

## INVITED REVIEW

# Prediction and management of bleeding in cardiac surgery

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**Summary.** Excessive bleeding after cardiac surgery can result in increased morbidity and mortality related to transfusion- and hypoperfusion-related injuries to critical organ systems. Our objective was to review mechanisms that result in bleeding after cardiac surgery as well as current and emerging interventions to reduce bleeding and transfusion. We discovered that point-of-care (POC) tests of hemostatic function can facilitate the optimal management of excessive bleeding and reduce transfusion by facilitating administration of specific pharmacologic or transfusion-based therapy and by allowing physicians to better differentiate between microvascular bleeding and surgical bleeding. Emerging interventions like recombinant FVIIa have the potential to reduce bleeding and transfusion-related sequelae and may be life-saving; however, randomized, controlled trials are needed to confirm safety before they can be used as either first-line therapies for bleeding or bleeding prophylaxis. In conclusion, careful investigation of the role of new interventions is essential as the ability to reduce use of blood products, to decrease operative time and/or re-exploration rates has important implications for overall patient safety and health care costs.

**Keywords:** bleeding, cardiac surgery, factor concentrates, point-of-care testing, transfusion.

## Introduction and bleeding mechanisms

The hemostatic system limits hemorrhage when vascular integrity is compromised and includes several major components such as platelets, von Willebrand factor (VWF), coagulation and fibrinolytic factors and the blood vessel wall. A substantial percentage of patients undergoing cardiac surgical procedures are at risk for development of bleeding that may result in hemodynamic consequences necessitating volume/vasopressor resuscitation along with transfusion support. Accordingly, many studies have examined the role of interven-

tions designed to optimize the management of this clinical problem (e.g. point-of-care diagnostics).

Excessive microvascular bleeding after cardiac surgery can result in re-exploration, which has been shown to be associated with a variety of negative outcomes such as a 3- to 4-fold increase in mortality, renal failure, sepsis, atrial arrhythmias, prolonged mechanical ventilation and longer length of stay [1]. Moulton *et al.* [1] demonstrated that excessive bleeding is the most likely cause of increased mortality, as mortality was increased 3-fold when patients, who were not re-explored, bled more than 2 L within the first 24 h after surgery. Patients with excessive bleeding and who require transfusion support are predisposed to target organ injury, the result of one or more potential mechanisms. These may include ischemic injury as related to bleeding with hypotension/hypo-perfusion or anemia, microemboli or microthrombi [i.e. as related to cardiopulmonary bypass (CPB) or transfusion] or aggravation of ischemic injury by white-cell priming lipids within transfusion. This is supported by several recent studies that have demonstrated that transfusion of non-leuko-reduced units may potentially increase the incidence of multi-organ system failure (MOSF). Stroke, short-term or long-term mortality may be increased in cardiac surgical patients who receive transfusion [2].

## *Mechanisms for excessive bleeding after cardiac surgery*

Although excessive bleeding during and after surgery may be related to isolated defects within the hemostatic system, excessive bleeding is probably more likely related to a series of events or 'multiple hits'. The incidence of bleeding complications and/or the severity of a specific bleeding event can be related to the number of defects or 'hits' as well as the degree or severity of the individual or multiple defects. Potential defects that can influence the incidence and severity of bleeding after cardiac surgery include pre-existing inherited or preoperatively acquired (e.g. pharmacologic agents, other co-existing disorders that affect the hemostatic system) defects as well as those acquired defects that are secondary to the use of extracorporeal circulation. Hereditary deficiencies in either coagulation factors or platelets may lead to excessive bleeding, however, these are uncommon causes of bleeding after cardiac surgery relative to the incidence of

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**Table 1** Hereditary vs. acquired defects after cardiac surgery [2]

