

REVIEW ARTICLE

Recombinant activated factor VII and the anaesthetist

I. J. Welsby,¹ D. M. Monroe,² J. H. Lawson³ and M. Hoffmann⁴

1 Assistant Professor, Department of Anaesthesiology, 2 Assistant Professor, Departments of Surgery and Pathology, Duke University Medical Center, Durham, NC 27710, USA

3 Department of Medicine, University of North Carolina, Chapel Hill, NC 27514, USA

4 Professor, Department of Medicine, University of North Carolina, Chapel Hill, NC 27514, USA and Professor and Director of Transfusion Services, Durham VA Medical Center, Fulton Street, Durham, NC 27705, USA

Summary

Recombinant activated factor VII is a safe and effective for the treatment and prevention of haemorrhage in haemophiliacs with circulating inhibitors to replacement factors, and patients with Glanzmann's thrombasthenia refractory to platelet transfusion. By restoring thrombin generation on the surface of tissue factor bearing cells, such as activated platelets and monocytes, recombinant activated factor VII has the potential to effect haemostasis in the setting of many coagulopathic states encountered by the anaesthetist in the operating theatre or the intensive care unit. Case reports of successful rescue therapy make up the majority of the literature covering other, numerous, off-label uses of recombinant activated factor VII, although some randomised, controlled studies, mostly underpowered to address safety concerns, have been performed. However, off-label use is becoming increasingly popular judging by the number of published case reports. Additional randomised, controlled trials to determine the safe and appropriate use of this potentially valuable therapy in broader patient groups are eagerly awaited.

Correspondence to: I. J. Welsby
E-mail: welsb001@mc.duke.edu
Accepted: 26 June 2005

This review summarises the knowledge and understanding of a prohaemostatic agent, recombinant activated factor VII (rFVIIa), which may have the potential to affect our clinical practice to a degree that rivals aprotinin use in high-risk cardiac surgery and liver transplantation. Regulatory approval has been granted in Europe and the US for rFVIIa use in the treatment or prophylaxis of bleeding in Haemophilia A or B with high titres of circulating inhibitors to factor VIII or factor IX, respectively, and in Europe for Glanzmann's thrombasthenia. Such patients require treatment with a 'bypassing' agent, as the inhibiting antibodies render certain haemophiliacs unresponsive to exogenous factor supplementation and many patients with Glanzmann's thrombasthenia are refractory to platelet transfusion. The first generation of bypassing agents contained plasma derived factors II, VII, IX and X (prothrombin complex concentrate, PCC), some of which may be present in an activated form (activated prothrombin complex concentrate, aPCC, or factor eight inhibitor bypassing agent, FEIBA[®], Baxter Healthcare, Deerfield, IL). However, their efficacy is only moderate

[1] and thrombo-embolic complications are well described [2]. After success with plasma-derived factor VIIa, transfected baby hamster kidney cells were used to produce recombinant factor VIIa (rFVIIa; NovoSeven[®], Novo Nordisk, Bagsvaerd, Denmark) and it was approved for use as a bypassing agent in Europe in 1996 and in the US in 1999. The availability of rFVIIa as an alternative bypassing agent has led to extensive reports of successful surgery being safely performed in haemophiliacs with circulating inhibitors [3]. When used in haemophiliacs with inhibitors (a group with a severe congenital coagulopathy at extremely low risk of thrombosis), and at recommended doses (90 µg.kg⁻¹ every 2 h until haemostasis is achieved), rFVIIa use appears remarkably safe compared to aPCC. However, use in other patients represents off-label use without safety or efficacy data.

Safety concerns

Tissue factor bearing cells (such as subendothelial stromal fibroblasts exposed after endothelial disruption) or

activated platelets) should theoretically localise rFVIIa-mediated thrombin generation to sites of tissue injury, as discussed later. In the surgical setting, this could either be desirable (a site of diffuse injury) or potentially disastrous (the anastomotic line of a vascular graft or an atherosclerotic plaque). Monocytes can express tissue factor in response to inflammatory stimuli either *in vitro* or *in vivo* [4]. This raises the concern that the interaction of rFVIIa with activated monocytes expressing tissue factor on their surface could lead to disseminated intravascular coagulation (DIC), but this is not supported by the minimal incidence of thrombo-embolic complications despite use in some patients at risk of DIC [5]. In contrast to aPCC, rFVIIa does not induce a hypercoagulable state *in vitro* [6] and in over a decade of experience using rFVIIa, > 400 000 doses have been administered with only 18 thrombotic complications spontaneously reported. While typically underestimating the true incidence of complications, this is consistent with a study by the Hemophilia Research Society of North America that described a < 1% incidence of treatment-related adverse events [5]. Macrophages present in atherosclerotic plaques abundantly express tissue factor [7] and the tissue factor expressed on atherosclerotic plaques binds factor VIIa, determining the thrombogenicity of the plaque [8]. Myocardial infarctions have been described in haemophiliacs with risk factors for, or a history of, coronary artery disease. Co-administration of aPCC has been identified as a risk factor for thrombosis associated with rFVIIa use [9, 10], yet rFVIIa has been safely used in patients with myocardial infarction complicating prior treatment with aPCC [11]. The incidence of thrombotic complications in patients with normal coagulation systems receiving rFVIIa is unknown.

Mechanism of action

A dependence on surface-located tissue factor is consistent with the low incidence of reported thrombo-embolic complications and the commonly held view that thrombin generation and subsequent clot formation following rFVIIa administration is injury site specific. Tissue factor is required for rFVIIa to restore thrombin generation in an *ex vivo* model of haemophilia [12]. However, the addition of pharmacologic concentrations of rFVIIa to haemophilic blood can correct clotting time and markedly increase platelet activation in the absence of tissue factor [12], and rFVIIa shortens the tissue factor-independent activated partial thromboplastin time (aPTT) as well as the tissue factor-dependent prothrombin time (PT) [13].

