

RECOMBINANT ACTIVATED FACTOR VII IN THE MANAGEMENT OF SEVERE HEMORRHAGE FOLLOWING CARDIOPULMONARY BYPASS.

Maria Helena L. Souza & Decio O. Elias

INTRODUCTION

The use of blood products in cardiac surgery and cardiopulmonary bypass (CPB) dates back to the very birth of this technology. In the earliest days of cross-circulation, systemic hypothermia, inflow occlusion, and subsequently with the development of the heart lung machine, red blood cell transfusion and, later, component therapy have been intimately related to the successful evolution of cardiac surgery [1,2]. As the morbidity and mortality of cardiac operations have decreased, the risk of the transfusions of allogeneic "bank" blood or directed donor blood have come to represent an increased percentage of the overall risk of cardiac operations. The risks of transfusion can be stated mathematically, but the perception of risks and their significance to the individual patient or physician are much more complex [3]. Cardiopulmonary bypass is associated with a multifactorial hemostatic defect. Given the interdependence and interplay by the vascular system, the platelets, the coagulation system, the fibrinolytic system, and the inflammation system during normal hemostasis, it is not surprising that no single defect predominates. Consequently, the search for therapy and especially for prophylaxis for postbypass coagulopathies proves to be difficult. Single-armed approaches directed at individual systems have not proven to be successful, neither in the research for the etiology of coagulation defects nor in clinical treatment [4]. Cardiopulmonary bypass imposes extremes on the hemostatic system. Ideally, complete arrest of coagulation and inflammation would be maintained throughout the bypass period; then separation from CPB would be

accompanied by the full return of coagulation and immunologic function. In reality, the coagulation "arrest" achieved by current anticoagulation techniques is partial at best, and the subsequent restoration of coagulation is frequently suboptimal and occasionally profoundly impaired, resulting in excessive blood loss and the need for transfusion [5].

Aggressive blood conservation techniques and the use of algorithms to standardize transfusions practices have reduced the average number of allogeneic transfusions to a few units per CPB patient, although the variation among cardiac surgical centers is impressive. It has been stated that over 35% of patients having a surgical procedure requiring CPB bled more than 1 liter in the first 24 postoperative hours [6]. Treatment of bleeding frequently is not based on demonstrated laboratory abnormalities, but rather is largely empiric and highly institution-specific [7]. Perioperative bleeding may be caused by surgical factors or an impaired hemostasis. The bleeding of impaired hemostasis associated with cardiac surgery and the use of CPB is multifactorial. Three to four percent of patients undergoing coronary artery bypass graft surgery require reexploration for bleeding, which increases the mortality rate 2-3 times.

Massive perioperative bleeding is a potential complication of any surgical procedure, and results in increased morbidity and mortality. Massive bleeding represents a major challenge to the surgical team; if uncontrollable, the patient will not survive [8]. Life-threatening bleeding may persist despite conventional medical therapy and transfusions. In the last few years there have been several reports of the use of recombinant activated factor VII (rFVIIa) in the management of massive hemorrhage with encouraging results not supplanted by any of the combination of therapies conventionally used. The aim of the present study is to review some of the published experiences with the

administration of recombinant activated factor VII in the setting of massive bleeding following the use of cardiopulmonary bypass.

BLOOD COAGULATION AND FACTOR VII

Blood coagulation comprises a series of reactions in which plasma zymogens are converted into active enzymes. The final event of these reactions is the formation of an insoluble fibrin clot. These reactions are regulated by certain stimulatory and inhibitory mechanisms. Accordingly, coagulation is a finely regulated system of reactions that maintains blood in a fluid phase but can rapidly respond to injury and form clots. Several coagulation factors are directly produced in the liver through a vitamin K-dependent metabolic pathway. Factor VII is a vitamin K-dependent serine protease glycoprotein (also known as proconvertin or stable factor) with a pivotal role in hemostasis and coagulation. Other vitamin K-dependent factors include prothrombin, factors IX and X, and proteins C and S. The discovery of vitamin K-dependent factors evolved slowly, after the initial identification of the role of prothrombin in blood clotting. Shortly thereafter it was recognized that factor VII is the key initiator of coagulation when the first case of factor VII deficiency in a child was reported [9].

