFVIIa is used when patients continue to bleed excessively despite having received maximal standard hemostatic therapy.

RATIONALE

The evidence on rFVIIa in refractory bleeding associated with cardiac surgery is currently limited to observational studies consisting of case reports (not referenced), case series,[27–40] and case-control studies.[41–45] These observational studies have important limitations such as reporting bias in favour of the intervention and inability to fully adjust for the effects of confounding variables. These studies, however, have consistently found a strong, temporal relationship between rFVIIa administration and reduced hemorrhage in patients with refractory blood loss. Taken together, therefore, these reports indicate that rFVIIa might be effective in reducing blood loss and the need for blood product transfusions in patients with refractory hemorrhage after cardiac surgery.

On the other hand, in several of the case series there was a troublingly high rate of thromboembolic complications and mortality. Lacking control groups, however, these studies could not determine if this relationship was causal, nor could they determine if the observed adverse event rates were greater than the expected rates in this high-risk patient population. The case-control studies,[41–45] which are better able to address the latter issue, found no excess risk associated with rFVIIa, although their sample sizes were not large enough to detect small but clinically important differences in the rates of these complications. A general pattern seemed to emerge from these studies: when rFVIIa was used as a last resort, after many hours had elapsed from completion of CPB and after massive amounts of blood products were transfused, there were indications that it was less effective and associated with greater harm than when it was used early in the course of refractory blood loss.

Additional safety data were obtained from non-cardiac surgery studies. In hemophiliacs, rFVIIa is safe with a less than 1% incidence of serious adverse events.[46] In non-hemophiliac bleeding patients, there have been multiple reports of thromboembolic events after rFVIIa use; however, these reports could not establish causation and, lacking a denominator, did

not quantify this risk.[47] In a meta-analysis of placebo-controlled RCTs in non-hemophiliac bleeding patients, rFVIIa was not associated with thromboembolic complications (odds ratio 1.17, $P = 0.57$), although the confidence interval of the odds ratio estimate was wide (0.68–2.10).[48] In a placebo-controlled RCT of non-coagulopathic patients with intracerebral hemorrhage rFVIIa increased the risk of myocardial injury and stroke (5% *vs* 0%, $P = 0.01$).[49]

Based on the available evidence, the panel concluded that the risk of thrombotic complications after rFVIIa in patients undergoing coagulopathic surgery is likely higher than for untreated patients. The panel further concluded that the risk-benefit profile is most likely to be favourable for rFVIIa in cardiac surgical patients with refractory hemorrhage if it is administered as soon as possible after completion of CPB, in patients without known risk factors for cerebrovascular accidents.

The dosage recommendations are weak because the minimally effective dose for rFVIIa is not known, and all indications are that there are wide inter-individual variations.[50] Recommended dose in hemophiliacs is 90 $\mu g \cdot kg^{-1}$ every second hour for at least 24 hr.[50] In cardiac surgery, however, many patients tend to respond to one or two doses of 35–70 $\mu g \cdot kg^{-1}$.[44]

RECOMMENDATIONS

The panel recommends that rFVIIa be considered in cardiac surgical patients who develop refractory hemorrhage, as the current evidence suggests that potential benefits of rFVIIa for this indication might outweigh its risks. In lieu of randomized controlled trials, however, the panel's recommendation is weak (grade 2C) and has restrictions.

The panel recommends that extreme caution be used in patients who are at high risk for thromboembolic complications, particularly those who are prone to cerebrovascular accidents, as RCTs of rFVIIa generally excluded this group and there have been reports of cerebrovascular accidents with rFVIIa use in cardiac surgery and other clinical scenarios.

The panel further recommends that, to maximize the benefits and minimize the risks of rFVIIa, refractoriness should be established early in the course of blood loss by aggressively and rapidly instituting all appropriate standard hemostatic interventions (grade 2C). The panel recognizes that institutions will differ in what they consider timely and maximal standard hemostatic interventions, and consequently did not review the merits of available protocols (examples cited).[9,51]

On dosage, the panel suggests that the initial dose be 35–70 $\mu g \cdot kg^{-1}$ rounded to the nearest 1.2, 2.4 or 4.8 mg vial size combinations, which is lower than that used in RCTs, to minimize thrombotic risks and costs. If there is no response after the first dose, the panel suggests that, based on the relatively short half-life of rFVIIa in bleeding patients (about two hours),[52] a second dose be administered soon thereafter (within 30 to 60 min) to take advantage of possibly enhanced effectiveness with cumulative circulating levels of rFVIIa (grade 2C).

The panel recommends that, whenever circumstances permit, the decision to use rFVIIa be made in consultation with patients' next of kin (un-graded recommendation).

Summary

Recombinant factor VIIa is a potent hemostatic drug, and as such, has clear risks of thromboembolic complications. Much work remains in delineating its risk-benefit profile in the cardiac surgery setting. Based on the available evidence, the panel recommended against its prophylactic or routine use in cardiac surgery, but made a weak (grade 2C) recommendation that it be considered in patients who develop refractory hemorrhage after on-pump cardiac surgery despite aggressive standard hemostatic strategies.

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