The conversion of factor X to factor Xa is a key step in haemostasis and is catalysed by both 'extrinsic' and

'intrinsic' tenase (Xase). Initially, the 'extrinsic' tissue factor–FVIIa complex generates small amounts of factor Xa on the cell surface that facilitates factor IXa generation by the tissue factor–FVIIa complex, inefficiently generating small amounts of thrombin essential for local activation of platelets, factor V and factor VIII. Thus 'extrinsic' Xase sets the stage for 'intrinsic' Xase (VIIIa–IXa complex) that generates Xa far more efficiently, feeding into the Va–Xa 'prothrombinase' catalytic complex that rapidly and efficiently converts prothrombin to thrombin [14]. Independent of tissue factor, rFVIIa can activate factor X on the surface of both monocytes [15] and platelets [16], potentially augmenting both 'intrinsic' and 'extrinsic' Xase function. The ability to increase thrombin generation at sites rich in tissue factor and to generate thrombin on the surface of activated platelets and monocytes compensates for the inability to construct the 'intrinsic' Xase enzyme in haemophiliacs, and may be the mechanism of action of rFVIIa in the wide variety of clinical settings we describe.

Cell-based model of haemostasis

Studies of the biological action of rFVIIa have led to the proposal of a hypothetical, cell-based model of haemostasis (Fig. 1). Factor VIIa plays a key role at various stages, providing sites for the mechanism of action of rFVIIa [17].

In this model, there are three stages leading to the explosive thrombin generation necessary for haemostasis and the formation of a stable fibrin clot. The '*initiation stage*' (Fig. 1a) involves the generation of small amounts of factor Xa and thrombin on the surface of a tissue factor-bearing cell, platelet or monocyte by the tissue factor–VIIa 'extrinsic' Xase. This inefficient generation of small amounts of thrombin is essential for local activation of platelets, factor V and factor VIII, and is augmented by exogenous rFVIIa. It is possible that this process occurs at a basal level outside the vascular wall, which is permeable to smaller proteins such as factor VII, factor X and prothrombin. The '*amplification stage*' (Fig. 1b) starts with vascular disruption and exposure of tissue factor-bearing cells to platelets, von Willebrand factor and factor VIII. The thrombin generated in the 'initiation stage' activates the platelets forming the platelet plug, and their surface is primed with factor Va, factor VIIIa and factor XIa. Both the tissue factor–factor VIIa complex and factor XIa activate factor IX, which leads to the '*propagation stage*' (Fig. 1c) with the construction of the efficient, 'intrinsic' Xase (IXa–VIIIa) on the platelet surface generating factor Xa. The plentiful factor Xa provided above complexes with factor Va (factor Va–factor Xa; prothrombinase) to generate large amounts of thrombin, cleaving fibrin-

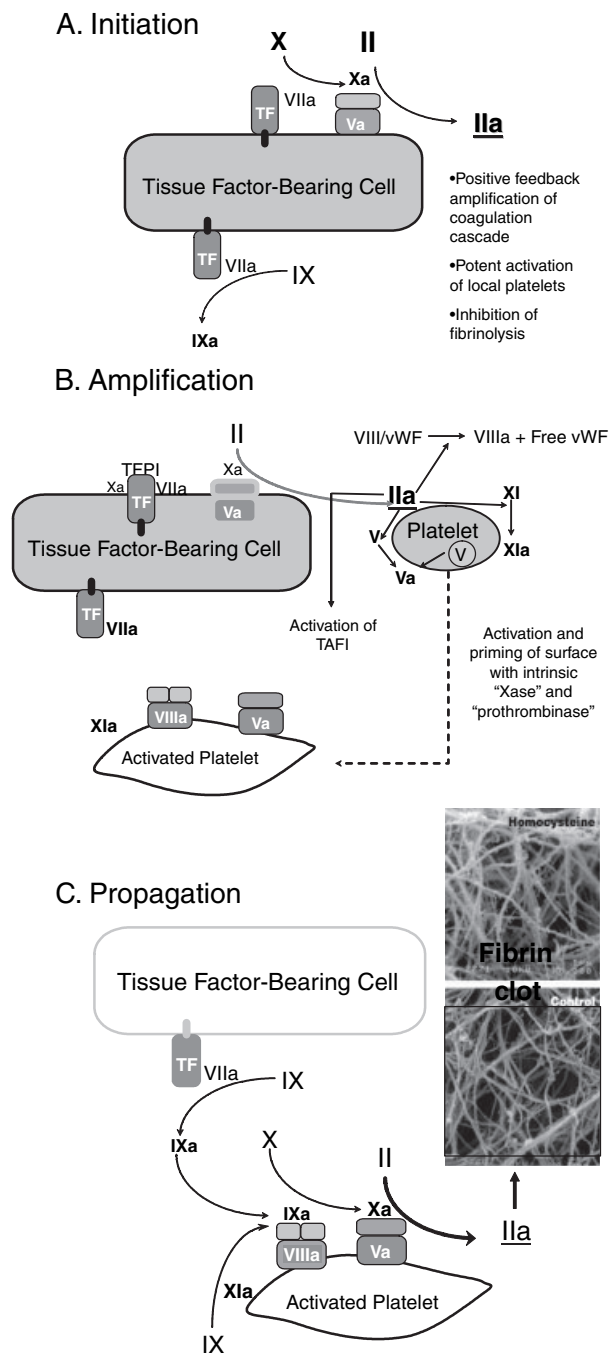


Figure 1 A cell-based model of haemostasis with three stages: A: Initiation, B: Amplification, C: Propagation. TFPI, tissue factor pathway inhibitor. TAFI, thrombin-activatable fibrinolysis inhibitor. TF, tissue factor. II, prothrombin. IIa, thrombin. VIIa, factor VII (activated). Other coagulation factors are similarly described.