Tissue factor (also known as Factor III, tromboplastin) is an intrinsic membrane glycoprotein that is normally not exposed on the surface of intact blood vessels. When the vascular lumen is damaged, tissue factor is exposed and then binds to the small amounts of circulating factors VIIa and VII. This facilitates conversion of factor VII to factor VIIa. Factor VIIa bound to tissue factor in the presence of calcium and phospholipids facilitates the conversion of factor IX to factors IXa and X to factor Xa. Coagulation has traditionally been considered to occur via extrinsic and intrinsic pathways. Although this division is useful for understanding in vitro laboratory coagulation tests, no such division

occurs in vivo because the tissue factor VIIa complex is a potent activator of factor IX and factor X.

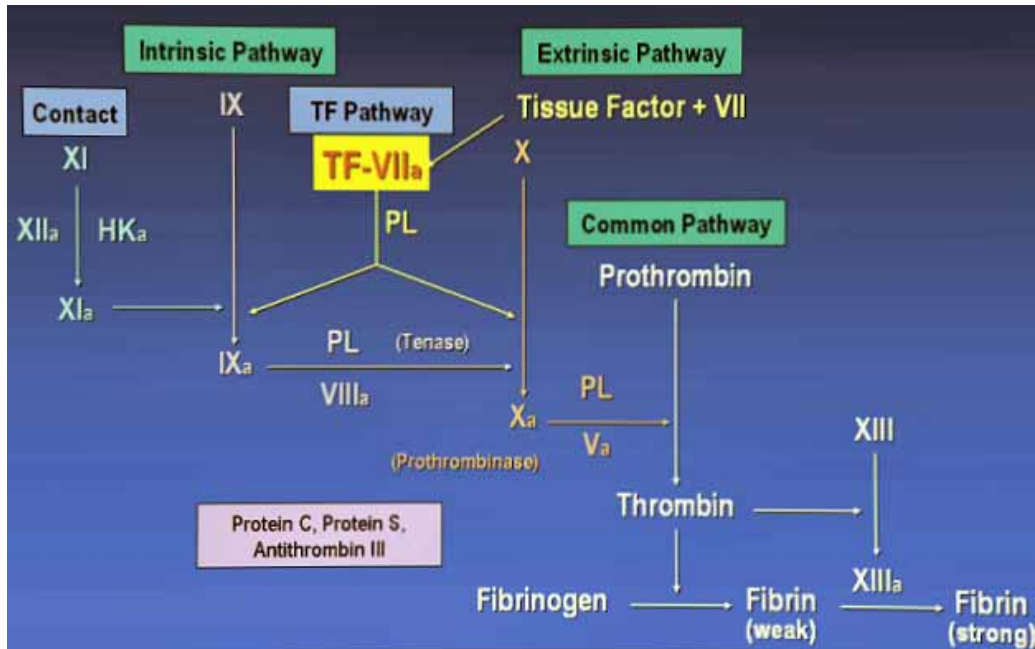


Figure 1. Chain of events in coagulation pathways and FVII role [10].

Coagulation may be initiated by vascular injury, however, multiple coagulation pathways are involved in the actual formation of clot. Vasoconstriction occurs immediately following vascular injury and is followed by platelet adhesion to collagen in the vessel wall exposed by injury. Subsequently platelet aggregation results in a platelet plug which is later strengthened by fibrin.

Fibrin production may begin with the conversion of factor X to factor X_a. Factor X can be activated by means of two reaction sequences. One requires tissue factor (TF) which is exposed to the blood as a result of vascular injury. Because TF is not in the blood, it is an extrinsic element in coagulation, hence the name "extrinsic" pathway for this sequence. The catalytic action of TF is the central precipitating event in the clotting cascade. TF acts in concert with factor VII_a and phospholipid (PL) to convert factor IX to IX_a and factor X to X_a. The "intrinsic" pathway is initiated by the "contact" activation of factor XI by the XII_a/activated high molecular weight kinogen

(HKa) complex. Factor XIa also converts factor IX to IXa and factor IXa in turn converts factor X to Xa, in concert with factors VIIIa and phospholipid (the "tenase complex"). However factor Xa is formed, it is the active catalytic ingredient of the "Prothrombinase" complex, which includes factor Va and PL and converts prothrombin to thrombin. Thrombin cleaves fibrinopeptides (FPA, FPB) from fibrinogen, allowing the resultant fibrin monomers to polymerize, and converts factor XIII to XIIIa which crosslinks the fibrin clot. Thrombin accelerates the clotting cascade by its potential to activate factors V and VIII, but continued proteolytic action also activates protein C which degrades Va and VIIIa [10].