Source of hemostatic defect (S)	Prevalence/incidence
<b>Hereditary</b>	
Platelet disorders (e.g. abnormal adhesion or aggregation receptors, storage defects)	One hundred and thirty cases described in the literature 0.4% of general population and 8% of pts with history of bleeding/abnormal screening tests < 1:1 000 000
Severe bleeding (i.e. as related to adhesion or aggregation defects)	
Mild bleeding (storage pool defects, signal transduction defects)	Incidence unknown, less common than von Willebrand disease
<b>Coagulation factor deficiency</b>	
Factor VIII	1:5000–10 000
Factor IX	1:30 000
Factor XI	1:1 000 000 or 1:50 (Ashkenazi Jewish births)
Factor VII	1:500 000
Factor V, X	1:1 000 000
Afibrinogenemia, Dysfibrinogenemia	1:1 000 000
Factor XIII	1:2 000 000
Factor II (prothrombin deficiency)	1:2 000 000
von Willebrand disease (75% Type 1)	1.5% – 1:10 000
<b>Acquired with extracorporeal circulation</b>	
<b>Thrombocytopenia</b>	
< 50 000 $\mu\text{L}^{-1}$	6%
< 100 000 $\mu\text{L}^{-1}$	60%
<b>Qualitative platelet abnormalities</b>	
Reduced TRAP-mediated activation in PRP	10%
Reduced PAF-mediated activation in whole blood	33%
Coagulation factor deficiency (<20% activity)	30%
Hypofibrinogenemia (fibrinogen < 100 mg $\text{dL}^{-1}$ )	9%

TRAP, thrombin receptor agonist peptide; PRP, platelet-rich-plasma; PAF, platelet activating factor.

acquired defects (Table 1) [2]. Pre-existing preoperative disseminated intravascular coagulation (DIC), significant hepatic or renal impairment, or connective tissue disorders (e.g. Ehlers-Danlos syndrome) may also predispose patients to excessive bleeding after surgery.

Patients undergoing cardiac surgery with CPB are at increased risk for microvascular bleeding secondary to acquired hemostatic system abnormalities as related to use of extracorporeal circulation which include: (i) Hemodilution secondary to volume resuscitation or loss (i.e. via bleeding or use of cell salvage) of platelets and coagulation factors; (ii) The type of solution used to replenish the intravascular space (e.g. Use of large doses of Hespán may lead to specific abnormalities in coagulation factors and platelet adhesion/function; (iii) The effects of hypothermia on both plasma coagulation factors and platelet function; (iv) Consumption or a 'DIC-like' state secondary to tissue injury, contact activation and most importantly, as related to transfusion of shed pericardial blood; (v) Excessive fibrinolysis as either a primary or more likely a secondary process (i.e. as related to thrombin-mediated activation); and (vi) Residual heparin or 'heparin' rebound [2].

Activation of both intrinsic and extrinsic pathways results in excessive thrombin generation and fibrinolytic activity which can lead to consumption of platelets and labile coagulation factors. The risk of excessive, non-surgical bleeding is influenced by the type of procedure [3], the duration of CPB [2] and other patient-related factors (age, gender, body surface area or

BSA, co-existing disease, preoperative hematocrit etc.). These mechanisms ultimately can lead to multiple abnormalities involving either coagulation factors and/or platelets as sum-

**Table 2** A summary of hemostatic abnormalities that may precipitate or aggravate excessive bleeding associated with cardiac surgery involving extracorporeal circulation [2]

Disseminated intravascular coagulation (DIC)
Excessive fibrinolysis because of either primary or secondary fibrinolysis
(i.e. as related to CPB-mediated DIC and/or reduced fibrinolysis inhibitors such as PAI1, $\alpha$ -2 antiplasmin)
Decreased or denatured coagulation factors
Platelet-related
Thrombocytopenia
Platelet activation/desensitization
Prolonged bleeding time
Decreased platelet reactivity to one or more platelet agonists
Loss of platelet glycoprotein receptors
Fibrinogen (Gp IIb/IIIa)
von Willebrand Factor receptor (Gp Ib)
Platelet Degranulation (i.e. as demonstrated by release of BTG, PF4, ADP)
Changes in platelet signaling/adhesion molecule expression
Hypothermia-related effects
Heparin-related inhibition
Heparin-related activation
Protamine-related platelet dysfunction

PAI1, plasminogen activator inhibitor 1; Gp, glycoprotein; BTG, beta thromboglobulin; PF4, platelet factor 4; ADP, adenosine diphosphate.

marized in Table 2. Although excessive bleeding after cardiac surgery can be related to reduced circulating levels of coagulation factors [3] and other abnormalities such as heparin rebound, hypothermia and/or acidosis [2], platelet-related abnormalities listed in Table 2 are considered the most important hemostatic abnormality in this setting.