ogen into fibrin monomers, which polymerise to consolidate the initial platelet plug and form a stable fibrin clot. This burst of thrombin generation also exerts positive feedback into the coagulation process by activa-

rFVIIa generates Xa on the platelet surface in haemophiliacs

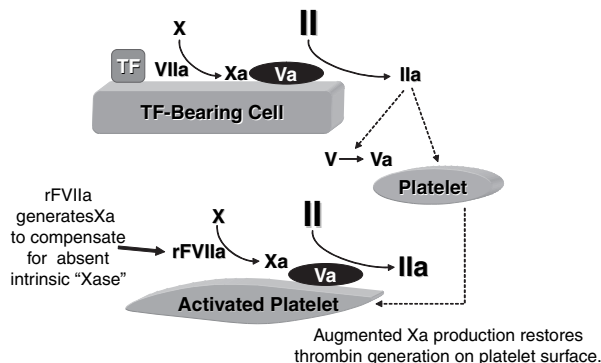


Figure 2 A schematic model of the proposed mechanism of action of recombinant activated factor VII in haemophiliacs. TF, tissue factor. II, prothrombin. IIa, thrombin. VIIa, factor VII (activated). Other coagulation factors are similarly described. rFVIIa, recombinant activated factor VII.

ting factor V, factor VIII, factor XI and thrombin activatable fibrinolysis inhibitor (TAFI). Direct activation of TAFI, either via factor XI or the thrombin–thrombomodulin complex, has been demonstrated *in vitro* after rFVIIa administration, and has been postulated as a contributory mechanism of action in haemophiliacs [18]. However, this occurs at high concentrations only, so rFVIIa will not replace the rational use of appropriately dosed antifibrinolytic drugs (aprotinin, tranexamic acid or ε-aminocaproic acid). Concomitant use of antifibrinolytic drugs is recommended when administering rFVIIa [19, 20].

The ability to increase thrombin generation at sites rich in tissue factor and generate factor Xa and thrombin on the surface of activated platelets and monocytes compensates for the failure to construct the ‘intrinsic’ Xase in haemophiliacs, as illustrated in Fig. 2 [15, 21], and may be the mechanism of action of rFVIIa in the wide variety of clinical settings we describe.

Off-label use of rFVIIa

The ability of rFVIIa to restore thrombin generation as described above has led to numerous off-label uses for rFVIIa either in closely monitored and audited groups of haematology patients or, increasingly, in the form of rescue therapy in other patients who have failed conventional haemostatic therapy. The case reports describing rescue therapy are subject to positive reporting bias and appropriately designed, controlled studies are currently lacking in many areas where off-label use is becoming commonplace.

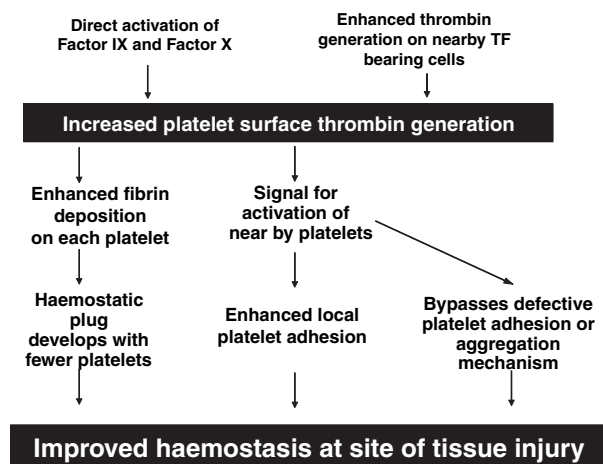


Figure 3 Theoretical mechanisms by which increased thrombin generation and fibrin deposition, as a result of treatment with recombinant activated factor VII, may lead to improved haemostasis in patients with bleeding disorders. TF, tissue factor.

Use of rFVIIa in thrombocytopenia and thrombocytopathia

High dose factor VIIa restores factor Xa and thrombin generation on the platelet surface (Figs 1 and 3), allowing clot formation to proceed. Optimisation of this process by rFVIIa may facilitate thrombin generation in the face of insufficient or otherwise dysfunctional platelets, and *in vitro* work suggests a basis for effective use of rFVIIa in a model of thrombocytopenia [22]. Thrombin is a potent platelet agonist and this increased thrombin generation on the platelet surface has multiple effects. It improves platelet deposition via the GP1b receptor complex [23], then enhances platelet activation and aggregation via the PAR-1 thrombin receptor [12, 24], which may restore the ability to produce a stable platelet plug, even in the setting of severe, congenital thrombocytopathia [25, 26]. An International Registry of 'Recombinant Factor VIIa and Congenital Platelet Disorders' has been established in an attempt to monitor the safety and efficacy of rFVIIa treatment of spontaneous or surgical haemorrhage in this patient group [20, 27], and in patients with thrombocytopenia [27]. Such patients often receive multiple platelet transfusions and HLA allo-immunisation may render future platelet transfusions ineffective, analogous to haemophiliacs with inhibitors, necessitating the use of a bypassing agent. Theoretically, rFVIIa should also be effective in patients experiencing bleeding associated with platelet inhibitors [26] (such as high dose clopidogrel or eptifibatide), where infused platelets are neutralised by circulating drug. The postulated effect of rFVIIa on platelets is summarised in Fig. 3.

Overall, rFVIIa appears to be safe and effective in these patients at the recommended dose of $90 \mu\text{g.kg}^{-1}$ ($80\text{--}120 \mu\text{g.kg}^{-1}$) every 2 h; at least three doses should be administered to secure haemostasis and should be continued until lasting haemostasis is achieved. One late, postoperative, thrombo-embolic event was described in a patient with Glanzmann's thrombasthenia undergoing major gastrointestinal surgery who received rFVIIa for over a week after surgery without any evidence of ongoing bleeding [27]. In Europe, approval has recently been given for the use of rFVIIa in patients with Glanzmann's thrombasthenia but other platelet-related indications remain off-label.

Stroke

Intracerebral haemorrhage carries a high mortality and residual disability in survivors, and it is difficult to improve outcome when much of the damage has occurred by the time patients present to hospital. However, haematoma growth occurs as an ongoing secondary process. Rebleeding may occur at multiple sites over several hours, with > 25% of patients showing a > 30% increase in haematoma volume at 1 h, and an additional 12% showing similar growth on CT scans between 1 and 20 h [28]. Haematoma volume is a crucial factor in predicting mortality and functional outcome, so by promoting haemostasis at sites of initial vascular disruption, rFVIIa can potentially limit secondary haematoma growth and improve outcome following intracerebral haemorrhage.