Factor VII is one of the vitamin K-dependent coagulation factors synthesized in the liver. The concentration of factor VII in circulating plasma is low (0.5 mcg/mL) and its circulating half-life is as short as 3-4 hours. Plasmatic FVII predominantly exists in the form of the inactive single-chain zymogen, but approximately 1% circulates in the activated form (FVIIa). Activation of FVII is the initiating event of in vivo coagulation. The ability of FVIIa to cleave other clotting factors depends on binding to its cofactor tissue factor (TF), which is expressed on the surface of endothelial cells and monocytes in response to injury or inflammation. With formation of the TF/VIIa complex, FVIIa rapidly activates clotting factors VII, IX, and X, initiating the coagulation cascade [11]. The protein coagulation system is dynamically entwined with the platelet and vascular system in the formation of clot and linked with the fibrinolytic system in dissolution and limitation of clot [12,13]. Cardiopulmonary bypass disrupts part or all of these mechanisms to such a point where all patients present a certain amount of post CPB bleeding regardless of the surgical procedure performed and its duration. Certain patients are at a higher risk for bleeding and a few of these will present excessive bleeding requiring intervention. The coagulopathy for CPB starts with the

contact of blood with nonendothelial surfaces: the synthetic surface of the extracorporeal circuit, blood-air interfaces, or exposed subendothelial surfaces after surgically induced vascular injury. In addition, blood is subjected to mechanical trauma and shear stress forces. The result is the activation and amplification of the vascular, platelet, coagulation, fibrinolytic, and inflammation systems [14].

RECOMBINANT ACTIVATED FACTOR VII

Recombinant Factor VIIa is a synthetic hemostatic drug that is approved for use in hemophiliacs with antibodies to factor VIII or factor IX. It is used for the prevention and control of hemorrhagic episodes in certain patients with hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency) who developed inhibitors (alloantibodies) to antihemophilic factor or factor IX [15]. Safety and efficacy of rFVIIa have been evaluated in a dose-ranging study and in open-label, uncontrolled studies. Only limited interpretation of safety and efficacy data from these studies is possible since rFVIIa dosages generally were selected by treating clinicians and/or there were no predetermined end points. Some of the commonly used names for rFVIIa are: coagulation factor VIIa (recombinant), eptacog alfa, factor 7, proconvertin, recombinant activated factor VIIa, recombinant coagulation factor VIIa, recombinant factor VIIa. Recently, rFVIIa has shown its potential usefulness in situations of severe bleeding with major coagulopathies when other types of treatment have failed. Reported results of empiric use of rFVIIa have been rewarding. We will review some of the reported series in order to clarify indications, adequate dosing and expected results in the management of massive bleeding following cardiopulmonary bypass.

Trade name for rFVIIa in the United States and most other countries is NovoSeven (Novo Nordisk Pharmaceuticals Inc). NovoSeven is supplied as a sterile, white lyophilized powder in a single-use vial for injection and is available in nominal strengths of 60 KIU, 120 KIU, and 240 KIU per vial. The units are measured with reference to the first International Standard of FVIIa. After reconstitution of the lyophilized powder with the appropriate volume of diluent water for injection (USP), each vial contains 0.6 mg/ml (corresponding to 30 KIU/mL).

The recommended dose of rFVIIa for hemophilia A or B patients with inhibitors is 90 mcg/kg given every two hours until hemostasis is achieved, or until the response has been judged to be inadequate. Doses between 35 and 120 mcg/kg have been used successfully in clinical trials, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved. The minimal effective dose has not been established. For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds. The majority of patients who reported adverse experiences received more than twelve doses.

The active ingredient is a 406-amino acid glycoprotein (MW 50 kDa) that is produced in baby hamster kidney cells. Recombinant FVII is secreted into the culture media in its single-chain form and then proteolytically converted to the active two-chain form, rFVIIa, during a chromatographic purification process. The two-chain activated form is composed of a light chain (N-terminal) of 20 kDa and a heavy chain (C-terminal) of 30 kDa connected by a single disulfide bond. The serine protease activity resides in the heavy chain. NovoSeven is structurally similar to human plasma-derived factor VIIa [16].