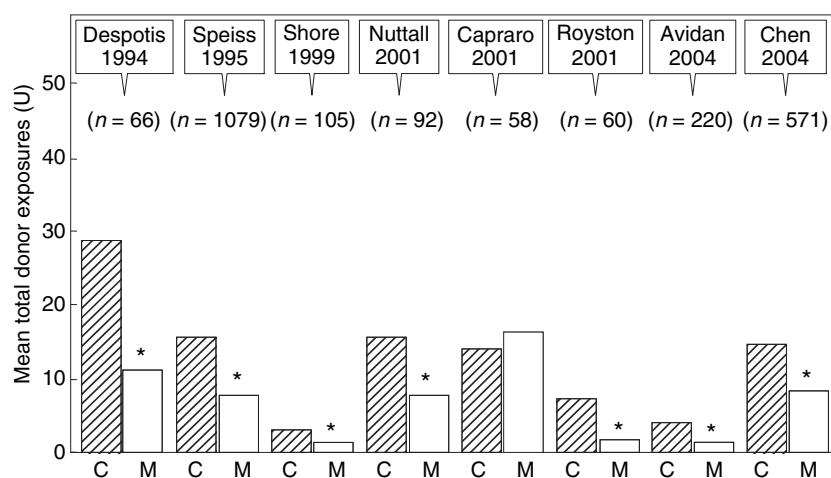
Although the use of aspirin and non-steroidal anti-inflammatory agents can lead to bleeding in a subset of patients who display evidence of an exaggerated response to these agents (i.e. hyper-responders), the majority of patients do not bleed excessively because the majority of patients manifest a normal response to aspirin (i.e. mild platelet inhibition) [4]. Similarly, although patients on preoperative warfarin may bleed after cardiac surgery, two studies have demonstrated an inverse relationship between postoperative International Normalized Ratio (INR) and blood loss, which may be secondary to warfarin-mediated hemostatic system-preservation during CPB. The introduction and use of lower molecular-weight heparin compounds, direct inhibitors of thrombin (e.g. hirudin, argatroban, bivalirudin, dermatan, Orgaran), and platelets (e.g. abciximab, eptifibatid, tirofiban and most importantly long-acting adenosine diphosphate (ADP) antagonists such as clopidogrel [2]) as well as fibrinolytic agents (e.g. recombinant tissue plasminogen activator) can potentially increase bleeding and complicate clinical management. The risk of bleeding related to these agents depends on their relative potency, pharmacodynamic half-life, time-interval from most recent dose before surgery, and whether or not a reversal agent is available. Although, the exact association between these agents and either the severity of bleeding or transfusion requirements in patients undergoing cardiac surgical procedures is evolving, several reports have demonstrated severe, intractable bleeding with use of either the direct thrombin inhibitors for anticoagulation with CPB or with preoperative use of clopidogrel [2].

## Management of bleeding

### Hemostatic blood components: therapy and dosing

Traditional management of excessive bleeding has involved intravenous administration of hemostatic-augmenting pharmacologic agents or hemostatic blood components. Replenishment of coagulation factors can be achieved either with the use of fresh-frozen plasma (FFP), cryoprecipitate or factor concentrates. Both National Institutes of Health (NIH) [5] and American Association of Anesthesiologists (ASA) [6] guideline recommendations for the use of FFP in the perioperative setting have previously been published [5]. The ASA guidelines recommend that FFP be used in the setting of active bleeding that may be related to substantial reductions in coagulation factor levels (i.e. prothrombin time (PT) and activated partial thromboplastin time (APTT)  $> 1.5\times$  the mean value of a normal reference population) [6]. Approximately 15 mL kg<sup>-1</sup> of FFP will result in a rise in factor values by 30% (i.e. 0.3 U mL<sup>-1</sup>) in the average adult. Cryoprecipitate is generally administered for either hypofibrinogenemia ( $< 80\text{--}100$  mg dL<sup>-1</sup>) or dysfibrinogenemia. Approximately 10 U of cryoprecipitate will increase fibrinogen by 100 mg dL<sup>-1</sup> and administration of 15 mL kg<sup>-1</sup> of FFP will increase fibrinogen to nearly the same degree. With non-urgent requirements, Vitamin K can be administered to reverse the effects of warfarin (i.e. reductions in factors II, VII, IX and X as well as protein C and S) within 6–8 h after intravenous administration.