A randomised, double-blind, placebo-controlled phase II dose escalation study did not identify any major safety concerns [29], and a smaller case series reported the effective reversal of a warfarin effect and no safety concerns [30] with the early use of rFVIIa in patients with intracerebral haemorrhage. Following these studies, Mayer *et al.* [31] recently reported a randomised, placebo-controlled trial demonstrating that rFVIIa significantly decreased the volume of intracerebral haematoma growth, mortality and incidence of severe disability, compared to placebo, when given no later than 4 h after the onset of symptoms of intracerebral haemorrhage, confirmed by CT scanning. There was no detectable difference in outcome between the three doses of rFVIIa: $40 \mu\text{g.kg}^{-1}$ ($n = 108$), $80 \mu\text{g.kg}^{-1}$ ($n = 92$) and $160 \mu\text{g.kg}^{-1}$ ($n = 103$); 96 patients were given placebo. Arterial thrombo-embolic events, including myocardial ischaemia ($n = 7$) and cerebral infarction ($n = 9$) were significantly increased in patients receiving rFVIIa (5%) compared to placebo (0%). However, *post hoc* analysis of thrombo-embolic events that were disabling or likely to be related to treatment yielded an incidence equal to the placebo group. Overall, given the mortality benefits,

40 $\mu\text{g.kg}^{-1}$ of rFVIIa seems to be a safe and effective early treatment for intracerebral haemorrhage [31].

Trauma

Trauma patients are treated for bleeding prehospital, in the operating theatre and in the intensive care unit. While vascular disruption requires surgical intervention, extensive soft tissue trauma, certain blunt injuries [32] and coagulopathic bleeding may potentially benefit from rFVIIa-enhanced thrombin generation at the site of injury, where tissue factor expression and activated platelets will be abundant. Case studies and case series report positive results when rFVIIa is used as a 'rescue' prohaemostatic agent [33, 34] but, more importantly, preliminary results of a phase II, multinational, prospective, randomised, placebo-controlled trial of rFVIIa in traumatic shock were presented at the American Association for the Surgery of Trauma in October 2004. Blunt and penetrating trauma were randomised separately; patients were enrolled during transfusion of the sixth unit of red blood cells and the drug was given after the eighth unit of blood had been administered. The primary endpoint for the study was transfusion requirement; secondary endpoints were mortality and organ failure, and drug dosing was 200 $\mu\text{g.kg}^{-1}$ rFVIIa initially, followed by 100 $\mu\text{g.kg}^{-1}$ at 1 h and 3 h after the first dose. Of the 301 patients enrolled (143 blunt and 137 penetrating trauma), 24 were excluded for protocol and data collection violations. There was no significant difference in outcome measures between treatment and placebo groups analysed on an intention to treat basis. However, *post hoc* exclusion of early deaths (before 48 h) revealed a significant reduction in blood transfusion requirements following rFVIIa administration in the blunt trauma group, a trend towards decreased use in the penetrating trauma patients, a trend towards a decreased incidence of multiple organ failure and adult respiratory distress syndrome (ARDS) in the blunt trauma group ($p = 0.07$) and a significantly decreased incidence of multiple organ failure and ARDS (rFVIIa: 8.6% vs. placebo: 20.3%; $p = 0.006$) when blunt and penetrating trauma were analysed together.

Obviously, these differences revealed by *post hoc* analysis are impossible to apply clinically without a risk stratification mechanism that is capable of identifying patients who will die within 48 h. A problem with the protocol is that an assessment of the need for prohaemostatic therapy based on clinical haemorrhage or laboratory evidence of coagulopathy was absent from the study design and, while adding further complexity to a study that was an achievement to accomplish, such stipulations may more realistically reflect clinical practice. Such design modifications would rely on identifying an appropriate test as a trigger and a monitor for rFVIIa therapy and,

as discussed later, this may be difficult to achieve. The timing of, and patient selection for, rFVIIa administration are also debatable, as early use may decrease overall blood loss in certain injuries [35], but may be ineffective after transection of larger blood vessels until after surgical repair, as possibly reflected by different results in blunt and penetrating trauma patients.

To assess the value of rFVIIa further in trauma surgery, 48 patients with high anticipated blood loss presenting for reconstructive surgery after pelvic trauma were randomised to receive placebo or 90 $\mu\text{g.kg}^{-1}$ rFVIIa just before skin incision [36]. The protocol allowed for an additional 90 $\mu\text{g.kg}^{-1}$ within 2 h if allogeneic blood transfusion was needed, in addition to cell salvage, and 38% of those randomised to rFVIIa received this second dose. A treatment effect was a decreased prothrombin time but this failed to translate into a decrease in peri-operative blood loss. However, this was a smaller sample than in the acute trauma study. Patients had no known haemostatic abnormalities before surgery, and this may explain the lack of clinical benefit from this relatively high dose of rFVIIa, as seen in the trauma study above and as discussed later in patients undergoing partial hepatectomy [37].

Urological and general surgery

The efficacy of rFVIIa in decreasing blood loss and need for transfusion has been demonstrated in a randomised, placebo-controlled trial during retropubic prostatectomy [38] in patients with intact haemostatic systems. The dose of rFVIIa started at 20 $\mu\text{g.kg}^{-1}$, escalating to 40 and then 80 $\mu\text{g.kg}^{-1}$ depending on safety committee recommendations after analysing data from cohorts of 12 patients (eight drug and four placebo). Patients were randomly allocated to receive placebo ($n = 12$) or treatment with 20 $\mu\text{g.kg}^{-1}$ rFVIIa ($n = 8$) and 40 $\mu\text{g.kg}^{-1}$ rFVIIa ($n = 16$); the higher dose was not administered. Both doses significantly decreased blood loss and transfusion requirement in a dose-dependent manner (no patients in the 40 $\mu\text{g.kg}^{-1}$ group were transfused). Despite significant increases in markers of thrombin generation and a decreased prothrombin time, no adverse thrombo-embolic events occurred during the study period. However, administering rFVIIa to prevent bleeding in urological surgery cannot be recommended based on this study alone, as it was not powered to examine safety or the risk of thrombo-embolic complications, and it ought to be compared to cheaper antifibrinolytic drugs that may also decrease bleeding in this setting [39]. The use of rFVIIa as a rescue agent for major bleeding complicating prostatectomy would be supported by this study.