Recombinant FVIIa is currently licensed in most countries worldwide for its use in the treatment of bleeding episodes in patients with hemophilia and the presence of inhibitors. Recently in the European Union, rFVIIa has been approved for use in congenital factor VII deficiency and Glanzmann's thrombasthenia. Furthermore, a large number of case series studies and anecdotal evidences, from patients with different bleeding conditions, have now shown that rFVIIa is actually a very valuable general hemostatic agent. It has been reported to reduce bleeding in patients with liver disease, thrombocytopenia/thrombocytopathia, trauma, spontaneous intracerebral hemorrhage and in the reversal of anticoagulant overdose or toxicity. A number of trials have been carried out, which have shown that it is a relatively safe and well tolerated drug with a few episodes of unwanted thrombosis [17].

RECOMBINANT ACTIVATED FACTOR VII IN CPB PATIENTS

Recombinant activated factor VIIa is currently approved for the management of bleeding related to hemophilia and a few other disorders such as congenital deficiency and thrombasthenia. Although the off-label use of this agent has been reported to be successful in reversing life-threatening bleeding in a number of scenarios, the body of literature for off-label use in cardiac surgery and CPB predominantly consists of case reports and anecdotal experience with limited data from randomized clinical trials.

Thrombotic risk profile has to be considered as one of the important issues that is still unresolved based on the infrequent reports of life-threatening thrombotic complications that have been described with use of this agent. Few thromboembolic events were reported, after administration of rFVIIa for massive hemorrhage after CPB.

RECOMBINANT FACTOR VII ACTIVATED IN PEDIATRIC CPB PATIENTS

Postoperative bleeding and blood product requirements can be substantial in children undergoing open-heart surgery, and reexploration is required in 1% of cases. Recombinant activated factor VII (rFVIIa) has been used in a group of 5 children with uncontrolled bleeding after open-heart surgery by Razon and colleagues [18]. The patients were treated with rFVIIa after failure of conventional treatment to control the bleeding. Blood loss, blood product consumption, and coagulation tests results were recorded before and after rFVIIa administration. In all cases, blood loss decreased considerably after rFVIIa administration (mean 7.8 ml/kg/h), almost eliminating the need for additional blood products, and the prolonged prothrombin time normalized. In two patients with thrombocytopathy, rFVIIa helped to discriminate surgical bleeding from bleeding caused by a defect in hemostasis. These cases support the impression that rFVIIa is efficient and safe in correcting hemostasis in children after cardiopulmonary bypass when other means fail. However the data are still limited, and more extensive research is needed.

Tobias and colleagues [19] evaluated the efficacy of recombinant factor VII (rFVIIa) in the treatment of bleeding following cardiac surgery in a pediatric population. The study included a case series of postcardiac surgical patients with chest output of ≥ 4 ml/kg/h for the initial 3 postoperative hours who received rFVIIa. Chest tube output for the 3 hours before and the 3 hours after rFVIIa was compared using a paired test. In addition, chest tube output for the initial 3 postoperative hours and the 3 hours following rFVIIa was compared to 8 control patients who did not require rFVIIa. Recombinant factor VIIa was administered to 9 children (age = 9 ± 4 years) following repair of tetralogy of Fallot (6), closure of ventricular septal defect (1), closure of sinus venosus atrial septal defect (1), and mitral valve repair (1).

Chest tube output for the initial 3 postoperative hours prior to the administration of rFVIIa was 5.8 +/- 2.8 mL/kg/h and decreased to 2.0 +/- 1.3 mL/kg/h for the 3 hours following the administration of rFVIIa (P=0.002). In the patients that did not receive rFVIIa, chest tube output for the 3 postoperative hours was 1.6 +/- 0.9 mL/kg/h and 1.2 +/- 0.6 mL/kg/h for the next 3 hours (P = nonsignificant when compared to chest tube for the 3 hours following rFVIIa in patients who received the drug). No adverse effects were noted. Recombinant factor VIIa decreased chest tubing bleeding following cardiac surgery in children. Given its potential therapeutic impact, rFVIIa warrants further investigation in the pediatric cardiac population.