Similarly, NIH [7] and ASA [6] consensus panels have suggested that platelets be administered in the following settings; for active bleeding with thrombocytopenia (i.e. platelets  $< 50\,000$   $\mu\text{L}^{-1}$ ), when abnormal platelet function is contributing to bleeding or for prophylaxis with a platelet count  $< 20\,000$   $\mu\text{L}^{-1}$  in patients at high risk of bleeding [7]. Platelets should be administered with massive blood transfu-



**Fig. 1.** The impact of use of an algorithm coupled to point-of-care monitoring with respect to mean total donor exposures observed in eight published studies. The first author and year of publication highlighted within each box at the top of the figure whereas the type of study (i.e. study design) and the series enrollment listed below. Hatched bar represents the mean total donor exposures within the control group (C) whereas the solid bar represents the mean total donor exposures within the group of patients who were treated with an algorithm coupled to point-of-care monitoring (M) peri-operatively. Asterisks represent  $P < 0.05$  between treatment cohorts [2].

sion (i.e. > 1–2 blood volumes lost with abnormal bleeding) [7]. However, prophylactic administration is contraindicated with cardiac surgery.[7] One apheresis-derived platelet unit is equivalent to six random-donor platelet units (i.e. >90% containing at least  $3 \times 10^{11}$  platelets) and should result in random-donor platelet units random-donor platelet units random-donor platelet units an 1-h post infusion rise by 30–60 000  $\mu\text{L}^{-1}$  in platelet count unless there is platelet refractoriness.

Factor concentrates are generally administered every 12–24 h depending on extra-intravascular distribution and the half-life of the particular factor being replenished at dose ranges that approximate 50–100 U  $\text{kg}^{-1}$  or 10–120  $\mu\text{g kg}^{-1}$  for recombinant activated Factor VII and 15–30 U  $\text{kg}^{-1}$  of recombinant Factor XIIIa. Hypothermia and especially severe acidosis should be corrected prior to institution of routine hemostatic therapy and factor concentrates as supported by a recent study [8].

Despite recommendations by consensus panels, blood component administration in patients with excessive bleeding after CPB is frequently either empiric or prophylactic as reflected by the variable transfusion rates for RBC, platelets and FFP among institutions [9], despite evidence that this practice is unwarranted [10]. The clinical utility of laboratory-based hemostatic tests is often limited by long turnaround time, which has led to investigation of the use of point-of-care (POC) tests to help physicians establish more appropriate management of excessive bleeding by targeting blood component therapy and/or pharmacologic augmentation of the hemostatic system according to identified abnormalities in the coagulation system.

#### *Augmenting hemostatic function with pharmacologic agents*

On occasion, administration of additional protamine is required to neutralize either residual heparin intraoperatively or heparin released from multiple *in vivo* binding sites postoperatively. Identifying heparin rebound and treating it with the appropriate dose of protamine can result in reduced bleeding [11]. The dose of protamine can vary from 20 to 60 mg and should be optimized based on evidence that indicates that excess protamine may aggravate platelet dysfunction [12] or increase complement activation. Desmopressin or 1-deamino-8-D-arginine vasopressin (DDAVP), which has been used off-label to manage excessive bleeding with some efficacy in various settings (i.e. for uremia-induced platelet dysfunction or hereditary platelet disorders, Type 1 von Willebrand disease and acquired platelet abnormalities after cardiac surgery), is generally administered at a dose of 0.3–0.4  $\mu\text{g kg}^{-1}$  over 30 min to minimize hypotension. Although the beneficial effects of prophylactic administration of desmopressin has been controversial, based on conflicting studies which either demonstrated or failed to demonstrate a positive effect. However, several subsequent published studies utilizing tests of hemostatic function have identified certain patient subsets at high risk for excessive bleeding that may benefit from treatment with desmopressin [13–15]. One of these

involved a prospective, blinded, placebo-controlled trial utilizing a point-of-care platelet function method (i.e. hemoSTATUS) which demonstrated that desmopressin-treated patients had an overall 69% reduction in total donor exposures (1.6 vs. 5.2 U) and 39% reduction in blood loss in the first 24 postoperative hours when compared with placebo patients [15].

#### *Clinical utility of point-of-care tests and transfusion algorithms*

A preponderance of published studies has demonstrated the usefulness of preset criterion for transfusion (i.e. transfusion algorithm) coupled to POC diagnostic tests (Fig. 1). Seven of eight studies demonstrated that preset transfusion triggers based on either laboratory and/or POC methods can dramatically affect transfusion requirements (i.e. average of 50% reduction) of patients undergoing cardiac surgery [2]. These studies have either employed standard tests of hemostatic function (e.g. PT, APTT and platelet count) with or without tests that evaluate the viscoelastic properties of whole blood (e.g. thromboelastography).