In other surgical specialties, the majority of the literature comprises positive case reports, small case series and efforts to combine such reports critically [40].

Recently, a multicentre, randomised, double blind, placebo-controlled study of rFVIIa (20 or 80 $\mu\text{g.kg}^{-1}$) given before skin incision in 204 non-cirrhotic adult patients undergoing partial hepatectomy for tumour excision [37] found no statistically significant difference in the primary outcome of peri-operative transfusion. Reassuringly, there were no safety issues in this relatively large sample from the standpoint of hepatic or venous thrombo-embolism. These results contrast with the prostatectomy study [38]. It is possible that a combination of the surgical procedure and pre-existing co-morbidities, such as cirrhosis, are important in determining which patients, if any, benefit from prophylactic rFVIIa.

Obstetrics

In the largest case series describing the use of rFVIIa as rescue therapy for massive *post partum* haemorrhage, the authors describe a good response in five of 16 patients, a partial response in six and a treatment failure in one [41]. Doses ranged from 40 to 120 $\mu\text{g.kg}^{-1}$ but there was no apparent dose-response relationship. Administration of rFVIIa occurred in conjunction with uterotonics, hysterectomy and arterial embolisation, so it was not possible to draw conclusions about the efficacy of rFVIIa in this patient group. Studying rare indications such as massive *post partum* haemorrhage will require multicentre efforts.

Cardiac surgery

Multiple haemostatic defects can develop after cardiac surgery with platelet dysfunction, thrombocytopenia, generalised coagulation factor deficiency and fibrinolysis all contributing to coagulopathic bleeding. The mechanism of action of rFVIIa (Fig. 1) ideally lends itself to these multifactorial haemostatic defects, as it has been shown to restore thrombin generation in the setting of thrombocytopenia, thrombocytopenia and coagulation factor deficiency, promoting the formation of a platelet plug and the fibrin clot. Activation of TAFI follows rFVIIa administration but the ability of rFVIIa to inhibit fibrinolysis is unclear. In contrast, the established role of antifibrinolytic drugs, especially aprotinin [42], mandates their use for candidates at high risk of haemorrhage, remembering that plasma levels may need to be supplemented after major blood loss. Once again, data in this area are mostly limited to case reports of 'rescue' therapy, with one catastrophic thrombosis during extracorporeal membrane oxygenation possibly the result of FEIBA/aPCC use following exhaustion of rFVIIa supplies [9]. Thrombotic side-effects of rFVIIa may possibly be increased by the concomitant use of antifibrinolytic drugs, despite their established role in this population and recommendations for their co-administration during rFVIIa therapy [20], although there is no evidence to

support this hypothetical problem. However, it is premature to conclude that graft thrombosis would not be a serious complication of FVIIa use in this population.

This concern is echoed by a 16-patient, retrospective case series over a 2-year period of rescue therapy for severe coagulopathic bleeding in high-risk cardiac surgery by Raivio *et al.* (Annals of Thoracic Surgery, in press). The cases were mostly complex, emergency operations involving redo thoracotomy and deep hypothermic circulatory arrest ($n = 6$), most patients having received aprotinin ($n = 10$) or tranexamic acid ($n = 6$). The mean[range] dose of rFVIIa was 56 [24–192] $\mu\text{g.kg}^{-1}$, and rFVIIa was haemostatic in 13/16 patients. A 25% incidence of major thrombo-embolic complications was described, including two patients undergoing aortic reconstruction for Type A aortic dissection who developed iliac artery thromboses. In one patient, this clearly coincided with the administration and haemostatic effect of rFVIIa. Acute graft failure in an orthotopic heart transplant was found on autopsy to be due to diffuse coronary artery thromboses, and the fourth patient suffered multiple cerebral infarctions after aortic surgery with deep hypothermic circulatory arrest. Such complications may be related to underlying pathology, technical difficulty, hyperacute rejection or the nature of the surgery, and randomised, controlled studies are required in this population to determine whether rFVIIa use increases the incidence of thrombo-embolic complications.

A larger case-control study from Toronto [43] used a propensity score to match cases with controls from the general cardiac surgical population, and reviewed 51 of 2225 (or 2.3%) cardiac surgical patients over a 2-year period who received rFVIIa according to predefined institutional guidelines. Patients were more varied and included coronary bypass surgery ($n = 21$), valvular surgery ($n = 28$), aortic surgery ($n = 15$), complex congenital defect surgery ($n = 8$) and transplantation ($n = 4$). Criteria allowed for earlier use of rFVIIa, stipulating massive, refractory blood loss defined as > 2000 ml blood loss requiring > 4 units of packed red cells that precluded sternal closure in the operating theatre (after exclusion of a surgical source) or caused postoperative bleeding of > 100 ml.h^{-1} from the chest drains despite administration of antifibrinolytic drugs, fresh frozen plasma and platelet transfusions. Similar to the series reported by Raivio *et al.* (in press) the use of cryoprecipitate (which contains fibrinogen, factor VIII, von Willebrand factor and factor XIII in higher concentrations than fresh frozen plasma) was not mandated before rFVIIa administration, which may be a weakness in the definition of refractory. When a dose of 2.4 mg (approximately 35 $\mu\text{g.kg}^{-1}$) was used, a repeat dose was required to stop bleeding in a third of the

patients, whereas a 4.8 mg dose was uniformly effective for non-surgical bleeding. A surgical source of bleeding was found in 8/51 cases. The patients who received rFVIIa had significantly prolonged ICU and hospital stays and a greater incidence of renal dysfunction. The incidence of peri-operative myocardial infarction was increased but in the 21 patients undergoing coronary bypass surgery, graft patency was not assessed. Unfortunately, case-control matching was not entirely effective, as cases had significantly higher quantities of blood products transfused and surgical re-exploration, confounding the cause and effect relationship between rFVIIa and outcomes.

The typical $90 \mu\text{g.kg}^{-1}$ dose of rFVIIa recommended for haemophiliacs may be inadvisable in this group of patients until more safety data, particularly with regard to graft thrombosis, become available. Single, lower-dose boluses of rFVIIa have been described as effective in this population [44] and administering smaller doses, e.g. $20\text{--}40 \mu\text{g.kg}^{-1}$, repeated if clinically indicated, may emerge as an appropriate dosing regimen in cardiac surgery patients.