In another report Pychynska-Pokorska et al [20] discuss their results with the administration of rFVII in eight consecutive pediatric patients with excessive bleeding after cardiac surgery with cardiopulmonary bypass that met the criteria for reexploration and did not respond to optimal transfusions of platelets and fresh frozen plasma. Recombinant FVIIa 30 microg/kg was given as a bolus injection. A higher dose of 60 microg/kg was used if a patient had preoperative coagulopathy, preoperative multiple-organ failure, or indications that required an emergency operation. The same dose was repeated 15 minutes after the previous injection if the bleeding had not decreased. If the bleeding had decreased but still exceeded 10 mL/h for body weight \leq 5 kg or exceeded 2 mL/kg/h for body weight $>$ 5 kg, the same dose was repeated 2 hours after the previous injection. A maximum of four doses could be given before rFVIIa was considered ineffective and a reexploration was needed. Postoperative blood loss was estimated from the volume of chest tube drainage. Recombinant FVIIa successfully controlled bleeding and prevented reexploration in all seven patients who received treatment according to the protocol. One patient who received only one dose of rFVIIa required reexploration because a second dose was not available. No adverse events related to

rFVIIa were seen. Thus, rFVIIa may be useful in preventing reexploration in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass. Randomized, placebo-controlled studies are needed to confirm the safety and efficacy of rFVIIa in this clinical setting.

RECOMBINANT FACTOR VII ACTIVATED IN ADULT CPB PATIENTS

Most reports concerning the use of rFVIIa refer to small groups of adult patients presenting serious bleeding or massive uncontrollable hemorrhage. Halkos et al [21] describe their experience with 9 patients presenting with intractable hemorrhage after complex cardiovascular operations. All nine patients received rFVIIa after aortic surgery (2), coronary artery bypass graft surgery (4), double valve operations (2), and mitral valve replacement (1). Four of these procedures were reoperations. Intraoperative aprotinin was used in all patients. All patients underwent standard heparinization (300 IU/kg) before cardiopulmonary bypass and reversal with protamine. Five patients underwent reexploration for mediastinal hemorrhage before treatment; 2 were reexplored twice. The average transfusion requirement before rFVIIa administration was 9 U of blood, 7 U of plasma, 22 U of platelets, and 19 U of cryoprecipitate. Recombinant FVIIa was administered as an intravenous bolus at 68 to 120 microg/kg. Mean time of administration from the first operation was 10.9 +/- 7.2 hours. At the time of rFVIIa administration, chest tube drainage averaged 640 mL/h. In all patients, chest tube drainage was dramatically reduced to less than 100 mL/h within 5 hours after drug delivery. None of the patients required reexploration after treatment. There were no postoperative neurologic or cardiovascular complications. When used as rescue therapy for intractable hemorrhage after cardiovascular surgery, rFVIIa may be effective in

promoting hemostasis, preventing reexploration, and reducing transfusion requirements.

Raivio and colleagues [22] analyzed retrospectively all consecutive cardiac surgical patients who have received rFIIa in the Helsinki University Hospital in order to evaluate the safety and efficacy of rFVIIa after cardiac surgery in their institution. Altogether, 16 patients were identified from operating room and intensive care unit databases from a total of approximately 2,800 patients. Cardiopulmonary bypass was performed using a noncoated circuit and a membrane oxygenator. Heparin (5,000 IU) was added to the CPB priming solution and an initial intravenous dose of 300 IU/kg of heparin was administered. In case of increased intraoperative or postoperative bleeding (chest tube bleeding > 200 mL/hour) fresh frozen plasma was administered. Platelet concentrates, prothrombin complex concentrate, human fibrinogen, human factor VIII concentrate and factor XII concentrate could be used as part of component therapy administered according to the anesthesiologist's discretion. The use of rFVIIa was reserved for life-threatening bleeding with no identifiable surgical source after adequate, conventional blood component therapy as suggested in the literature. The mean dose of rFVIIa used was 65 microg/kg (range, 24-192 microg/kg). In this series of high risk patients hospital mortality was high (25%). A definite hemostatic effect was seen after rFVIIa administration in all but three patients (82%). Mean amount of bleeding and amount of platelet and fresh frozen plasma transfusions decreased significantly after rFVIIa administration. Four patients had serious postoperative thromboembolic complications.