The efficacy of point-of-care testing coupled with a standardized approach (i.e. algorithm) to reduce transfusion may be related to several factors such as optimal management of bleeding [3], resetting of the transfusion trigger [16], and/or early identification of a surgical source of bleeding [17]. In these studies, investigators utilized hemostatic test results to identify the most accurate hemostatic therapy to be administered with respect to the management of excessive clinical bleeding. However, caution should be exercised with respect to using either point-of-care or laboratory-based test results to direct prophylactic administration (i.e. in the anticipation of bleeding as related to an abnormal test result) of either hemostatic blood components (e.g. platelets, plasma or cryoprecipitate) or pharmacologic agents. Unless there is clear evidence in the literature that a specific test result can consistently and clearly identify patients who are destined to bleed excessively, this approach may lead to inappropriate and/or unwarranted transfusion and perhaps even thrombotic complications. This is relevant as studies have not demonstrated that either laboratory-based or point-of-care test methods (i.e. PT, APTT, platelet count) can accurately predict which patients are destined to bleed excessively. However, both laboratory and point-of-care tests like the PT and APTT that indirectly evaluate coagulation factor levels can be used to identify patients (i.e. PT or APTT values with a high positive predictive value) who are likely to have a factor deficiency state (e.g. one or more coagulation factors < 20 or 30% activity) and who may benefit from plasma in the setting of a clinical bleeding problem [18].

#### *Management of intractable, life-threatening bleeding with factor concentrates*

Factor concentrates are used to prevent or manage excessive bleeding in patients with congenital (i.e. hemophilia A and B, von Willebrand disease) or acquired coagulation factor

deficiencies. Factor concentrates can vary in terms of source (e.g. purified, pooled human plasma vs. recombinant), properties (activation vs. non-activated coagulation factors) and content such as isolated (e.g. factor VIII, factor VIIa) or multiple (e.g. prothrombin complex concentrate (PCC) or PCC containing factors II, VII, IX and X) coagulation factors.

Recombinant activated Factor VIIa (rFVIIa) currently has FDA approval for the management of bleeding in hemophilia A and B patients with inhibitors to Factor VIII and IX respectively or in patients with congenital Factor VII deficiency. The mechanism of action of rFVIIa involves generation of thrombin via initial binding to tissue factor and subsequent activation of factor X (FXa) on the platelet surface; FXa in combination with activated factor V (i.e. Va/Xa or prothrombinase complex) accelerates to localized thrombin formation. One of the reasons postulated for the relative safety of rFVIIa is that it should be effective predominately at the sites of vessel injury, where there is localized expression of tissue factor by subendothelial cells. Currently, the decision whether to use factor concentrates such as rFVIIa for patients with uncontrolled bleeding continues to be one that has to be inevitably made by individual physicians, assisted by their hospital pharmacotherapeutics and transfusion committees.

The off-label use of this agent has been reported to be successful in reversing life-threatening bleeding in a number of clinical scenarios such as central nervous system and gastrointestinal bleeding, obstetrics, trauma, congenital or acquired factor VII deficiency, patients with VWF or platelet defects, neurosurgery, cardiac surgery, liver transplantation with the most compelling data for off-label use of rFVIIa involving effective management of spontaneous intracranial bleeding (i.e. 38% reduction in mortality) [19].

Accordingly, rFVIIa has been used off-label in the management of excessive, often life-threatening bleeding after cardiac surgery. The current literature describing the off-label use after cardiac surgery has been summarized in three recent reviews [2,20,21]. The first two [2,20] involve a summary of approximately 50 peer-reviewed publications (i.e. in 415 patients) consisting predominately of anecdotal experience (i.e. either case reports or case series) with limited data from randomized clinical trials while the third describes the off-label use in 503 patients in 22 Canadian centers [21]. The vast majority of these reports involved use of rFVIIa in the setting of severe, life-threatening bleeding which was unresponsive to routine hemostatic therapy (i.e. platelets, plasma, cryoprecipitate, DDAVP). These studies reported consistent demonstration of the efficacy of rFVIIa to achieve hemostasis as evidenced by markedly reduced transfusion requirements and blood loss (i.e. from 33–99% reduction) [20,21] even when pretreatment blood loss approximated 16 L per hour [20]. Many of the patients treated with rFVIIa were destined to expire based on the severity of bleeding that was described prior to intervention, which clearly illustrate the efficacy of rFVIIa as a rescue therapy in the setting of life-threatening bleeding.