Factor VII deficiency and liver disease

As an alternative to replacement therapy with plasma derived factor VII or aPCC, rFVIIa is effective (at a dose of $15\text{--}30 \mu\text{g.kg}^{-1}$ every 4–6 h until haemostasis is achieved) in the rare congenital factor VII deficiency [45]. Regulatory approval in Europe has recently been granted for this indication.

Acquired low factor VII levels are also a feature of liver disease resulting in decreased synthetic function, e.g. cirrhosis, as factor VII has the shortest half life of the hepatically synthesised enzymes, and as a result factor VII is also the coagulation factor most sensitive to oral anticoagulant therapy with vitamin K antagonists, e.g. warfarin and coumadin. Reversal of oral anticoagulants should also include vitamin K and at least 20ml.kg^{-1} fresh frozen plasma, which is adequate for most indications. However, rapid reversal of anticoagulation may be desirable in specific circumstances such as intracranial haemorrhage. This can be achieved with aPCC and has been described with $20 \mu\text{g.kg}^{-1}$ rFVIIa in conjunction with fresh frozen plasma [46].

A prolonged prothrombin time in cirrhotic patients is associated with acquired factor VII deficiency, and rFVIIa will transiently correct this abnormality in patients unresponsive to vitamin K administration [47]. Successful prophylactic use of rFVIIa for laparoscopic liver biopsy in cirrhotic patients with prolonged prothrombin times has been described [48] and anecdotal success has been reported in oesophageal variceal bleeding in cirrhotic patients [49].

Liver transplantation is an attractive area in which to use rFVIIa because of high blood product usage and the multifactorial aetiology of the associated coagulopathy. Transfusion requirements were markedly decreased in a pilot study when compared to historical controls during orthotopic liver transplantation in patients pretreated with rFVIIa $80 \mu\text{g.kg}^{-1}$ [50], which is encouraging for randomised, controlled trials in this area. Pretransplant liver disease covers the spectrum of haemorrhagic and thrombotic risk from fulminant hepatic failure to Budd–Chiari syndrome, respectively, so it may be imprudent to administer rFVIIa to all liver transplant candidates, as that would include some patients with hypercoagulable states. The need for randomised, controlled trials in the area of coagulopathy secondary to hepatic failure was emphasised in a recent review [51].

Reversal of other anticoagulant therapies

A therapy to reverse the anticoagulant effect of direct thrombin inhibitors, e.g. recombinant hirudin, argatroban or bivalirudin, would be desirable in the surgical population, as these drugs are increasingly used for anticoagulation in the setting of heparin-induced thrombocytopenia and regulatory approval is currently being sought for use of the oral direct thrombin inhibitor ximelagatran as an alternative to warfarin in patients with atrial fibrillation [52]. By directly binding to the thrombin molecule, even low plasma levels of direct thrombin inhibitors can produce a coagulopathy that is not amenable to reversal with haemostatic blood products. Similarly, the generation of a large quantity of thrombin would be required to compete with direct inhibition of the thrombin molecule, so it is no surprise that reports on the efficacy of rFVIIa in this setting have been mixed [53, 54]. While there is some evidence that aPCC may be a superior agent for this indication [55], effective reversal of these agents remains elusive.

The anticoagulant and profibrinolytic activities of the pentasaccharide anticoagulants fondaparinux and idraparinux, on the other hand, are reversible with rFVIIa [56, 57], and there is a single case report of reversal of low molecular weight heparin effect with rFVIIa $50 \mu\text{g.kg}^{-1}$ [58].

Monitoring

There is no established monitor of rFVIIa effect. While the prothrombin time (PT) is a logical choice, the sensitivity of this test to factor VII levels may exaggerate the *in vitro* vs. the *in vivo* effect [59]. In liver transplant patients, rFVIIa rapidly and significantly improved coagulation variables including PT, aPTT and thromboelastograph parameters [13], and the responsiveness of

thromboelastograph variables to rFVIIa administration has also been noted in cardiac surgery [44, 60]. However, it is unlikely that currently available monitoring will help determine an individualised dosing regimen, and levels of factor VII coagulant activity do not always predict efficacy [61]. Therefore, if the main effect of rFVIIa is truly at the site of injury, cessation of bleeding may be the best and only indication of efficacy.

Dosing rFVIIa in surgical patients

Linear pharmacokinetics are seen with rFVIIa infusion; median clearance is approximately $30 \text{ ml.kg}^{-1}.\text{h}^{-1}$ and the median half life is around 3 h in haemophiliacs, with children demonstrating greater clearance and a shorter half life. The dosing recommendation for haemophiliacs undergoing surgery starts with a $90 \text{ }\mu\text{g.kg}^{-1}$ bolus [3] at a dosing interval of every 2 h and increasing to every 4 h by the seventh postoperative day. Similar dosing regimens have been used for congenital thrombocytopathias [27], and simultaneous administration of antifibrinolytic drugs is standard practice. These are huge cumulative doses of rFVIIa and are only appropriate for surgical patients who are not expected to recover haemostatic function due to a pre-existing bleeding diathesis. Conversely, bolus doses as low as $20 \text{ }\mu\text{g.kg}^{-1}$ [62] and $45 \text{ }\mu\text{g.kg}^{-1}$ [44] have proven effective after cardiac surgery in which single-dose administration may be sufficient; lower doses are also effective in non-surgical situations in haemophiliacs [63]. Single doses of 20 and $40 \text{ }\mu\text{g.kg}^{-1}$ during prostatectomy [38] have also decreased effectively peri-operative bleeding and blood product requirements. Official dosage recommendations for off-label use are not available, but doses as low as $20 \text{ }\mu\text{g.kg}^{-1}$ have been shown to have some effect [38, 62], whilst doses in the area of $40 \text{ }\mu\text{g.kg}^{-1}$ have been effective in many clinical settings [31, 38, 44]. If ineffective, the dose can be repeated, and larger doses do not necessarily cause more thromboembolic complications [31]. Of note, a 2.4 mg vial of NovoSeven® (a $40 \text{ }\mu\text{g.kg}^{-1}$ dose for a 60 kg patient) costs in the region of \$6700. Considering such factors and understanding the mechanism of rFVIIa in various coagulopathic states may discourage irrational off-label use of rFVIIa.