Karkouti et al [23] described the outcomes of the first 51 cardiac surgery patients who received rFVIIa for intractable blood loss (from November 2002 to February 2004) at a single institution according to a standardized clinical guideline. The patients were compared to 51 matched controls identified from a large database and matched based

on the propensity for massive blood loss. Blood loss and blood product usage were significantly decreased after 2.4 to 4.8 mg of rFVIIa. In those treated after sternal closure (n=32), there was a significant reduction in blood loss from the hour before to the hour after treatment: 100 (70, 285) mL (median [25th, 75th percentiles]; P<0.0001). Except for a slower postoperative recovery and higher incidence of acute renal dysfunction, the adverse event rates were similar between the rFVIIa-treated patients and their matched controls. These results suggest that rFVIIa may be an effective rescue therapy for patients with intractable hemorrhage after cardiac surgery. A clinically important risk of stroke or other major thrombotic complications could not be ruled out by the study. Controlled clinical trials with adequate power to detect the impact of rFVIIa therapy on morbidity and mortality therefore are necessary before one can recommend its routine use in patients undergoing cardiac surgery who have excessive bleeding.

Stratmann and colleagues [24] reported the case of a 60-year-old male, who had undergone a Bentall aortic root replacement 19 years previously using a porcine-valved conduit for acute type A aortic dissection, scheduled for elective aortic replacement for severe prosthetic valve insufficiency and aneurysmal enlargement of the remaining ascending aorta. Final separation from CPB (total CPB time of almost 6 hours) was accompanied by diffuse bleeding and coagulopathy. After protamine was administered, blood loss persisted at a rate of 270 mL/min despite complete reversal of heparin, as evident by a heparin concentration of zero mg/ml (Hepcon plus, Medtronic). Over the next 90 minutes, 25 U of PRBC (6,250 mL), 22 U of fresh frozen plasma (4,400 mL), 10 six-packs of platelets (2,000 mL), and 8 ten-packs of cryoprecipitate (800 mL), in addition to 11,000 ML of shed mediastinal blood, were administered with no apparent therapeutic effect. We surmise that the replacement of the

patient's blood volume 4 to 6 times likely reduced the concentration of some critical coagulation factors including activated factor VII to levels too low to support thrombin formation. It was then decided to administer a dose of 90 microg/kg of rFVIIa intravenously. Three minutes later the bleeding had slowed down, so that rapid resuscitation with blood products was no longer necessary. The patient received no more blood products except for six units of platelet concentrate. An empiric second dose of rFVIIa was administered 2 hours after the initial dose had been given. Hemostasis was permanent. The patient recovered slowly, was extubated on the third postoperative day, and left the hospital six days later without any symptoms or signs of systemic thromboses.

DISCUSSION

A comprehensive study on the use of rFVIIa in intractable bleeding management in a larger number of cardiac patients is still missing in the literature. Only case histories or small number of patients have been published to date and they clearly support the highly positive effects of rFVIIa. The available studies vary widely in the rFVIIa dosage used; even a three-fold lower dosage than the recommended 90 microg/kg has been reported. Evaluation of the potential risk from vein and artery graft occlusion (thrombosis) after myocardial revascularization will be the subject of further studies, with particular focus on the use of rFVIIa in emergencies with imminent life-threatening bleeding [25].

Excessive perioperative bleeding remains a major complication following cardiac surgery resulting in increased morbidity and mortality. The principal causes of non-surgical hemostatic perioperative bleeding are a pre-existing undetected bleeding disorder, related to the nature of the operation itself or from

coagulation abnormalities arising from massive blood loss [26]. Very often, it is a combination and coexistence of various pathologies. Identifying patients at risk remains a major component of preventing excessive blood loss. Understanding the hemostatic changes occurring in the perioperative period, especially in complex procedures like cardiopulmonary bypass and orthotopic liver transplantation is crucial in developing new strategies for the management of perioperative bleeding. Pharmacological interventions, especially aprotinin, tranexamic acid, desmopressin and increasingly recombinant activated factor VII are being used both in prophylaxis and therapeutically to stop bleeding. The use of near patient testing like thromboelastography and platelet function analyser has allowed for more detailed assessment of the various steps of hemostasis. One of the main goals is to reduce the usage of allogeneic blood transfusion and its attendant risks.

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