With a tremendous increase in the off-label use of rFVIIa (from 300 doses in 1999 to 4500 doses in 2004) [22], important concerns about its safety, efficacy, and costs have also arisen. An increase in thrombotic complications as related to use of rFVIIa have also been observed in patients with intracranial bleeding where the observed 38% reduction in mortality by rFVIIa in the setting of intracranial bleeding was also paralleled by a tendency (placebo: 2% vs. rFVIIa: 7%) for an increased incidence of thrombotic complications (especially arterial thromboses, placebo: 0 vs. rFVIIa: 5%) [23]. With respect to safety, the risks of thrombosis associated with rFVIIa are theoretically increased when there is systemic expression of tissue factor, such as that occurring with DIC or other sites of localized endothelial damage such as a ruptured atheromatous plaque or iatrogenic trauma.

Although the complications and high mortality (i.e. 22–75%) reported in some of the case series after cardiac surgery are a matter of concern, it is also noted that the literature does not consistently reflect a high complication or mortality rate with use of rFVIIa after cardiac surgery. The discrepancy in adverse outcomes between cases reported and case series may be related to institutional differences with respect to the percentage of patients at high-risk for surgery-related complications and mortality, the relative severity of the patient's condition at the time of treatment (e.g. severe bleeding, severe hemodynamic compromise and/or hypoperfusion), concomitant use of other agents (e.g. antifibrinolytic agents, platelets, FFP, DDAVP) or interventions (e.g. topical hemostatic agents) or other pre-existing patient-related factors that may differ between the published reports.

Although a previous review that summarized administration of 170 000 doses of rFVIIa reported a low incidence of thrombotic complications (i.e. 1:11 300) [24], most of these cases involved use of this agent for the management of bleeding complications in Hemophilic patients with inhibitors. A summary of reported thromboembolic complications (i.e. MI, stroke, arterial/venous thrombosis etc) to the FDA (i.e. AERS 1999–2004) as related to the use of rFVIIa was recently published [22]. In this report, a 4.3% incidence of adverse events (half of which were thromboembolic in nature) associated with a 0.5% mortality were noted between 1999 and 2004 with predominately off-label use. A causality assessment was obtained in 61% of the described reports of which 81/102 of the thromboembolic complications (80%) were considered to be related to use of rFVIIa [22]. A substantial limitation of this analysis involved the elevated risk for thromboembolic complications in the population of patients who received rFVIIa on an off-label basis; these patients were probably at a much higher risk for developing thromboembolic complications based on their clinical circumstances (e.g. cardiac assist devices and on-going hemostatic system activation, trauma or cardiac surgical patients with intractable bleeding and with bleeding-related hypoperfusion) as well as the concomitant therapies used to manage bleeding (e.g. antifibrinolytic agents, activated PCC, hemostatic blood components, DDAVP) and rFVIIa use was not adjusted for these factors. Risk adjustment

was employed in the recent publication of the Canadian experience, which was not able demonstrate that use of rFVIIa was associated with an increase complication rate [21].

Nevertheless, until additional safety studies are completed, this agent should be used sparingly and cautiously in non-life-threatening settings or as a prophylactic measure especially in patients who are at increased risk for thrombotic complications such as patients with known hypercoagulability, established thrombotic disorders (i.e. Factor V Leiden, antiphospholipid syndrome, etc), patients who have excessive bleeding in the setting of DIC or other states of generalized activation of the hemostatic system. Previously suggested criteria [25] for off-label use of rFVIIa after cardiac surgery included the following: patients with life-threatening bleeding (e.g. CNS or  $>500\text{--}1000\text{ mL h}^{-1}$ ) that have no identifiable surgical source and who are unresponsive to transfusion of hemostatic components (e.g. 1–2 U platelets, 4–8 U FFP, 10–20 U cryoprecipitate) or pharmacologic therapy (e.g. DDAVP, EACA, tranexamic acid, aprotinin). In addition, other important considerations should include avoidance in patients who either have a documented congenital or acquired hypercoagulable state, administration of lower doses (e.g. rFVIIa  $10\text{--}30\text{ }\mu\text{g kg}^{-1}\text{ q }15\text{--}30\text{ min}$  for a total of  $90\text{--}180\text{ }\mu\text{g kg}^{-1}$ ) and confirmation that anticoagulation is therapeutic in patients with ongoing activation states (e.g. ECMO, VADs etc.) [25].

Many of these conclusions can be applied to recombinant activated Factor XIII (rFXIIIa), which is currently undergoing safety analyses. The potential usefulness of rFXIIIa is supported by two small trials that showed reduced blood loss after cardiac surgery when patients received this agent [26,27] which supports the findings of earlier studies which demonstrated an inverse relationship between Factor XIII levels and blood loss [28].

### Disclosure of Conflict of Interests

The authors state that they have no conflicts of interest.

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