Conclusions

Recombinant factor VIIa has proven safe and efficacious for the treatment and prevention of bleeding in haemophiliacs with inhibitors and patients with Glanzmann's thrombasthenia. Theoretically, indications may expand to include many medical and surgical patients but randomised, blinded, placebo-controlled trials are needed to

guide safe and effective use of a new medication gaining widespread use. Although off-label use will undoubtedly continue, particularly for 'rescue' indications, we would agree with policies whereby rFVIIa use is reserved for life-threatening bleeding with no identifiable surgical source in patients who fail to respond to adequate conventional blood component therapy [64].

References

- 1 Sjamsoedin LJ, Heijnen L, Mauser-Bunschoten EP, *et al.* The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. A double-blind clinical trial. *New England Journal of Medicine* 1981; **305**: 717–21.
- 2 Lusher JM. Use of prothrombin complex concentrates in management of bleeding in hemophiliacs with inhibitors – benefits and limitations. *Seminars in Hematology* 1994; **31**: 49–52.
- 3 Shapiro AD, Gilchrist GS, Hoots WK, *et al.* Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thrombosis and Haemostasis* 1998; **80**: 773–8.
- 4 Lo SK, Cheung A, Zheng Q, *et al.* Induction of tissue factor on monocytes by adhesion to endothelial cells. *Journal of Immunology* 1995; **154**: 4768–77.
- 5 Roberts HR. Clinical experience with activated factor VII: focus on safety aspects. *Blood Coagulation and Fibrinolysis* 1998; **9** (Suppl. 1): S115–8.
- 6 Gallistl S, Cvirn G, Muntean W. Recombinant factor VIIa does not induce hypercoagulability in vitro. *Thrombosis and Haemostasis* 1999; **81**: 245–9.
- 7 Mach F, Schonbeck U, Bonnefoy JY, *et al.* Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. *Circulation* 1997; **96**: 396–9.
- 8 Toschi V, Gallo R, Lettino M, *et al.* Tissue factor modulates the thrombogenicity of human atherosclerotic plaques. *Circulation* 1997; **95**: 594–9.
- 9 Bui JD, Despotis GD, Trulock EP, *et al.* Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. *Journal of Thoracic and Cardiovascular Surgery* 2002; **124**: 852–4.
- 10 Rosenfeld SB, Watkinson KK, Thompson BH, *et al.* Pulmonary embolism after sequential use of recombinant factor VIIa and activated prothrombin complex concentrate in a factor VIII inhibitor patient. *Thrombosis and Haemostasis* 2002; **87**: 925–6.
- 11 Hough RE, Hampton KK, Preston FE, *et al.* Recombinant VIIa concentrate in the management of bleeding following prothrombin complex concentrate-related myocardial infarction in patients with haemophilia and inhibitors. *British Journal of Haematology* 2000; **111**: 974–9.

- 12 Butenas S, Brummel KE, Branda RF, et al. Mechanism of factor VIIa-dependent coagulation in hemophilia blood. *Blood* 2002; **99**: 923–30.
- 13 Hendriks HG, Meijer K, de Wolf JT, et al. Effects of recombinant activated factor VII on coagulation measured by thromboelastography in liver transplantation. *Blood Coagulation and Fibrinolysis* 2002; **13**: 309–13.
- 14 Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. *Arteriosclerosis, Thrombosis and Vascular Biology* 2003; **23**: 17–25.
- 15 Hoffman M, Monroe DM, Roberts HR. Human monocytes support factor X activation by factor VIIa, independent of tissue factor: implications for the therapeutic mechanism of high-dose factor VIIa in hemophilia. *Blood* 1994; **83**: 38–42.
- 16 Monroe DM, Hoffman M, Oliver JA, et al. Platelet activity of high-dose factor VIIa is independent of tissue factor. *British Journal of Haematology* 1997; **99**: 542–7.
- 17 Hoffman M, Monroe DM 3rd. The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. *Seminars in Hematology* 2001; **38**: 6–9.
- 18 Lisman T, Mosnier LO, Lambert T, et al. Inhibition of fibrinolysis by recombinant factor VIIa in plasma from patients with severe hemophilia A. *Blood* 2002; **99**: 175–9.
- 19 Poon MC, Demers C, Jobin F, et al. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. *Blood* 1999; **94**: 3951–3.
- 20 Poon MC, D'Oiron R, Von Depka M, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *Journal of Thrombosis and Haemostasis* 2004; **2**: 1096–103.
- 21 Hoffman M, Monroe DM 3rd, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagulation and Fibrinolysis* 1998; **9**: S61–5.
- 22 Kjalke M, Ezban M, Monroe DM, et al. High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia-like conditions in a cell-based model system. *British Journal of Haematology* 2001; **114**: 114–20.
- 23 Ramakrishnan V, DeGuzman F, Bao M, et al. A thrombin receptor function for platelet glycoprotein Ib-IX unmasked by cleavage of glycoprotein V. *Proceedings of the National Academy of Sciences of the United States of America* 2001; **98**: 1823–8.
- 24 De Candia E, Hall SW, Rutella S, et al. Binding of thrombin to glycoprotein Ib accelerates the hydrolysis of Par-1 on intact platelets. *Journal of Biological Chemistry* 2001; **276**: 4692–8.
- 25 Lisman T, Adelmeijer J, Heijnen HF, et al. Recombinant factor VIIa restores aggregation of alphaIIb beta3-deficient platelets via tissue factor-independent fibrin generation. *Blood* 2004; **103**: 1720–7.
- 26 Lisman T, Moschatsis S, Adelmeijer J, et al. Recombinant factor VIIa enhances deposition of platelets with congenital or acquired alpha IIb beta 3 deficiency to endothelial cell matrix and collagen under conditions of flow via tissue factor-independent thrombin generation. *Blood* 2003; **101**: 1864–70.
- 27 Poon MC, d'Oiron R. Recombinant activated factor VII (NovoSeven) treatment of platelet-related bleeding disorders. International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders Group. *Blood Coagulation and Fibrinolysis* 2000; **11** (Suppl. 1): S55–68.
- 28 Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997; **28**: 1–5.
- 29 Mayer SA, Brun NC, Broderick J, et al. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 2005; **36**: 74–9.
- 30 Freeman WD, Brott TG, Barrett KM, et al. Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clinic Proceedings* 2004; **79**: 1495–500.
- 31 Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *New England Journal of Medicine* 2005; **352**: 777–85.
- 32 Lynn M, Jerokhimov I, Jewelewicz D, et al. Early use of recombinant factor VIIa improves mean arterial pressure and may potentially decrease mortality in experimental hemorrhagic shock: a pilot study. *Journal of Trauma* 2002; **52**: 703–7.
- 33 Martinowitz U, Kenet G, Lubetski A, et al. Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Canadian Journal of Anaesthesia* 2002; **49**: S15–20.
- 34 Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *Journal of Trauma* 2001; **51**: 431–8; discussion 38–9.
- 35 Schreiber MA, Holcomb JB, Hedner U, et al. The effect of recombinant factor VIIa on coagulopathic pigs with grade V liver injuries. *Journal of Trauma* 2002; **53**: 252–7; discussion 57–9.
- 36 Raobaikady R, Redman J, Ball JAS, et al. Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of the pelvis or pelvis and acetabulum: a double blind, randomized, placebo-controlled trial. *British Journal of Anaesthesia* 2005; **94**: 586–91.
- 37 Lodge JP, Jonas S, Oussoultzoglou E, et al. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology* 2005; **102**: 269–75.
- 38 Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; **361**: 201–5.
- 39 Miller RA, May MW, Hendry WF, et al. The prevention of secondary haemorrhage after prostatectomy: the value of antifibrinolytic therapy. *British Journal of Urology* 1980; **52**: 26–8.

- 40 O'Connell NM, Perry DJ, Hodgson AJ, *et al.* Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion* 2003; **43**: 1711–6.
- 41 Ahonen J, Jokel R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. *British Journal of Anaesthesia* 2005; **94**: 592–5.
- 42 Levi M, Cromheecke ME, de Jonge E, *et al.* Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; **354**: 1940–7.
- 43 Karkouti K, Beattie WS, Wijeyesundera DN, *et al.* Recombinant factor VIIa for intractable blood loss after cardiac surgery: a propensity score-matched case-control analysis. *Transfusion* 2005; **45**: 26–34.
- 44 Tanaka KA, Waly AA, Cooper WA, *et al.* Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology* 2003; **98**: 1513–5.
- 45 Mariani G, Testa MG, Di Paolantonio T, *et al.* Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sanguinis* 1999; **77**: 131–6.
- 46 Lin J, Hanigan WC, Tarantino M, *et al.* The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings. *Journal of Neurosurgery* 2003; **98**: 737–40.
- 47 Bernstein DE, Jeffers L, Erhardtsen E, *et al.* Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology* 1997; **113**: 1930–7.
- 48 Jeffers L, Chalasani N, Balart L, *et al.* Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002; **123**: 118–26.
- 49 Ejlersen E, Melsen T, Ingerslev J, *et al.* Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from oesophageal varices. *Scandinavian Journal of Gastroenterology* 2001; **36**: 1081–5.
- 50 Hendriks HG, Meijer K, de Wolf JT, *et al.* Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation* 2001; **71**: 402–5.
- 51 Caldwell SH, Chang C, Macik BG. Recombinant activated factor VII (rFVIIa) as a hemostatic agent in liver disease: a break from convention in need of controlled trials. *Hepatology* 2004; **39**: 592–8.
- 52 Albers GW, Diener HC, Frison L, *et al.* Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial [see comment]. *Journal of the American Medical Association* 2005; **293**: 690–8.
- 53 Stratmann G, deSilva AM, Tseng EE, *et al.* Reversal of direct thrombin inhibition after cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. *Anesthesia and Analgesia* 2004; **98**: 1635–9.
- 54 Malherbe S, Tsui BCH, Stobart K, *et al.* Argatroban as anticoagulant in cardiopulmonary bypass in an infant and attempted reversal with recombinant activated factor VII. *Anesthesiology* 2004; **100**: 443–5.
- 55 Elg M, Carlsson S, Gustafsson D. Effect of activated prothrombin complex concentrate or recombinant factor VIIa on the bleeding time and thrombus formation during anticoagulation with a direct thrombin inhibitor. *Thrombosis Research* 2001; **101**: 145–57.
- 56 Lisman T, Bijsterveld NR, Adelmeijer J, *et al.* Recombinant factor VIIa reverses the in vitro and ex vivo anticoagulant and profibrinolytic effects of fondaparinux. *Journal of Thrombosis and Haemostasis* 2003; **1**: 2368–73.
- 57 Bijsterveld NR, Vink R, van Aken BE, *et al.* Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *British Journal of Haematology* 2004; **124**: 653–8.
- 58 Hu Q, Brady JO. Recombinant activated factor VII for treatment of enoxaparin-induced bleeding. *Mayo Clinic Proceedings* 2004; **79**: 827.
- 59 Hoffman M. Laboratory monitoring of high dose Factor VIIa therapy. *Annals of Internal Medicine* 2003; **139**: 791.
- 60 Hendriks HG, van der Maaten JM, de Wolf J, *et al.* An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. *Anesthesia and Analgesia* 2001; **93**: 287–9.
- 61 Santagostino E, Morfini M, Rocino A, *et al.* Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Thrombosis and Haemostasis* 2001; **86**: 954–8.
- 62 Zietkiewicz M, Garlicki M, Domagala J, *et al.* Successful use of activated recombinant factor VII to control bleeding abnormalities in a patient with a left ventricular assist device. *Journal of Thoracic and Cardiovascular Surgery* 2002; **123**: 384–5.
- 63 Lusher JM, Roberts HR, Davignon G, *et al.* A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. RFXVIIa Study Group. *Haemophilia* 1998; **4**: 790–8.
- 64 Goodnough LT, Lublin DM, Zhang L, *et al.* Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; **44**: 1325–31.